NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	sNDA
Application Number(s)	NDA 211675/S-004
Priority or Standard	Priority
Submit Date(s)	October 15, 2020
Received Date(s)	October 15, 2020
PDUFA Goal Date	July 15, 2021
Division/Office	Division of Dermatology and Dentistry/Office of Immunology and Inflammation
Review Completion Date	January 13, 2022
Established/Proper Name	upadacitinib
(Proposed) Trade Name	RINVOQ
Pharmacologic Class	Janus kinase inhibitor and immunomodulator agent
Code name	N/A
Applicant	AbbVie Inc.
Dosage form	15 mg extended-release tablets and 30 mg extended-release tablets
Applicant proposed Dosing Regimen	15 mg or 30 mg orally once daily
Applicant Proposed Indication(s)/Population(s)	(b) (4) [redacted]
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	24079001 | Atopic Dermatitis
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of adults and pediatric patients 12 years of age and older with refractory, moderate to severe atopic dermatitis whose disease is not adequately controlled with other systemic drugs, including biologics, or when use of those therapies are inadvisable.
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	24079001 | Atopic Dermatitis
Recommended Dosing Regimen	Pediatric Patients 12 Years of Age and Older Weighing at Least 40 kg and Adults Less than 65 years of Age: Initiate treatment with 15 mg once daily. If an adequate response is not achieved, consider increasing the dosage to 30 mg once daily. Discontinue RINVOQ if an adequate response is

	not achieved with the 30 mg dose. Use the lowest effective dose needed to maintain response. Adults 65 Years of Age and Older: The recommended dosage is 15 mg once daily.

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Signatures

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Glossary

AC	advisory committee
AD	atopic dermatitis
ADL	activities of daily living
ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
BID	twice daily
BLA	biologics license application
BSA	body surface area
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CMH	Cochran-Mantel-Haenszel
COA	clinical outcome assessment
CrCL	creatinine clearance
CPK	creatine phosphokinase
CSR	clinical study report
CSS	clinical summary of safety
CTCAE	Common Terminology Criteria for Adverse Event
CTCL	cutaneous T-cell lymphoma
DB	double-blind
DEPI	Division of Epidemiology
DHOT	Division of Hematology Oncology Toxicology
DPMH	Division of Pediatric and Maternal Health
DSC	Drug Safety Communication
DVT	deep vein thrombosis
EASI	Eczema Area and Severity Index
ECG	electrocardiogram
eCTD	electronic common technical document
ER	extended release
FDA	Food and Drug Administration
GI	gastrointestinal
HDL-C	high-density lipoprotein cholesterol
ICH	International Conference on Harmonisation
IGA	Investigator's Global Assessment
IND	Investigational New Drug
iPSP	initial pediatric study plan
ISE	integrated summary of effectiveness

ISS	integrated summary of safety
ITT	intent to treat
JAK	Janus kinase
LDL-C	low-density lipoprotein cholesterol
MACE	major adverse cardiovascular events
MCMC	Markov Chain Monte Carlo (MCMC)
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
mITT	modified intent to treat
MPPRC	Medical Policy and Program Review Council
NCI	National Cancer Institute
NDA	new drug application
NMSC	non-melanoma skin cancer
NRI-C	Non-Responder Imputation while incorporating multiple imputation to handle missing data due to COVID-19
OL	open-label
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBO	placebo
PCS	potentially clinically significant
PD	pharmacodynamics
PDE-4	phosphodiesterase-4
PE	pulmonary embolism
PeRC	Pediatric Review Committee
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PO	orally
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PV	Pharmacovigilance
PY	patient year
QD	once daily
RA	rheumatoid arthritis
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SIB	suicidal ideation and behavior
SLC	Safety Labeling Change
sNDA	supplemental new drug application
SSA IR	Study Size Adjusted Incidence Rate

STAT	Signal Transducers and Activators of Transcription
TCI	topical calcineurin inhibitors
TCS	topical corticosteroids
TEAE	treatment emergent adverse event
TEOI	treatment-emergent opportunistic infections
TREAT	TREatment of ATopic eczema
ULN	upper limit of normal
UPA	upadacitinib
v-IGA-AD	validated Investigator Global Assessment of Atopic Dermatitis
VTE	thromboembolic events
WI-NRS	Worst Itch Numeric Rating Scale

1 Executive Summary

1.1. Product Introduction

Upadacitinib (ABT-494, RINVOQ) is a reversible Janus kinase (JAK) inhibitor approved for the treatment of rheumatoid arthritis (RA) on August 16, 2019. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Within the signaling pathway, JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. Upadacitinib modulates the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs. In a cell-free isolated enzyme assay, upadacitinib had greater inhibitory potency at JAK1 and JAK2 relative to JAK3 and TYK2. In human leukocyte cellular assays, upadacitinib inhibited cytokine-induced STAT phosphorylation mediated by JAK1 and JAK1/JAK3 more potently than JAK2/JAK2 mediated STAT phosphorylation.

The proposed indication for upadacitinib is for the (b) (4)

The recommended indication:

- Upadacitinib is indicated for the treatment of adults and pediatric patients 12 years of age and older with refractory, moderate to severe atopic dermatitis. Upadacitinib is reserved for patients whose disease is not adequately controlled with other systemic drugs, including biologics, or when use of those therapies are inadvisable.

The recommended dosage and dosing regimen

- Pediatric Patients 12 Years of Age and Older Weighing at Least 40 kg and Adults Less than 65 years of Age:
  Initiate treatment with 15 mg once daily. If an adequate response is not achieved, consider increasing the dosage to 30 mg once daily. Discontinue RINVOQ if an adequate response is not achieved with the 30 mg dose. Use the lowest effective dose needed to maintain response.

- Adults 65 Years of Age and Older:
  The recommended dosage is 15 mg once daily.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant provided substantial evidence of effectiveness from 3 adequate and well controlled studies that evaluated upadacitinib for treatment of subjects 12 years and older with moderate-to severe atopic dermatitis who are candidates for systemic therapy. Two replicate studies evaluated upadacitinib as monotherapy, and the third study evaluated upadacitinib with protocol-specified, concomitant use of topical corticosteroids (TCS). Upadacitinib was

statistically superior to placebo in all 3 studies in the target AD population for the co-primary endpoints, the proportion of subjects with both Investigator's Global Assessment (IGA) 0 to 1 (on a 5-point scale) with at least reduction of ≥2 grades from Baseline and the proportion of subjects achieving 75% improvement of Eczema Area and Severity Index (EASI) score, at Week 16. The treatment response was generally similar across the 3 studies and subgroups.

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1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Upadacitinib (ABT-494, RINVOQ), a janus kinase (JAK) inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. In a cell-free isolated enzyme assay, upadacitinib had shown greater inhibitory potency at JAK1 and JAK2 relative to JAK3 and TYK2. In human leukocyte cellular assays, upadacitinib inhibited cytokine-induced STAT phosphorylation mediated by JAK1 and JAK1/JAK3 more potently than JAK2/JAK2 mediated STAT phosphorylation.

The proposed indication is for (b) (4)

Atopic dermatitis (AD) is a chronic, relapsing, inflammatory cutaneous disorder, which is characterized by intensely pruritic, xerotic skin. Other clinical features may include erythema, edema, erosions, oozing, and lichenification. Although it may affect all age groups, AD is most common in children. Onset is typically between the ages of 3 and 6 months, with approximately 60% of patients developing the disease during the first year of life and 90% by the age of 5 years. For 10-30% of individuals, AD persists into adulthood. Risk factors that predispose patients for persistence of the disease into adulthood include late onset (late childhood or adolescence) and more severe disease. Approximately 80% of childhood AD does not persist beyond 8 years of age. The overall prevalence of AD is estimated to be approximately 3% of adults.

The Applicant provided substantial evidence of effectiveness from 3 adequate and well controlled studies that evaluated upadacitinib for treatment of subjects 12 years and older with moderate-to severe atopic dermatitis who are candidates for systemic therapy. Two replicate studies evaluated upadacitinib as monotherapy, and the third study evaluated upadacitinib with protocol-specified, concomitant use of topical corticosteroids (TCS). Upadacitinib was statistically superior to placebo in all 3 studies in the target AD population for the co-primary endpoints of the proportion of subjects with both, Investigator's Global Assessment (IGA) 0 to 1 (on a 5-point scale) with at least a reduction of ≥2 grades from Baseline and, the proportion of subjects achieving 75% improvement of Eczema Area and Severity Index (EASI) score, at Week 16. The treatment response was generally similar across all 3 studies and subpopulations.

In Study M16-045, IGA 0 or 1 responders for 15 mg QD, 30 mg QD doses and placebo were 48%, 62% and 8%, respectively for the overall population, (38%, 69% and 8%, respectively, for the adolescents only); the EASI-75 responders were 70%, 80% and 16%, respectively, for the

overall population (71%, 83%, and 8%, respectively, for the adolescents only).

In Study M16-047, IGA 0 or 1 responders for 15 mg QD, 30 mg QD doses and placebo were 40%, 59% and 11%, respectively, for the overall population (31%, 65% and 8% for the adolescents only); the EASI-75 responders were 65%, 77% and 26%, respectively, for the overall population (56%, 76%, and 30%, respectively, for the adolescents).

In Study M18-891, IGA 0 or 1 responders for 15 mg QD, 30 mg QD doses and placebo were 39%, 52% and 5%, respectively, for the overall population (42%, 62% and 3% for the adolescents only); the EASI-75 responders were 60%, 73% and 13%, respectively, for the overall population (67%, 74%, and 14%, respectively, for the adolescents).

The Applicant adequately characterized the safety profile of upadacitinib through analyses of data from the safety database of 2485 subjects in the 3 Phase 3 studies, including 333 adolescents. The safety profile of upadacitinib was similar to that reported for the rheumatoid arthritis indication. The most frequently reported adverse reactions in upadacitinib 15mg and 30mg treatment groups compared to placebo were: upper respiratory tract infection (23%; 25% and 17%), acne (10%; 15% and 2%), herpes simplex (4%; 8% and 2%), headache (6%; 6% and 4%) and increased blood creatine phosphokinase (5%; 6% and 2%) respectively. A dose dependent increase of adverse reactions rates was apparent for 30mg dose.

During the review of this efficacy supplement, the FDA received the results from a post-marketing required (PMR) study A392113 for another JAK inhibitor, tofacitinib, conducted in rheumatoid arthritis (RA) patients. The data showed increased risk for major adverse cardiovascular events (MACEs), mortality, malignancies, and thrombosis. Tofacitinib is an orally administered, small-molecule inhibitor of JAK approved for the treatment of rheumatoid arthritis (RA), psoriatic arthritis, and ulcerative colitis. FDA first approved tofacitinib, dosed at 5 mg twice daily (BID), in November 2012 for the treatment of patients with RA. Upon approval, FDA required Pfizer to conduct "a controlled clinical trial to evaluate the long-term safety of tofacitinib in patients with RA. The trial should include two doses of tofacitinib and an active comparator. The trial should be of sufficient size and duration to evaluate safety events of interest, including cardiovascular adverse events, opportunistic infections, and malignancy." Study A3921133 enrolled RA patients 50 years of age and older with at least one cardiovascular risk factor and evaluated the long-term safety of two doses of tofacitinib (5 and 10 mg BID) compared to tumor necrosis factor inhibitors (etanercept and adalimumab). The evaluated safety events of interest included major adverse cardiovascular events (MACEs), opportunistic infections, and malignancies. In 2019, interim results from the study showed an increased risk of thrombosis and death with the 10 mg BID dose, and FDA required updates to the tofacitinib labeling as a result. Following review of the final data from the study, on January 19, 2021, the Sponsor informed the Agency about an Emerging Safety Issue for tofacitinib, including an increased incidence of adjudicated MACE and adjudicated malignancies. Based on the information, the Agency issued a Drug Safety Communication on February 04, 2021.

The information from postmarketing tofacitinib trial was presented to the Medical Policy and Program Review Council (MPPRC) on April 14, 2021. MPPRC considered, based on data available from the tofacitinib program, whether the magnitude of risks associated with tofacitinib can be reasonably expected to apply across the entire JAK inhibitor drug class. The MPPRC took into consideration that JAK inhibitors exhibit a spectrum of pharmacodynamic profiles and, at present, it is not known which JAK (or related enzyme) is responsible for the adverse drug reactions seen with tofacitinib. Also, although the selectivity profiles of the various JAK inhibitors differ, it is not known whether these differences are relevant to risk of the adverse events seen with tofacitinib. There is no animal model showing that inhibition of particular JAKs leads to an outcome that is comparable to those seen in the tofacitinib outcome study. The pharmacokinetic, pharmacodynamic, toxicity, and animal model data would be needed to enhance the understanding of JAK inhibitors and to see if there is evidence that differences in profile of enzyme inhibition may lead to differences in safety profile.

Given the serious safety concerns identified with tofacitinib, the lack of data and information to reliably quantify or rule out these risks with the other JAK inhibitors, and the lack of available alternative therapies, MPPRC recommended that each JAK inhibitor indication for an inflammatory condition (approved and pending) be revised to reserve use in patients who have a favorable benefit-risk assessment. In addition, the baricitinib and upadacitinib Boxed Warnings should each be revised to add mortality and MACE; these sections and existing sections of the Boxed Warning (malignancies and thrombosis) will state that increased risk of each of these events was observed in RA patients treated with another JAK inhibitor compared with TNF blockers. The Boxed Warnings and Warnings and Precautions sections for each of the JAK inhibitors should include these risk factors and steps to take to prevent, mitigate, monitor, and/or manage these serious safety concerns. The Medication Guide of each JAK inhibitor should be revised to convey the risk information to patients as a result of these safety labeling changes to the Package Insert.

Given that several JAK inhibitors were under review as new drug applications (NDAs)/ supplementary NDAs or under development in ongoing clinical trials and development programs spanning a range of indications and multiple divisions, it was important to consider the relevance of the findings from the tofacitinib safety PMR study to the safety and benefit-risk assessment of other JAK inhibitor programs including upadacitinib. Based on the new safety information from the tofacitinib study, the division requested that the AbbVie provide an updated assessment of the benefit-risk profile for upadacitinib for the proposed indication of treatment of adults and adolescents 12 years and older with moderate to severe atopic dermatitis who are candidates for systemic therapy, and to consider whether additional changes would be appropriate to the proposed indication to support a favorable benefit-risk for their application. The Applicant responded with the following proposed changes:

- For adults with moderate to severe AD, based on the demonstrated dose response for efficacy and available safety data for both doses, there is a favorable benefit-risk profile for both the 15 mg and 30 mg QD upadacitinib doses.

- In patients aged 65 and older, although upadacitinib demonstrated efficacy benefits in treatment of moderate to severe AD, the limited data in this subgroup precludes a definitive conclusion regarding the added benefit of the 30 mg dose relative to the 15 mg dose. Safety data suggest a higher risk for serious infections and malignancies with the 30 mg dose versus the 15 mg dose. Based on the need for treatment options, and the favorable benefit risk profile of the 15 mg dose, the 15 mg dose is recommended for patients > 65 years of age.
- In adolescents, available data indicate a favorable benefit risk profile for both the 15 and 30 mg doses, however, AbbVie recommended the 15 mg dose for adolescents based on rationale that there is a need for further characterization of the upadacitinib 30 mg dose in this population.

The data on efficacy and safety for upadacitinib, (b) (4) was presented to MPPRC on April 14, 2021. The MPPRC considered the appropriateness of the Applicant's proposed indication as well as the approval of 15 mg and 30 mg doses in regard to the subpopulations of adolescents (b) (4) The Council members agreed that, in view of the benefit risk assessment and the unmet medical need for additional therapies, the indication should be narrowed to include subjects with moderate to severe AD of upper disease severity which is refractory to prior systemic treatments. The Council recommended approving the 15 and 30 mg doses, for both the adult and adolescent patients. They also recommended stepwise dosing labeling such that initially the 15 mg dose would be prescribed and increased to 30 mg only if necessary. Due to MACE events, higher risk of malignancy, and serious infections in adults >65 years of age, (b) (4) Based on the higher risk for serious infections in adults >65 years of age, the Division recommended the approval of 15mg dose only in this subpopulation.

This reviewer recommends approval of upadacitinib for the treatment of adults and pediatric patients 12 years of age and older with refractory, moderate to severe atopic dermatitis. Upadacitinib is reserved for patients whose disease is not adequately controlled with other systemic drugs, including biologics, or when use of those therapies are inadvisable.

The recommended dosage and dosing regimen:

- Pediatric Patients 12 Years of Age and Older Weighing at Least 40 kg and Adults Less than 65 years of Age:
  Initiate treatment with 15 mg once daily. If an adequate response is not achieved, consider increasing the dosage to 30 mg once daily. Discontinue RINVOQ if an adequate response is not achieved with the 30 mg dose. Use the lowest effective dose needed to maintain response.

- Adults 65 Years of Age and Older:

The recommended dosage is 15 mg once daily.

According to recommendations from PeRC, the Agency will issue Pediatric Research Equity Act (PREA) PMRs for efficacy and safety studies in pediatric subjects 6 months to 11 years of age. A PMR for long term safety evaluation will also be issued per recommendation from Office of Surveillance and Epidemiology (OSE). In addition, pregnancy PMRs will be issued.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• AD is a chronic, relapsing, inflammatory cutaneous disorder, which is characterized by intensely pruritic, xerotic skin. Other clinical features may include erythema, edema, erosions, oozing, and lichenification. Although it may affect all age groups, AD is most common in children. In 60% of patients, the onset of disease is in the first year of life, with onset by the age of 5 years in approximately 85% of affected individuals. • The prevalence of AD in the United States in individuals 4-8 years of age has been reported as 10.63% and as 9.96% in those 9-12 years of age. For 10-30% of individuals, AD persists into the adult years. • AD is clinically diagnosed and relies principally on disease pattern (morphology and distribution), disease history, and medical history (e.g., personal and/or family history of atopy). In patients older than 2 years of age, the presentation is like that in adults. It is particularly characterized by lichenified plaques in flexural regions of the extremities (antecubital and popliteal) and that may also involve the neck, wrists, and volar aspects of the wrists. AD may be generalized. Common comorbidities include asthma, allergic rhinitis/rhino-conjunctivitis, and food allergies.	While AD is not a life-threatening condition, it may be serious. It may significantly impact the quality of life of the patient, as well as family members. The dysfunctional skin barrier, further compromised from scratching, may predispose patients to secondary infections. The primary and secondary disease-related skin changes may distort the appearance of the skin. Patients with AD often experience sleep disturbance, largely attributable to the associated extreme pruritus. During disease flares, approximately 80% of patients may experience disturbed sleep. The disruption in sleep could have carryover effects to impact behavior and neurocognitive functioning. Sleep disturbance in the affected individual may also disrupt the sleep of family members. Affected children may also experience depression, anxiety, social isolation, and impaired psychosocial functioning.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• For the Applicant's target population, the only systemic therapy approved for the treatment of moderate-to-severe atopic dermatitis is DUPIXENT (dupilumab) and systemic corticosteroids. The American Academy of Dermatology recommends that systemic corticosteroids generally be avoided because of the potential for short- and long-term adverse reactions. Potential adverse effects include reversible hypothalamic-pituitary-adrenal axis suppression with the potential for glucocorticoid insufficiency, hyperglycemia, and other endocrine effects. A particular concern with their use in children and adolescents is the risk of decreased linear growth during treatment. • Phototherapy is considered safe and effective treatment for AD patients who are candidates for systemic therapy, including children. Its drawbacks include a potentially time intensive, in-office treatment schedule. Risks from phototherapy may vary according to the type of phototherapy and may include actinic damage, sunburn-like reactions, skin cancer (nonmelanoma and melanoma), and cataracts. • Systemic products that are used off-label to treat moderate-to-severe AD include cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil. The reported effectiveness for the products varies from "efficacious" (cyclosporine) to "inconsistent" (mycophenolate mofetil). Similarly, the safety profiles vary, although each product carries the potential for significant adverse effects, and all of these product labels include boxed warnings. The labeled risks include nephrotoxicity (cyclosporine), cytopenias (azathioprine), hepatotoxicity (methotrexate), and embryofetal toxicity (mycophenolate mofetil).	Until recently, the medical needs of children (6 to < 12 years) with moderate-to-severe AD were not being adequately met by available therapies. DUPIXENT (dupilumab) was approved for use in patients 6 years and older with moderate-to-severe atopic dermatitis in May-2020. The addition of an oral product, such as upadacitinib, to the armamentarium for the treatment of moderate-to-severe atopic dermatitis would represent an alternative to having injections or systemic steroids. Additionally, upadacitinib would represent a safe and effective alternative to the several systemic immunomodulating agents that are used off-label for treatment of this population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• To establish efficacy in monotherapy, the clinical trials compared co-primary endpoints for upadacitinib to placebo: o IGA responder proportion of clear (0) or almost clear (1) with upadacitinib 15 mg QD was 43.5% and with 30 mg QD was 57%, compared to 6.6% with placebo. o EASI-75 responder proportion with upadacitinib 15 mg QD was 64.9% and with 30 mg QD was 76.3%, compared to 14.8% with placebo. • In addition, Worst Pruritus NRS ≥ 4 reductions at Week 16 were observed.	The adult data for the use of upadacitinib in moderate-to-severe atopic dermatitis has been established in the clinical trials provided by AbbVie. Upadacitinib 15mg and 30mg doses are safe and effective for the treatment of moderate to severe atopic dermatitis, in adolescents and adult 12 to < 65 years of age). Due to limited safety data in subjects ≥ 65 years of age and the increased risks for serious infections and malignancies observed for 30mg dose in clinical trials, 15mg dose is recommended in this patient population. Upadacitinib has an acceptable risk-benefit profile for the treatment of moderate-to-severe atopic dermatitis in patients 12 years and above who failed other systemic therapies.
Risk and Risk Management	• The Applicant evaluated the safety and efficacy of oral upadacitinib for the treatment of moderate-to-severe atopic dermatitis in subjects 12 years and above. The most frequently reported adverse reactions in upadacitinib 15mg and 30mg treatment groups compared to placebo were: upper respiratory tract infection (23%; 25% and 17%), acne (10%; 15% and 2%), herpes simplex (4%; 8% and 2%), headache (6%; 6% and 4%) and increased blood creatine phosphokinase (5%; 6% and 2%) respectively. A dose dependent increase of adverse reactions rates was apparent for 30 mg QD dosage compared to 15mg dosage. No death was reported for the placebo-controlled safety pool. An increased rate of infections and opportunistic infections also increased, especially with herpes zoster, herpes simplex, and eczema herpeticum. Anemia and neutropenia were also	Postmarketing safety studies on tofacitinib showed increased risks such as death, malignancies, MACE, and thrombosis in comparison to TNF inhibitors, which raised safety concerns, and led to safety labeling changes for JAK inhibitors as a class. The Applicant reported 2 ongoing long term safety studies in US and Europe for rheumatoid arthritis indication to compare the incidence of malignancies, venous thromboembolism, major adverse cardiovascular events, and serious infection events in patients treated

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	observed on laboratory evaluations. • In light of the results of tofacitinib postmarketing study and, on the request of the Division, the Applicant provided additional benefit/risk considerations that included charges in dosage and dosing regimen for upadacitinib in subpopulations of patients with AD. The Applicant proposed 15mg QD dosing in adolescents and in adults ≥65 years of age. The rational for this proposal was that there was a need for further characterization of the upadacitinib 30 mg dose in adolescent population and, for the population of patients 65years and older, due to the limited available data available and a higher risk for serious infections and malignancies with the 30 mg dose compared to the 15 mg dose, definitive conclusion regarding the added benefit of the 30mg could not be made. For adults <65 years of age, the Applicant recommended 15mg QD and 30mg QD dosing. • Post-hoc efficacy analysis of upadacitinib in subjects who failed or could not tolerate prior systemic therapies showed similar results as those who did not. • The efficacy and safety data on upadacitinib was presented to the Medical Policy and Program Review Committee (MPPRC), who recommended that based on the available information and in light of data from tofacitinib postmarketing study, upadacitinib should be considered for approval as a third line therapy in patients with moderate to severe AD who have failed or unable to tolerate available systemic therapies. The Council also recommended a stepwise dosing such that initially the 15 mg dose would be prescribed and increased to 30 mg only if adequate response is not achieved. The Committee recommended approval of 15mg and 30mg dosage in adolescents and adults less than 65 years of age. For adults	with upadacitinib relative to patients treated with biologic medications approved for the treatment of moderately to severely active RA. (b) (4) . The Agency recommends: Upadacitinib is indicated for the treatment of adults and pediatric patients 12 years of age and older with refractory, moderate to severe atopic dermatitis. Because of serious and potentially life-threatening risks associated with its use, upadacitinib is reserved for patients whose disease is not adequately controlled with other systemic drugs, including biologics, or when use of those therapies are inadvisable. Treatment is to be initiated with 15 mg orally once daily. If an adequate response is not achieved, consider increasing the dosage to 30 mg orally once daily; and discontinue upadacitinb if an adequate response is not seen after increasing the dosage to 30 mg. Risk management strategies include product Labeling and post-marketing requirements for long term safety, and pregnancy studies are

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	≥ 65 years old, the Division recommended approval of 15mg QD only due to increased risk of serious infections and malignancies observed in 30mg dosing group compared to 15mg. In addition, MPPRC recommended class labeling for all products of JAK inhibitor class that would include information on increased risks of MACE, mortality, malignancies, and thrombosis, including upadacitinib. • Labeling will incorporate all relevant warnings and precautions established from the use of Janus Kinase inhibitors.	sufficient for long term safety evaluation, if approved. A REMS is not required.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		8.1, 18.5
		X	Patient reported outcome (PRO)	8.1, 18.5
		☐	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	8.1, 18.5
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Atopic dermatitis (AD) or commonly known as eczema, is a chronic, relapsing inflammatory skin condition characterized by dry, pruritic skin that occurs most frequently in children but also affects many adults. It is the leading non-fatal health burden attributable to skin disease, inflicts a substantial psychosocial burden on patients and their relatives, and increases the risk of food allergy, asthma, allergic rhinitis, other immune-mediated inflammatory diseases, and mental health disorders (Weidinger and Novak 2016). Clinical features of AD include skin dryness, erythema, oozing and crusting, and lichenification. Pruritis is a hallmark of the condition and responsible for much of the disease burden for patients and their families.

AD may have different endotypes, including race, ethnicity and age, and patients with and without filaggrin mutations (Czarnowicki, He et al. 2019). In 60% of patients, the onset of disease is in the first year of life, with onset by the age of 5 years in approximately 85% of affected individuals (Weston and How 2020). Shaw et al. reported the prevalence of AD in the United States in individuals 4-8 years of age to be 10.63% and in those 9-12 years of age to be 9.96% (Shaw, Currie et al. 2011). For 10-30% of individuals, AD persists into the adult years (Eichenfield, Tom et al. 2014).

AD is clinically diagnosed and relies principally on disease pattern (morphology and distribution), disease history, and medical history (e.g., personal and/or family history of atopy). In patients older than 2 years of age, the presentation is like that in adults. It is particularly characterized by lichenified plaques in flexural regions of the extremities (antecubital and popliteal) and that may also involve the neck, wrists, and volar aspects of the wrists. AD may be generalized.

The pathogenesis involves a complex interplay of genetic, immunological, and environmental factors that result in abnormal skin barrier function and immune system dysfunction. Irregularities in the terminal differentiation of the epidermal epithelium lead to a faulty stratum corneum which permits the penetration of environmental allergens. The exposure to allergens may ultimately result in systemic sensitization and may predispose AD patients to other conditions, such as asthma and food allergies (Leung and Guttman-Yassky 2014).

Acute AD is associated with cytokines produced by T helper 2 type (Th2) cells (as well as other T-cell subsets and immune elements). These cytokines are thought to play an important role in the inflammatory response of the skin, and IL-4 and IL-13 may have distinct functional roles in Th2 inflammation (Bao and Reinhardt 2015). IL-4 has been shown to stimulate immunoglobulin E (IgE) production from B cells (May and Fung 2015). IL-13 expression correlates with disease severity and flares. IL-4 mediates its biological activity via binding to IL-4Rα. IL-13 receptor alpha 1 (IL-13Rα1) may then be recruited to form a signaling complex. IL-13 mediates its biological activity via binding to IL-13Rα1 and subsequent recruitment of IL-4Rα, forming a signaling

complex (Leung and Guttman-Yassky 2014). IL-4 and IL-13 reside on chromosome 5q23-31, among a grouping of genes related to development of allergic diseases. Dupilumab inhibits IL-4 and IL-13 by blocking the shared IL-4Rα subunit (DUPIXENT package insert).

2.2. Analysis of Current Treatment Options

Food and Drug Administration (FDA)-approved or -licensed treatments for AD fall in the categories of corticosteroids (topical and systemic), calcineurin inhibitors (topical), phosphodiesterase-4 (PDE-4) inhibitors (topical), and IL-4 receptor antagonist (dupilumab).

Prior to the licensure of dupilumab, corticosteroids were the only systemically-administered products that were FDA-approved for treatment of an AD indication in any age group. Corticosteroids are available for treatment of AD by various routes of administration, including topical, oral, and parenteral. Although their use may result in rapid improvement, the AD commonly recurs with worse severity on discontinuation of the systemic corticosteroids (rebound). For this reason and because of the potential for adverse effects, the American Academy of Dermatology recommends that systemic steroids generally be avoided in the treatment of AD because potential risks generally outweigh the benefits (Sidbury, Davis et al. 2014). Potential adverse effects include reversible hypothalamic-pituitary-adrenal axis suppression with the potential for glucocorticoid insufficiency, hyperglycemia, and other endocrine effects. A particular concern in children and adolescents is the risk of decreased linear growth during treatment. Labels for systemic corticosteroids do not specify any limitations on the age of indication.

Topical corticosteroids (TCS) represent the cornerstone of anti-inflammatory treatment of AD in all age groups (Eichenfield, Tom et al. 2014). Numerous TCS, in various dosage forms and potencies, are available for treatment of AD, and some are specifically indicated for pediatric use. For example, fluticasone propionate lotion, 0.05%, a medium potency TCS, is indicated for relief of the inflammatory and pruritic manifestations of atopic dermatitis in patients 3 months of age and older. According to product labels, TCS may be sufficiently absorbed to lead to systemic adverse effects. Additionally, pediatric patients may be more susceptible to systemic toxicity doses due to their larger skin surface to body mass ratios. Labeled potential local adverse effects include skin atrophy, striae, telangiectasias, and hypopigmentation.

The topical calcineurin inhibitors (TCI), tacrolimus ointment and pimecrolimus cream, are also indicated for treatment of AD in pediatric patients (2 years and older): tacrolimus for moderate-to- severe AD and pimecrolimus for mild-to-moderate AD. However, both are labeled for second-line, short-term use when other topical prescription treatments have failed or are inadvisable. The calcineurin inhibitors carry boxed warnings advising that the safety of their long-term use has not been established. More specifically, the boxed warnings describe that rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors; a causal relationship has not been established. Crisaborole ointment, 2%, a PDE-4 inhibitor, is approved for treatment of AD in pediatric patients (3 months

of age and older). However, the product is indicated for a somewhat different AD population (mild-to-moderate AD) than the target population for dupilumab (moderate-to-severe AD).

Nonpharmacologic care is critical to AD management and includes attention to bathing practices and the regular use of moisturizers, which are available in several delivery systems, such as creams, ointments, oils, lotions. Moisturizers are directed at the xerosis and transepidermal water loss that are central elements of the disease. They may also relieve pruritus, lessen erythema and fissuring, and improve lichenification. Moisturizers themselves may be the principal treatment for mild disease. Although there are no standardized or universal recommendations regarding the use of moisturizers, repeated application of generous amounts is thought to be important and required, irrespective of the severity of disease. The use of moisturizers during maintenance may stave off flares and may lessen the amounts of pharmacologic agents needed to control the disease (Eichenfield, Tom et al. 2014).

Dupilumab is currently indicated for use in patients > 6 years of age with moderate-to-severe atopic dermatitis (Supplement-17) who have failed topical therapies or when those therapies are inadvisable. Dupilumab is given by injection. New treatment, focused on oral therapies are needed in the armamentarium for the treatment of moderate-to-severe AD. Phototherapy (UVA and UVB) is considered safe and effective treatment for AD patients who are candidates for systemic therapy, including children. However, phototherapy may require frequent in-office visits (e.g., several times a week) and time missed from school (and also, possibly from work for caregivers). Risks from phototherapy may vary according to the type of phototherapy and may include actinic damage, sunburn-like reactions (erythema, tenderness, pruritus), skin cancer (nonmelanoma and melanoma), and cataracts. However, long-term risks from phototherapy treatment of AD in children have not been evaluated. Narrowband UVB therapy may be considered first-line because of the safety profile relative to psoralen + UVA (PUVA).

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

This product was initially approved in the U.S for the treatment of rheumatoid arthritis in 2019.

3.2. Summary of Presubmission/Submission Regulatory Activity

- The Applicant opened the IND 128180 for upadacitinib (ABT-494, RINVOQ) on October 7, 2016 with a Phase 2b, dose-ranging study dose-ranging study in adult subjects with moderate to severe AD who have had an inadequate response to treatment with topical corticosteroids or topical calcineurin inhibitors.
- An End-of-Phase 2 meeting was held on February 21, 2018. The Applicant was given feedback on proposed Phase 3 endpoints, safety database and pruritus NRS scales. In addition, the Agency discussed the initial pediatric development plan.
- On November 6, 2017, the Applicant submitted a Breakthrough Therapy Designation Request. Upadacitinib received a Breakthrough Therapy Designation on January 2, 2018.
- On October 17 2019, the Applicant submitted an amended agreed iPSP proposing to (b) (4) . The amended agreed iPSP was reviewed by the Pediatric Review Committee (PeRC) on December 3, 2019. The Agency disagreed with the amended agreed iPSP because the Applicant had not provided sufficient information to justify an application for AD that (b) (4).
- On January 15, 2020, the Division informed the Applicant of the non-agreement with the amended agreed iPSP because the Applicant had not provided sufficient information to justify an application for AD that (b) (4). The Applicant requested and was granted a meeting with the Division to discuss the amended agreed iPSP.
- At a guidance meeting on March 30, 2020, the Agency informed the Applicant that adolescent data are required to be included in the initial marketing application. The Applicant re-submitted the amended iPSP to provide the Agency with (b) (4) . The amended iPSP was discussed at PeRC on May 5, 2020. DDD and PeRC disagreed with the sponsor's amendments to the iPSP. Atopic dermatitis is a disease associated with children and as such, adolescents need to contribute to the safety and efficacy of the drug product for approval. While the Agency disagreed with the amended iPSP, the previously agreed iPSP remained in effect and can be submitted in the sNDA.

- A Type B pre-sNDA meeting was held on July 22, 2020, during which the content and format of the supplemental new drug application (sNDA) were discussed. The Agency reiterated the recommendation that for safety, 750 subjects should be exposed to upadacitinib for at least 1 year and that of those subjects, 30% (225) should be adolescent subjects.
- This supplemental application was initially granted priority review because it received a Breakthrough Therapy Designation. During the review process, the Division requested updated assessment of the benefit-risk profile for the proposed indication due to the new safety information from the tofacitinib study. The Applicant submitted major amendment on March 26, 2021, which led to the Division's decision of extending the review goal date by three months to provide time for a full review of the submission.

Safety Labeling Change

On 08/23/2021, the FDA issued Safety Labeling Change (SLC) notifications to the holders of the applications for the JAK inhibitors tofacitinib, baricitinib, and upadacitinib. The SLC notifications require holders of approved drug and biological product applications to make safety labeling changes based upon new safety information that FDA becomes aware of after approval of the drug or biological product. The new safety information pertained to the high risks of death and sudden death, malignancy, and cardiovascular disorders from assessment of a postmarketing safety trial. The FDA determined that JAK inhibitors represent a class of products that have the potential for the same serious risks of death and sudden death, malignancy, and cardiovascular disorders. The SLC notifications advised that the new safety information should be included in the product labeling.

Drug Safety Communication

The FDA issued a Drug Safety Communication (DSC) on 09/01/2021 to alert the public that the final results from the safety trial in subjects with rheumatoid arthritis (trial referenced above) showed "an increased risk of serious heart-related events such as heart attack or stroke, cancer, blood clots, and death" in subjects treated with tofacitinib compared with TNF blockers. Additionally, subjects treated with tofacitinib showed an increased risk of blood clots. (Note: The FDA previously communicated information relating to this safety trial to the public in 02/2019, 07/2019, and on 02/04/2021).

The DSC also advised that the FDA would require new and updated warnings for baricitinib and upadacitinib. However, two other JAK inhibitors, fedratinib and oral ruxolitinib, would not be included in the requirement for labeling updates, as those two drugs are not indicated for the treatment of inflammatory conditions. Fedratinib and oral ruxolitinib required different updates to their prescribing information.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Dr. Phil Phuc Nguyen, Medical Officer from the Office of Scientific Investigations (OSI)provided the following overall assessment of findings and recommendations:

Two phase-3 studies: M18-891 and M16-045 were submitted to the Agency in support of a New Drug Application (NDA 211675) Supplement (S-004) for Upadacitinib Tablet for the above proposed indication. Three clinical investigators (Drs. Emma Guttman-Yassky, Navid Nami, and Mark Knautz) who contributed to the data were selected for surveillance clinical inspections.

The inspection and remote regulatory assessments revealed no significant findings at the audited clinical investigator sites. Based on the results of this inspection and remote regulatory assessments, the studies M18-891 and M16-045 overall appear to have been adequately conducted, and the study data generated appear acceptable in support of the respective indications for this supplemental NDA.

4.2. Product Quality

Not applicable for this supplemental application.

4.3. Clinical Microbiology

Not applicable for this supplemental application.

4.4. Devices and Companion Diagnostic Issues

Not applicable for this supplemental application.

5 Nonclinical Pharmacology/Toxicology

Executive Summary
A Pharmacology/Toxicology review is not needed for this supplemental application.

APPEARS THIS WAY ON ORIGINAL

6 Clinical Pharmacology

6.1. Executive Summary

RINVOQ (upadacitinib) is a Janus kinase (JAK) inhibitor, which was approved for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. The approved dose is 15 mg once daily (QD).

The purpose of this supplement is to seek an additional indication (b) (4)

In support of this supplement, the clinical development program included the following studies:

- One Phase 1 study (M20-017), evaluating the relative bioavailability of the formulation used in the Phase 3 studies and the commercial formulation under fasting and fed conditions for both the 15 mg and 30 mg tablets in healthy adult subjects
- One Phase 2b study (M16-048) evaluating efficacy and safety following multiple doses (1.5, 15, and 30 mg QD) of upadacitinib monotherapy compared to placebo in adult subjects with moderate to severe AD
- Four Phase 3 studies
    - M16-045: Efficacy and safety of upadacitinib (15 and 30 mg QD); adolescent (≥ 12 years) and adult subjects with moderate to severe AD
    - M16-047: Efficacy and safety of upadacitinib (15 and 30 mg QD) combined with topical corticosteroids (TCS); adolescent (≥ 12 years) and adult subjects with moderate to severe AD
    - M18-891: Efficacy and safety of upadacitinib (15 and 30 mg QD); adolescent (≥ 12 years) and adult subjects with moderate to severe AD
    - M17-377: Safety of upadacitinib (15 and 30 mg QD) combined with TCS in Japanese subjects (adolescents ≥ 12 years and adults) with moderate to severe AD
- Population PK analysis to explore dose-response relationships and evaluate the effect of intrinsic factors on upadacitinib PK

The key review findings with specific recommendations and comments are summarized below in Table 1.

Table 1. Summary of Clinical Pharmacology Review

Review Issues	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The efficacy of RINVOQ for the treatment of moderate to severe AD was established in the Phase 3 studies. In addition, the exposure-response relationship based on PK samples collected from the

	Phase 3 studies provides supportive evidence of effectiveness.
General dosing instruction	The Applicant's proposed dosing regimens (b) (4) with or without food. Based on the totality of data submitted, including similar PK and exposure-response trends for efficacy and safety between adolescent 12 years and older (weighing at least 40 kg) and adult subjects, there is no need for different dosing regimens between adults and adolescents 12 years and older (weighing at least 40 kg) from a clinical pharmacology perspective. However, due to the higher rate of safety findings observed in subjects ≥ 65 years of age (See Section Error! Reference source not found. for details), (b) (4) 15 mg QD in this age group is recommended. In summary, the recommended dosing regimens are as follows: <u>Adolescent patients 12 years of age and older weighing at least 40 kg and adults less than 65 years of age:</u> Initiate with 15 mg once daily and consider increasing the dosage to 30 mg orally once daily if an adequate response is not achieved <u>Adults 65 years of age and older:</u> 15 mg once daily
Pharmacokinetics (PK)	PK of upadacitinib in subjects with AD was evaluated in a Phase 2b study and Phase 3 studies. In addition, population PK analysis was conducted.
Food effect	Food effect on RINVOQ was evaluated under the original NDA submission. It was determined that RINVOQ can be taken with or without food.
Formulation	The proposed to-be-marketed formulation is 15 mg in purple or 30 mg in red extended release (ER) tablet (b) (4) intended for oral administration. The tablets will have the commercial logo and will be manufactured at the AbbVie commercial site in Ireland.

	The formulation used in the Phase 3 studies has the same (b) (4) as the market-image formulation; but is yellow in color without the commercial logo and was manufactured at the AbbVie pilot plant in the US.
Bridge between the market-image and the Phase 3 clinical trial formulations	The relative bioavailability between the market-image formulation and the Phase 3 trial formulation were evaluated for both 15 mg and 30 mg tablets, under fasting and fed conditions in M20-017.
Pediatric subjects	Pediatric subjects 12 years and older and weighing at least 40 kg were included in the four Phase 3 studies. No meaningful differences in PK and exposure-response between pediatric subjects and adults were observed.

Abbreviations: PK = pharmacokinetic, AD=atopic dermatitis, NDA = New Drug Application

6.1.1. Recommendations

The clinical pharmacology data for this supplement are determined to be adequate to support approval for the AD indication in adults and adolescents 12 years and older weighing at least 40 kg.

6.1.2. Post-Marketing Requirements and Commitments

Two PREA PMRs are recommended:

1) for evaluating efficacy, safety and PK of RINVOQ in pediatric subjects 6 to 11 years of age with AD.
2) for evaluating RINVOQ in pediatric subjects 6 months to 6 years of age with AD; the need for this study and data required from this study will be determined after review of the first PREA PMR in older pediatric subjects.

See Section 10 for details.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Mechanism of Action	Upadacitinib is a JAK inhibitor which inhibits cytokine-induced signal transducers and activators of transcription phosphorylation. However, the exact mechanism of upadacitinib in the treatment of AD is unknown.
PK in AD subjects	The table below summarizes the model-estimated plasma exposures of upadacitinib at steady-state, following 15 mg and 30 mg QD dosing in adolescent and adult subjects with AD.

		C_{avg} (ng/mL) Median (90% CI)	C_{max} (ng/mL) Median (90% CI)	C_{min} (ng/mL) Median (90% CI)
	15 mg QD Adolescent	14.7 (9.63 - 22.3)	37.7 (27.3 - 43.6)	3.52 (1.62 - 13.7)
	15 mg QD Adult	14.6 (9.54 - 29.2)	35.3 (25.5 - 44.0)	3.90 (1.56 - 23.9)
	30 mg QD Adolescent	29.2 (20.1 - 53.5)	73.4 (56.0 - 81.9)	7.85 (3.61 - 40.4)
	30 mg QD Adult	29.0 (19.6 - 52.8)	70.8 (54.4 - 88.7)	7.38 (3.09 - 43.5)
	Source: Table 13.9_2, R&D/20/0641			
Relative bioavailability between the market-image and the Phase 3 clinical trial formulations	The 90% confidence intervals of the geometric mean ratio for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were within the no effect boundary of limits of 80% to 125% for both 15 mg and 30 mg strengths, under fasting and fed conditions. The relative bioavailability between the market-image formulation and the Phase 3 formulation, both 15 and 30 mg strengths, were within the no effect boundary of 80% to 125%.			
Bioanalytical Method	Two bioanalytical assays, both LC-MS/MS, were used to analyze plasma samples in this supplement. The analytical methods were adequately validated, and no issues were identified from the bioanalytical study reports. See Section 18.4.4 for additional details.			

Abbreviations: JAK=Janus kinase, AD=atopic dermatitis, QD=once daily, AUC=area under the curve, LC-MS/MS= Liquid Chromatography with tandem mass spectrometry

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant has proposed different dosing regimens for adults and adolescents 12 years and older, (b) (4)

Based on the totality of the submitted data, which showed comparable PK and exposure-response between adults and adolescents and a higher rate of safety findings in adults 65 years and older, the following dosing regimens are recommended for the treatment of AD:

- Adolescent patients 12 years of age and older weighing at least 40 kg and adults less than 65 years of age: Initiate with 15 mg once daily and consider increasing the dosage to 30 mg orally once daily if an adequate response is not achieved

- Adults 65 years of age and older: 15 mg once daily

Therapeutic Individualization

For patients with severe renal impairment [creatinine clearance (CrCL) < 30 mL/min], the recommended dosage is 15 mg orally once daily, regardless of age. This is due to the absence of

renal impairment study with the 30 mg strength and findings from the renal impairment study conducted under the original NDA submission with the 15 mg strength which showed 19%, 33% and 45% increases in AUC in subjects with mild, moderate and severe renal impairment, respectively, compared to subjects with normal renal function. Also, there were no subjects with severe renal impairment enrolled in the Phase 3 trials.

Outstanding Issues

There are no outstanding issues that would preclude the approval of this supplement from a Clinical Pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

In subjects with AD
The PK of upadacitinib following administration of RINVOQ in subjects with AD was evaluated in a Phase 2b study (M16-048) and four Phase 3 studies (M16-045, M16-047, M18-891 and M17-377).

Phase 2 Study (M16-048): This was an 88-week Phase 2b, randomized, double-blind, parallel-group, placebo-controlled multicenter study to evaluate the safety and efficacy of upadacitinib in adult subjects with moderate to severe AD. The study included a 16-week double-blind treatment period (Period 1), followed by a 72-week double-blind treatment period (Period 2) for a total of 88 weeks of treatment. A total of 167 subjects were randomized in a 1:1:1:1 ratio to one of the four treatment groups:

- Group 1: upadacitinib 7.5 mg once daily QD (Day 1 to Week 16) → upadacitinib 7.5 mg QD or placebo (Week 16 and thereafter)
- Group 2: upadacitinib 15 mg QD (Day 1 to Week 16) → upadacitinib 15 mg QD or placebo (Week 16 and thereafter)
- Group 3: upadacitinib 30 mg QD (Day 1 to Week 16) → upadacitinib 30 mg QD or placebo (Week 16 and thereafter)
- Group 4: Group 4: matching placebo for (Day 1 to Week 16) → upadacitinib 30 mg QD
- or placebo (Week 16 and thereafter)

A total of 126 subjects (75.4%) completed the treatment through Week 16 (Period 1) and were re-randomized into Period 2. In Period 2, 81 subjects (64.3%) received rescue with upadacitinib 30 mg treatment (i.e., received rescue therapy after the first instance of a <EASI 50 response starting at the Week 20 visit [4 weeks after the re-randomization into Period 2]), 85 subjects (67.5%) completed study drug, and 41 subjects (32.5%) subjects discontinued study drug.

For PK assessment, blood samples were collected at Weeks 2 and 4 prior to dosing and at Weeks 8, 12, 16, 20, 24, 32, 40 and every 12 weeks until Week 88 post dosing. Since upadacitinib showed minimal accumulation after multiple once-daily administrations as

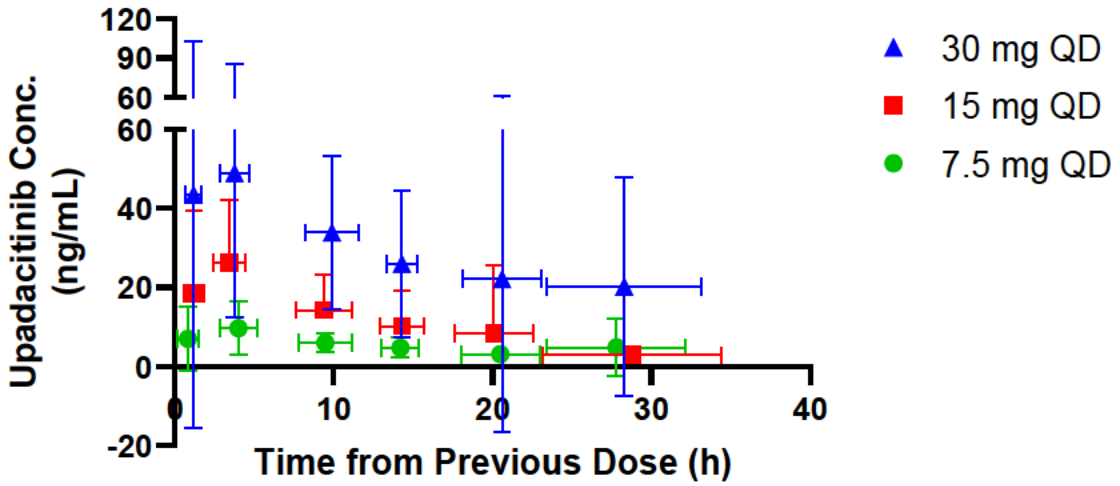
observed in clinical studies conducted under the original NDA submission and is stated in the currently approved RINVOQ labeling, plasma concentrations were analyzed by combining data from all visits. The mean upadacitinib plasma concentrations categorized by treatment group and time from previous dose is shown in Table 2. The mean upadacitinib plasma concentrations versus time from the last dose per treatment group are illustrated below in Figure 1. The PK between 15 and 30 mg dose was roughly dose proportional.

Table 2. Mean Plasma Upadacitinib Concentrations Categorized by Treatment Group and Time from Previous Dose from Study M16-048

Treatment Group	Time Categories (h)	# of Samples	# of Subjects	Mean Time (SD) from Previous Dose (h)	Mean (SD) UPA Concentration (ng/mL)
UPA 7.5 mg QD	> 0 – 2	19	12	0.842 (0.688)	6.94 (8.06)
	> 2 – 6	12	7	4.02 (1.20)	9.69 (6.85)
	> 6 – 12	22	10	9.47 (1.68)	5.98 (2.24)
	> 12 – 16	39	15	14.2 (1.18)	4.72 (2.54)
	> 16 – 24	68	24	20.5 (2.49)	3.07 (2.03)
	> 24 – 48	52	21	27.8 (4.35)	4.82 (7.32)
UPA 15 mg QD	> 0 – 2	13	11	1.22 (0.634)	18.5 (20.9)
	> 2 – 6	20	11	3.43 (1.04)	26.3 (15.9)
	> 6 – 12	36	11	9.38 (1.77)	14.3 (9.10)
	> 12 – 16	32	13	14.3 (1.37)	10.2 (8.87)
	> 16 – 24	71	27	20.1 (2.52)	8.38 (17.3)
	> 24 – 48	76	20	28.8 (5.65)	2.81 (2.27)
UPA 30 mg QD	> 0 – 2	50	27	1.19 (0.493)	43.5 (59.0)
	> 2 – 6	68	28	3.76 (0.935)	49.0 (36.7)
	> 6 – 12	86	29	9.89 (1.71)	33.9 (19.3)
	> 12 – 16	160	48	14.3 (0.927)	26.0 (18.6)
	> 16 – 24	220	62	20.6 (2.50)	22.1 (38.8)
	> 24 – 48	213	69	28.3 (4.88)	20.2 (27.9)

Source: Table 12, CSR R&D/19/0125
Abbreviations: UPA=upadacitinib; QD=once daily; SD=standard deviation

Figure 1. Mean Plasma Upadacitinib Concentrations vs. Time from Previous Dose from Study M16-048



Source: Reviewer generated figure (source data: Tables 14.2-3.3.1 to 14.2-3.3.3, CSR R&D/19/0125)

Phase 3 Studies: In the four Phase 3 studies (M16-045, M16-047, M18-891 and M17-377), PK of upadacitinib in adolescent (≥12 yrs old) and adult (≤75 yrs old) subjects with moderate to severe AD was evaluated. In each of these studies, sparse PK samples were collected at Weeks 2, 8, 12 and 16 (4 samples per subject). The summary of descriptions of these studies are in Table 3 below.

Table 3. Summary of the Phase 3 Studies Evaluating Efficacy, Safety and PK in Subjects with AD

Study ID	Objective(s)	Study Design	Dose	# of Subjects[a]
M16-045[b]	To assess the efficacy and safety of UPA for the treatment of adolescent (≥12 yrs old) and adult (≤75 yrs old) subjects with moderate to severe AD who are candidates for systemic therapy	Multicenter 2 period (16-week randomized, DB, parallel-group, controlled treatment period followed by a long-term blinded extension period up to Week 136)	DB period: 15 mg UPA, 30 mg UPA or PBO QD Blinded Extension period: 15 mg UPA or 30 mg UPA QD	847
M16-047[b]	To assess the efficacy and safety of UPA combined with TCS for the treatment of adolescent (≥12 yrs old) and adult (≤75 yrs old) subjects with moderate	Multicenter 2 period (16-week randomized, DB, parallel-group, controlled treatment period followed by a long-term blinded	DB period: 15 mg UPA, 30 mg UPA or PBO QD with TCS or TCI	901

	to severe AD who are candidates for systemic therapy	extension period up to Week 136)	Blinded Extension period: 15 mg UPA or 30 mg UPA QD with TCS or TCI	
M18-891[b]	To assess the efficacy and safety of UPA for the treatment of adolescent (≥12 yrs old) and adult (≤75 yrs old) subjects with moderate to severe AD who are candidates for systemic therapy	Multicenter 2 period (16-week randomized, DB, parallel-group, controlled treatment period followed by a long-term blinded extension period up to Week 136)	DB period: 15 mg UPA, 30 mg UPA or PBO QD Blinded Extension period: 15 mg UPA or 30 mg UPA QD	836
M17-377[c]	To assess the safety of UPA combined with TCS in adolescent (≥12 yrs old) and adult (≤75 yrs old) subjects in Japan with moderate to severe AD who are candidates for systemic therapy	Multicenter, 2-period (16-week randomized, DB, parallel-group, controlled treatment period followed by a long-term blinded extension (up to Week 52), followed by an OL extension (up to Week 136	DB period: 15 mg UPA, 30 mg UPA or PBO QD with topical cortico-steroids Blinded Extension period: 15 mg UPA or 30 mg UPA QD	272

[a]PK samples were collected in only select number of study sites and subjects
[b]Study still ongoing; full CSR available up to Week 16
[c]Study still ongoing; full CSR available up to Week 24
Abbreviations: AD = atopic dermatitis; BA = bioavailability; DB = double-blind; OL = open-label; PBO = placebo; TCI = topical calcineurin inhibitor; TCS = topical corticosteroids; UPA = upadacitinib

The observed upadacitinib plasma concentrations in these Phase 3 studies were comparable, as shown in Table 4, Table 5, Table 6 and Table 7 below. The comparison of mean plasma concentrations observed from these four Phase 3 studies and Study M16-048 per dose group is shown in Figure 2.

Reviewer's comment: Some of the large variability observed in mean upadacitinib concentrations may be partly due to the fact that exact timepoints for PK sample collection were different for these studies. Despite such limitation, the comparison of PK profiles across the four Phase 3 studies and a Phase 2 study (M16-048) were generally similar as shown in Figure 2.

Table 4. Mean Plasma Upadacitinib Concentrations Categorized by Treatment Group and Time from Previous Dose from Study M16-045

Treatment Group	Time Categories (h)	# of Samples	# of Subjects	Mean Time (SD) from Previous Dose (h)	Mean (SD) UPA Concentration (ng/mL)
UPA 15 mg QD	> 0 – 2	3	2	1.25 (0.846)	42.6 (21.8)
	> 2 – 6	11	7	3.51 (1.00)	40.4 (31.4)
	> 6 – 12	35	16	10.4 (1.22)	17.4 (13.3)
	> 12 – 16	45	26	14.4 (1.26)	9.56 (6.12)
	> 16 – 24	98	43	20.3 (2.45)	8.75 (9.62)
	> 24 – 48	70	34	27.6 (2.66)	5.90 (8.71)
UPA 30 mg QD	> 0 – 2	5	5	1.34 (0.768)	56.7 (39.9)
	> 2 – 6	17	11	2.89 (0.873)	69.3 (38.9)
	> 6 – 12	19	14	9.77 (1.73)	34.7 (13.3)
	> 12 – 16	43	18	14.4 (0.967)	22.6 (23.4)
	> 16 – 24	91	40	21.3 (2.05)	10.9 (19.6)
	> 24 – 48	64	35	26.9 (2.13)	14.9 (24.8)

Abbreviations: UPA=upadacitinib; QD=once daily; SD=standard deviation
Source: Table 17, CSR R&D/20/0172

Table 5. Mean Plasma Upadacitinib Concentrations Categorized by Treatment Group and Time from Previous Dose from Study M16-047

Treatment Group	Time Categories (h)	# of Samples	# of Subjects	Mean Time (SD) from Previous Dose (h)	Mean (SD) UPA Concentration (ng/mL)
UPA 15 mg QD plus TCS	> 0 – 2	24	18	1.34 (0.38)	25.3 (15.2)
	> 2 – 6	43	22	3.62 (1.12)	29.0 (15.3)
	> 6 – 12	29	13	10.5 (1.49)	15.7 (11.5)
	> 12 – 16	130	57	14.1 (1.21)	12.9 (11.0)
	> 16 – 24	200	89	20.2 (2.47)	6.35 (9.17)
	> 24 – 48	150	78	27.7 (3.66)	9.31 (17.7)
UPA 30 mg QD plus TCS	> 0 – 2	31	24	1.32 (0.51)	48.7 (35.0)
	> 2 – 6	43	26	3.41 (0.82)	58.3 (33.1)
	> 6 – 12	31	19	10.5 (1.21)	43.7 (28.5)
	> 12 – 16	90	42	14.2 (1.09)	20.2 (17.9)
	> 16 – 24	150	77	20.5 (2.55)	17.5 (41.8)
	> 24 – 48	182	85	26.7 (3.12)	20.0 (29.7)

Abbreviations: UPA=upadacitinib; QD=once daily; TCS=topical corticosteroids; SD=standard deviation
Source: Table 18, CSR R&D/20/0182

Table 6. Mean Plasma Upadacitinib Concentrations Categorized by Treatment Group and Time from Previous Dose from Study M18-891

Treatment Group	Time Categories (h)	# of Samples	# of Subjects	Mean Time (SD) from Previous Dose (h)	Mean (SD) UPA Concentration (ng/mL)
UPA 15 mg QD	> 0 – 2	7	7	1.48 (0.31)	34.1 (19.4)
	> 2 – 6	9	9	3.06 (0.82)	47.5 (23.2)
	> 6 – 12	19	14	10.4 (1.51)	19.1 (16.3)
	> 12 – 16	48	26	13.7 (1.17)	12.3 (12.6)
	> 16 – 24	102	49	20.4 (2.68)	7.35 (10.9)
	> 24 – 48	114	53	27.2 (2.76)	14.2 (22.2)
UPA 30 mg QD	> 0 – 2	4	3	1.44 (0.53)	53.4 (46.0)
	> 2 – 6	17	12	3.99 (1.26)	70.6 (45.8)
	> 6 – 12	20	12	9.78 (1.74)	39.1 (20.2)
	> 12 – 16	78	34	14.2 (1.17)	19.2 (16.1)
	> 16 – 24	106	51	20.1 (2.19)	14.2 (31.0)
	> 24 – 48	108	48	27.2 (3.13)	14.8 (23.1)

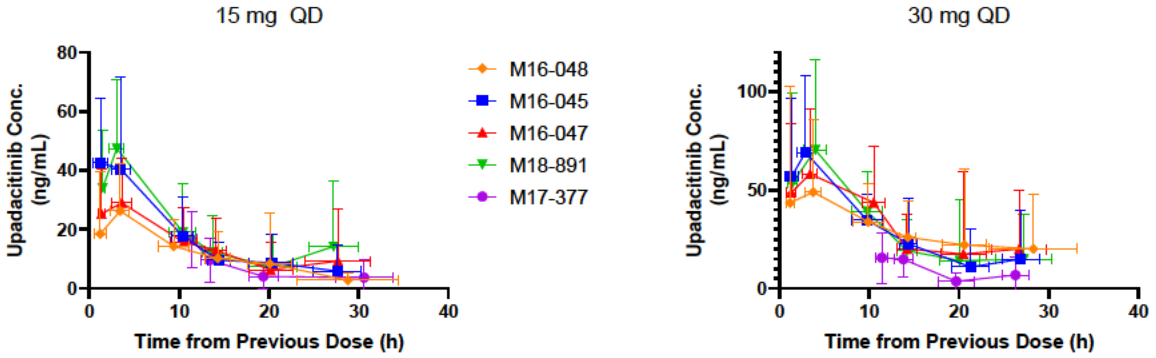
Abbreviations: UPA=upadacitinib; QD=once daily; SD=standard deviation
Source: Table 17, CSR R&D/20/0650

Table 7. Mean Plasma Upadacitinib Concentrations Categorized by Treatment Group and Time from Previous Dose from Study M17-377

Treatment Group	Time Categories (h)	# of Samples	# of Subjects	Mean Time (SD) from Previous Dose (h)	Mean (SD) UPA Concentration (ng/mL)
UPA 15 mg QD	> 6 – 12	5	4	11.4 (0.52)	16.6 (9.49)
	> 12 – 16	14	7	13.4 (0.98)	9.61 (7.58)
	> 16 – 24	26	10	19.4 (1.64)	4.09 (4.10)
	> 24 – 48	12	5	30.6 (3.20)	3.73 (5.89)
UPA 30 mg QD	> 6 – 12	9	6	11.4 (0.62)	15.7 (12.9)
	> 12 – 16	17	10	13.8 (1.02)	14.8 (8.87)
	> 16 – 24	23	9	19.7 (1.98)	3.65 (4.50)
	> 24 – 48	8	4	26.3 (1.44)	6.86 (9.06)

Abbreviations: UPA=upadacitinib; QD=once daily; SD=standard deviation
Source: Table 10, CSR R&D/19/1332

Figure 2. Comparisons of the Mean Plasma Upadacitinib Concentrations from Four Studies Conducted in Subjects with AD



Source: Reviewer generated figures

In healthy adult subjects; relative bioavailability of the market-image formulation and the Phase 3 formulation

Study M20-017: This study was conducted to evaluate the relative bioavailability of the market-image formulation and the Phase 3 formulation. This study was a Phase 1 single-dose, open-label, randomized, four-period, four-sequence, two-part crossover study, conducted in 80 healthy adult subjects (40 subjects per each study part). The treatment groups were as follows:

- Part 1 (15 mg Dose)
  - A: single 15 mg dose of Phase 3 formulation under fasting conditions
  - B: single 15 mg dose of market-image formulation under fasting conditions
  - C: single 15 mg dose of Phase 3 formulation after high-fat/high-calorie meal
  - D: single 15 mg dose of market-image formulation after high-fat/high-calorie meal
- Part 2 (30 mg Dose)
  - E: single 30 mg dose of Phase 3 formulation under fasting conditions
  - F: single 30 mg dose of market-image formulation under fasting conditions
  - G: single 30 mg dose of Phase 3 formulation after high-fat/high-calorie meal
  - H: single 30 mg dose of market-image formulation after high-fat/high-calorie meal

In all periods, each dose was taken orally with approximately 240 mL of water. For groups C, D, G and H, study drug was taken approximately 30 minutes after starting a high-fat/high-calorie breakfast. For groups A, B, E and F, study drug was taken after a minimum 10-hour fast and approximately 4 hours before lunch. A washout interval of 4 days separated the doses between the four study periods in each part of the study.

The contents of a high-fat/high-calorie meal given to groups C and D in Part 1 and groups G and H in Part 2 are summarized in Table 8 and Table 9 below.

Table 8. Meal Content for Groups C and D in Part 1

Menu	Meal Composition
breakfast croissant (3 oz), sliced cheddar cheese (0.5 oz), hard fried egg, sliced ham (1 oz), Swiss cheese (0.75 oz) peanut butter, apple	826 Kcal; 51.5% calories from fat, 33.6% calories from carbohydrates, and 15% calories from protein

Table 9. Meal Content for Groups G and H in Part 2

Menu	Meal Composition
2 slices white toast, hash browns fried in 1 teaspoon butter (4 oz), two eggs fried in 2 teaspoons butter, 2 slices bacon, 1 carton milk 2 packets jelly	880 Kcal; 49.2% calories from fat, 37.5% calories from carbohydrates, and 13.4% calories from protein

Reviewer's comment: The meals provided in Part 1 and Part 2 of the study are acceptable for a high-fat and high-calorie meal. The fasted conditions, timing of the meal and drug administration for the fed conditions and the drug administration instructions (i.e., administered with 240 mL of water) are also acceptable. Based on the elimination half-life reported in the label, which is between 8 to 14 hours, the washout period of 4 days ensured in the study is acceptable.

Blood samples for PK assessment were collected prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after dosing in each period.

The relative bioavailability results of the 15 mg Phase 3 Formulation under fasting conditions and following a high-fat/high-calorie meal are summarized in Table 10 below. The relative bioavailability results of the 30 mg Phase 3 Formulation under fasting conditions and following a high-fat/high-calorie meal are summarized in Table 11 below.

Table 10. *Relative Bioavailability of the 15 mg Strength Phase 3 Formulation and the Market-Image Formulation*

Regimens Test vs. Reference	Pharmacokinetic Parameter(units)	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
Regimen B vs. A	C_{max} (ng/mL)	29.1	28.1	1.038	0.936 – 1.150
	AUC_t (ng•h/mL)	250	256	0.973	0.919 – 1.031
	AUC_{inf} (ng•h/mL)	254	265	0.960	0.907 – 1.015
	AUC_{0-12} (ng•h/mL)	184	184	1.003	0.938 – 1.072
	AUC_{12-t} (ng•h/mL)	62.7	70.3	0.892	0.823 – 0.968
Regimen D vs. C	C_{max} (ng/mL)	47.4	48.4	0.980	0.915 – 1.049
	AUC_t (ng•h/mL)	318	335	0.949	0.906 – 0.994
	AUC_{inf} (ng•h/mL)	323	339	0.952	0.910 – 0.997
	AUC_{0-12} (ng•h/mL)	267	281	0.949	0.897 – 1.004
	AUC_{12-t} (ng•h/mL)	49.1	51.4	0.956	0.882 – 1.036

Regimen A: Single 15 mg dose of upadacitinib Phase 3 formulation (ER17Y) administered under fasting conditions (reference for B).

Regimen B: Single 15 mg dose of upadacitinib market-image formulation (ER17) administered under fasting conditions (test for A).

Regimen C: Single 15 mg dose of upadacitinib Phase 3 formulation (ER17Y) administered after a high-fat/high-calorie meal (reference for D).

Regimen D: Single 15 mg dose of upadacitinib market-image formulation (ER17) administered after a high-fat/high-calorie meal (test for C).

Source: Table 8, CSR R&D/19/1115

Table 11. Relative Bioavailability of the 30 mg Strength Phase 3 Formulation and the Market-Image Formulation

Regimens Test vs. Reference	Pharmacokinetic Parameter (units)	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
Regimen F vs. E	C_{max} (ng/mL)	69.4	62.1	1.117	1.042 – 1.197
	AUC_t (ng•h/mL)	513	499	1.029	0.971 – 1.091
	AUC_{inf} (ng•h/mL)	524	509	1.029	0.971 – 1.091
	AUC_{0-12} (ng•h/mL)	394	369	1.069	0.995 – 1.149
	AUC_{12-t} (ng•h/mL)	113	121	0.931	0.837 – 1.036
Regimen H vs. G	C_{max} (ng/mL)	94.7	94.9	0.998	0.930 – 1.070
	AUC_t (ng•h/mL)	622	627	0.992	0.952 – 1.032
	AUC_{inf} (ng•h/mL)	630	634	0.994	0.954 – 1.035
	AUC_{0-12} (ng•h/mL)	511	514	0.993	0.946 – 1.043
	AUC_{12-t} (ng•h/mL)	106	107	0.986	0.915 – 1.063

Regimen E: Single 30 mg dose of upadacitinib Phase 3 formulation (ER18Y) administered under fasting conditions (reference for F).

Regimen F: Single 30 mg dose of upadacitinib market-image formulation (ER18) administered under fasting conditions (test for E).

Regimen G: Single 30 mg dose of upadacitinib Phase 3 formulation (ER18Y) administered after a high-fat/high-calorie meal (reference for H).

Regimen H: Single 30 mg dose of upadacitinib market-image formulation (ER18) administered after a high-fat/high-calorie meal (test for G).

Source: Table 11, CSR R&D/19/1115

Reviewer's comment: The 90% confidence intervals of the geometric mean ratio for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were within the no effect boundary of limits of 80% to 125% for both 15 mg and 30 mg strengths, under fasting and fed conditions. The market-image formulation and the Phase 3 formulation, both 15 and 30 mg strengths, were found to be bioequivalent.

Additional clinical pharmacology information, specifically on population PK analysis and exposure-response for efficacy and safety can be found in Sections18.4.1, 18.4.2 and 18.4.3.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The efficacy of RINVOQ for the treatment of moderate to severe AD was established in the Phase 3 studies. In addition, the exposure-response relationship based on PK samples collected from the Phase 3 studies provides supportive evidence of effectiveness.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The recommended dosing regimen for the treatment of AD is as follow:

- Adolescent patients 12 years of age and older weighing at least 40 kg and adults less than 65 years of age: Initiate with 15 mg once daily and consider increasing the dosage to 30 mg orally once daily if an adequate response is not achieved
- Adults 65 years of age and older: 15 mg once daily

The recommendation is based on and is supported by the PK, efficacy and safety data obtained from the Phase 3 studies, as well as exposure-response analysis.

The use of RINVOQ in adolescent patients with AD is limited to those weighing at least 40 kg due to a lack of data in adolescents weighing less than 40 kg.

While the Applicant proposed 15 mg QD dosing for adolescent patients at this time as they accrue more safety data on the 30 mg dose, the PK (Figure 3) and exposure-response trends for efficacy and safety (Sections 18.4.2 and 18.4.3) were similar between adolescents and adults and thus, using the same dosing regimen for adolescents and adults appears reasonable.

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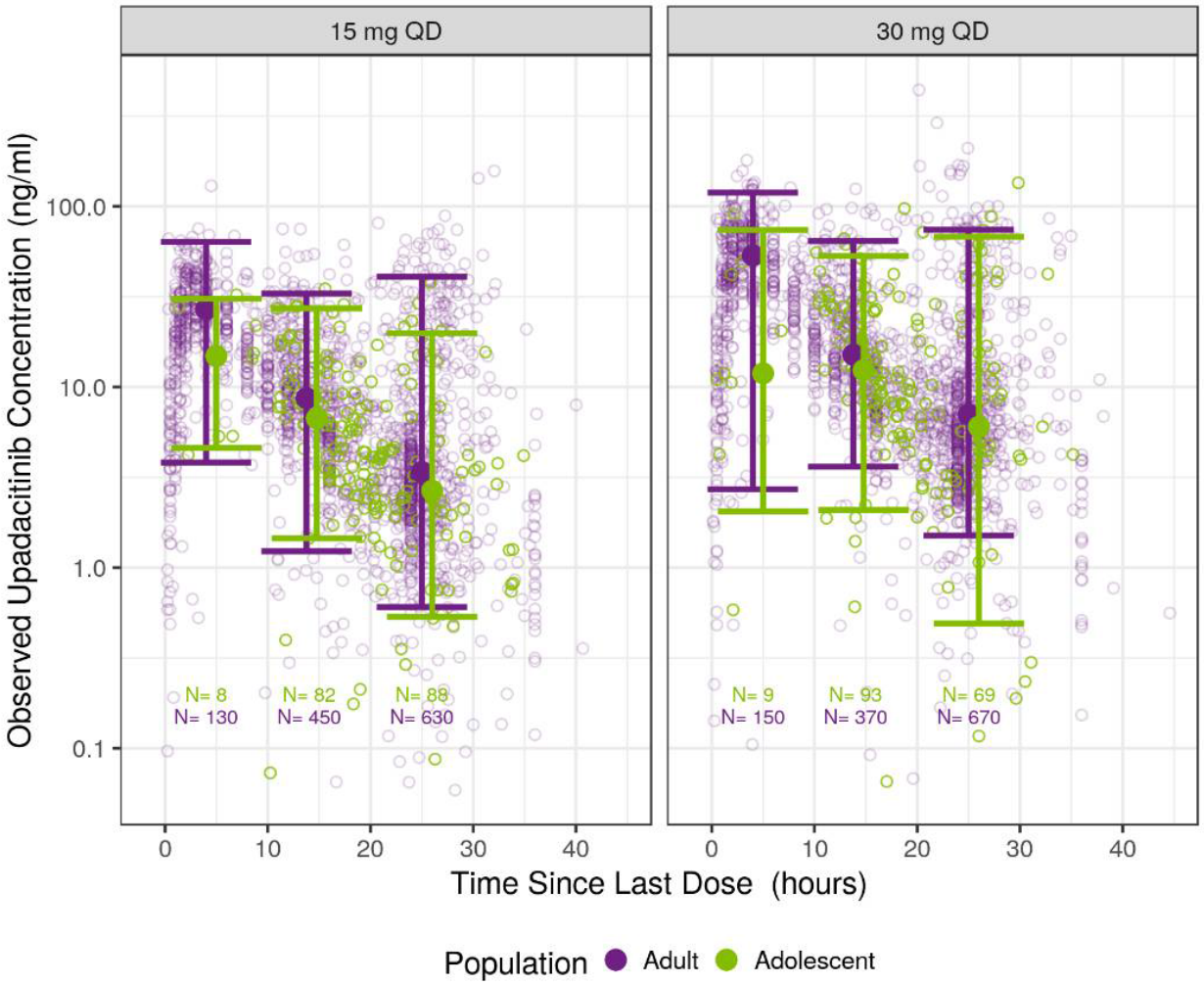
Figure 3. Comparisons of the Observed Upadacitinib Concentrations in Adolescent and Adult Subjects with AD

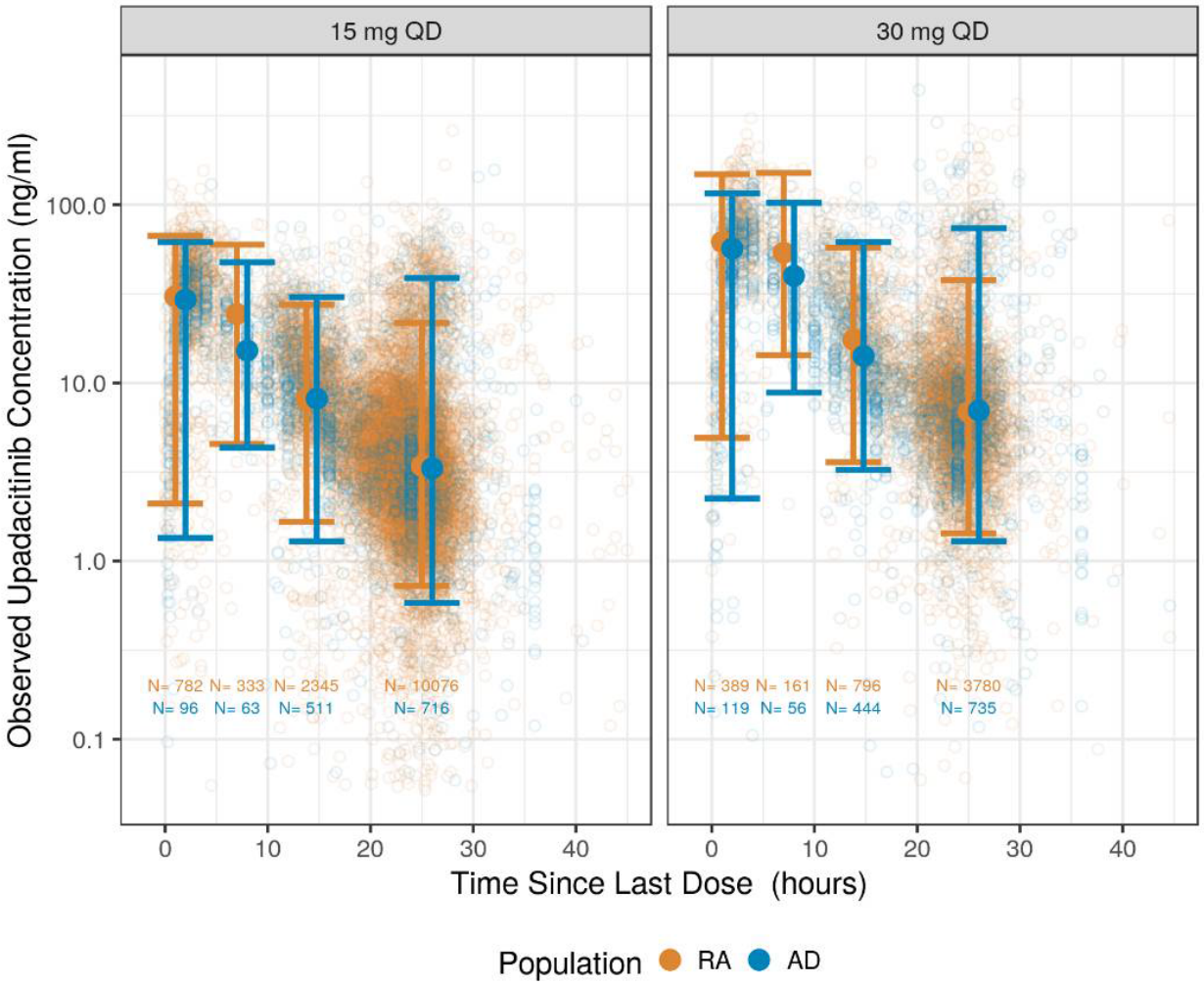


Purple circles represent observed upadacitinib concentrations from adult subjects (Studies M16-045, M16-047, M16-048, M17-377, M18-891). Green circles represent observed upadacitinib concentrations from adolescent subjects (Studies M16-045, M16-047, M17-377, M18-891). Closed circles and error bars represent median and 5th and 95th percentiles for the binned observed data.
Source: Figure 7, R&D/20/0641

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

For this supplement, the effect of intrinsic factors was not directly evaluated. Instead, information obtained from studies conducted under the original NDA for the rheumatoid arthritis (RA) program could be applied based on the similar PK between subjects with AD and subjects with RA (Figure 4 below) and the dose-proportionality between 15 mg and 30 mg observed from Study M16-048 (Figure 1 in Section 6.3.1).

Figure 4. Comparisons of the Observed Upadacitinib Concentrations in Subjects with RA and AD



Orange circles represent observed upadacitinib concentrations from subjects with RA with extended-release formulation (Studies M13-542, M13-545, M13-549, M14-465, M14-663, M15-555). Blue circles represent observed upadacitinib concentrations from subjects with AD (Studies M16-045, M16-047, M16-048, M17-377, M18-891). Closed circles and error bars represent median and 5th and 95th percentiles for binned observed data.
Source: Figure 6, R&D/20/0641

In the original NDA submission for the RA program, both hepatic and renal impairment studies were conducted with 15 mg strength, as the approved dose for the RA program is 15 mg only. In the renal impairment study with the 15 mg dose, increases in AUC were observed in subjects with mild, moderate and severe renal impairment compared to subjects with normal renal function (19%, 33% and 45%, respectively). Based on such findings, in addition to the absence of renal impairment study with the 30 mg strength and the fact that there were no subjects with severe renal impairment enrolled in the Phase 3 trials, the recommended dosage is 15 mg QD for patients with severe renal impairment [creatinine clearance (CrCL) < 30 mL/min].
In addition, patients with severe hepatic impairment were not included in the hepatic impairments study, thus the recommendation to avoid RINVOQ in patients with severe hepatic impairment is still valid for the treatment of AD.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The findings from the original NDA on the food-drug interaction and drug-drug interactions are applicable to this supplement for the treatment of AD. No additional drug interaction studies were conducted. Effect of food was also assessed in the relative BA study between Phase 3 and the to-be-marketed formulation, and the results indicated that there was no effect of food on the bioavailability of upadacitinib. Per the currently approved label, RINVOQ can be taken with or without food and this recommendation would apply for the AD indication.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

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Table 12. Tabular Listing of All Clinical Studies

Trial Identity	Trial Design	Regimen/Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
M16-045	Multicenter 2-period: 16-week randomized, DB, parallel-group, controlled treatment period followed by a long-term BE period up to Week 136	DB Period: 15 mg, 30 mg UPA or placebo QD, PO BE Period: 15 mg or 30 mg UPA QD, PO	• The co-primary efficacy endpoints included the proportion of subjects achieving at least a 75% reduction in EASI (EASI 75) from Baseline at Week 16 and the proportion of subjects achieving vIGA-AD of 0 or 1 with at least 2 grades of reduction from Baseline at Week 16.	DB Period: 16 weeks BE Period: Up to Week 136	847	12-75 years old, with a diagnosis of chronic AD who had an inadequate response to treatment with TCS, TCI, or for whom topical treatments were medically inadvisable	151 sites in 24 countries
M16-047	Multicenter 2-period: 16-week randomized, DB, parallel-group, controlled treatment period followed by a long-term BE period up to Week 136	DB Period: 15 mg, 30 mg UPA or placebo QD, PO with TCS or TCI BE Period: 15 mg or 30 mg UPA QD, PO with TCS or TCI	• The co-primary endpoints were the proportion of subjects achieving:1) at least a 75% reduction in EASI (EASI 75) from Baseline at Week 16 and 2) vIGA-AD of 0/1 (clear or almost clear) with at least two grades of reduction from Baseline at Week 16.	DB Period: 16 weeks BE Period: Up to Week 136	901	12-75 years old, with a diagnosis of chronic AD who had an inadequate response to treatment with TCS or TCI	171 study sites located in 22 countries

Trial Identity	Trial Design	Regimen/Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Enrolled	Study Population	No. of Centers and Countries
M18-891	Multicenter 2-period: 16-week randomized, DB, parallel-group, controlled treatment period followed by a long-term BE period up to Week 136	DB Period: 15 mg, 30 mg UPA or placebo QD, PO BE Period: 15 mg or 30 mg UPA QD, PO	• The co-primary efficacy endpoints included the proportion of subjects achieving at least a 75% reduction in EASI (EASI 75) from Baseline at Week 16 and the proportion of subjects achieving vIGA-AD of 0 or 1 with at least 2 grades of reduction from Baseline at Week 16.	DB Period: 16 weeks BE Period: Up to Week 136	836	12-75 years old, with a diagnosis of chronic AD who had an inadequate response to treatment with TCS, TCI, or for whom topical treatments were medically inadvisable	154 study sites located in 23 countries
Studies to Support Safety							
M16-048	Multicenter, 2-period: 16-week randomized, DB, parallel-group, controlled treatment period followed by a DB treatment period of 72 weeks	Period 1: 7.5 mg, 15 mg, 30 mg UPA or PBO QD, PO Period 2: 7.5 mg, 15 mg, 30 mg UPA or PBO QD, PO	• The primary endpoint was the mean percent (%) change from Baseline (Day 1) in EASI score at Week 16.	Period 1: 16 weeks Period 2: 72 weeks	167	18-75 years old, with diagnosis of chronic AD who had an inadequate response to treatment with TCS, TCI, or for whom topical treatments were medically inadvisable	36 sites, 8 countries

Trial Identity	Trial Design	Regimen/Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Enrolled	Study Population	No. of Centers and Countries
M17-377	Multicenter 2-period: 16-week randomized, DB, parallel-group, controlled treatment period, followed by a long-term BE (up to Week 52), followed by an OL extension up to Week 136)	DB Period: 15 mg, 30 mg UPA QD PO with TCS or PBO QD PO with topical corticosteroids BE Period: 15 mg or 30 mg QD UPA QD, PO	• To assess the safety of UPA combined with TCS in adolescent and adult subjects in Japan with moderate to severe AD who are candidates for systemic therapy. There were no primary or secondary efficacy endpoints	DB Period: 16 weeks BE Period: Up to Week 52 OL Period: Up to Week 136	272	12-75 years old, with a diagnosis of chronic AD who had an inadequate response to treatment with TCS or TCI	42 study sites located in Japan.

Abbreviations: AD = Atopic Dermatitis; DB = double-blind; EASI = Eczema Area and Severity Index; OL = open-label; PBO = placebo; PO =orally; QD = once daily; RA = rheumatoid arthritis; TCI = topical calcineurin inhibitors; TCS = topical corticosteroids; UPA = upadacitinib; v-IGA-AD = validated Investigator Global Assessment of Atopic Dermatitis

7.2. Review Strategy

Data Sources

The sources of data used for the evaluation of the efficacy and safety of upadacitinib for the proposed indication included final study reports submitted by the Applicant, datasets (Study Data Tabulation Model and Analysis Data Model), and literature references.

This application was submitted in electronic common technical document format and is entirely electronic. The electronic submission, including protocols, statistical analysis plans, clinical study reports, and SAS transport datasets in legacy, Study Data Tabulation Model, and Analysis Data Model format.

Data and Analysis Quality

In collaboration with the Office of Computational Science, the statistical and clinical team evaluated the fitness of the data. This included an assessment of the compatibility of the data with the review tools and data quality metrics such as the following:

- Availability of appropriate variables
- Variables populated by expected data points
- Appropriate use of standard terminology
- Data well-described by metadata

A final statistical analysis plan (SAP) was submitted and most relevant analysis decisions (e.g., pooling of sites, analysis population membership, etc.) were made prior to unblinding.

The databases required minimal data management prior to performing analyses. The Applicant submitted statistical programs for generating the multiple imputations for missing data and the confidence interval calculations for the primary efficacy endpoint. The data and analysis provided by the Applicant is acceptable per Agency guidance.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Trial Design

The Applicant conducted three Phase 3 trials (M16-045, M18-891, and M16-047). Trials M16-045 and M18-891 were identically designed monotherapy trials. Trial M16-047 evaluated the safety and efficacy of upadacitinib in combination with topical corticosteroids (TCS). For enrollment, the protocols for all three trials specified the following key inclusion criteria:

- Male or female, ≥ 12 and ≤ 75 years of age at screening
- Body weight ≥ 40 kg for subjects between ≥ 12 and < 18 years of age at baseline
- Chronic AD with onset of symptoms at least 3 years prior to baseline and meets the Hanifin and Rajka criteria
- Documented history (within 6 months of the baseline visit) of inadequate response to TCS or TCI OR documented systemic treatment for atopic dermatitis within 6 months prior to the baseline visit
- Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) score ≥ 3 (moderate) at screening and baseline visits, see Table 13 for details of the vIGA-AD
- Eczema Area and Severity Index (EASI) score ≥ 16 at screening and baseline visits, see Table 14 for details of the EASI
- Body surface area (BSA) of AD involvement ≥ 10% at screening and baseline visits
- Baseline weekly average of daily Worst Itch Numeric Rating Scale (WI-NRS) ≥4. The protocols specified that the baseline weekly average of daily WI-NRS will be calculated from the 7 days immediately preceding the baseline visit and a minimum of 4 daily scores out of the 7 days is required. Figure 5 presents the WI-NRS.

Table 13. Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD)

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

Source: page 150 of the protocol for Trial M16-045.

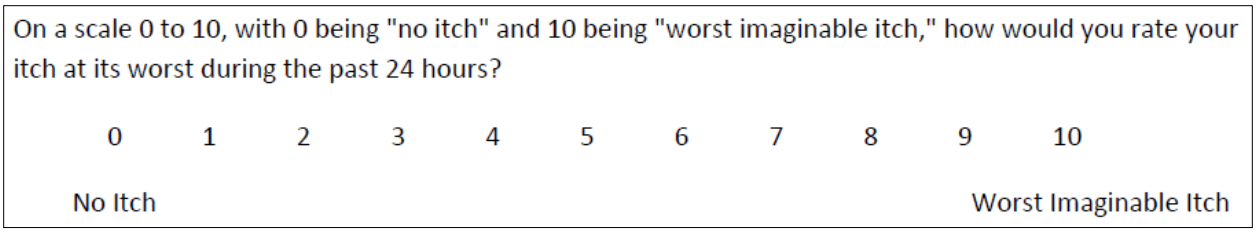
Table 14. Eczema Area and Severity Index (EASI)

Body Region	EASI Score

Head/Neck (H)	(E + I + Ex + L) x Area x 0.1
Upper limbs (UL)	(E + I + Ex + L) x Area x 0.2
Trunk (T)	(E + I + Ex + L) x Area x 0.3
Lower limbs (LL)	(E + I + Ex + L) x Area x 0.4
EASI =	Sum of the above 4 body region scores

The degree of severity of each sign (E=erythema, I=induration/papulation, Ex=excoriation, L=lichenification) in each of the 4 body regions is evaluated based on a scale ranging from 0 to 3 (0: none; 1: mild; 2: moderate; 3: severe), with half points allowed.
Area (the affected body area) is defined as follows: 0=0%; 1=1-9%; 2=10-29%; 3=30-49%; 4=50-69%; 5=70-89%; 6=90-100%. Among the four zones, trunk includes the genital area, and lower limbs include the buttocks.

Figure 5. Worst Itch Numeric Rating Scale (WI-NRS)



Source: page 120 of the protocol for Trial M16-045.

Phase 3 Monotherapy Trials (M16-045 & M18-891)

Trials M16-045 and M18-891 were identically designed, randomized, multicenter, double-blind, placebo-controlled, Phase 3 trials to evaluate the safety and efficacy of two doses upadacitinib (15 and 30 mg) compared to placebo. The trial design schematic for these trials is presented in Figure 6. The trials consisted of a 35-day screening period, a 16-week double-blind treatment period, a long-term blinded extension period of up to Week 136, and a 30-day follow-up visit.

Each trial was designed to enroll and randomize approximately 810 subjects from about 185 investigational sites. Subjects were randomized to one of the following treatment groups in a 1:1:1 ratio: upadacitinib 30 mg, upadacitinib 15 mg, and placebo. The randomization was stratified by baseline disease severity (vIGA-AD score), geographic region (US/Puerto Rico/Canada, Japan, China, and Other), and age (adolescent [ages 12-17 years] vs. adult [ages 18-75 years]). The protocols specified that a supplemental study will continue to enroll adolescent subjects (adolescent sub-study) until a total of 180 adolescent subjects are enrolled in the overall study (main study + adolescent sub-study) for each trial. The protocols specified that the randomization for the adolescent sub-study will be stratified by baseline disease severity (vIGA-AD score) and geographic region (US/Puerto Rico/Canada and Other). The adolescent sub-studies were ongoing at the time of sNDA submission.

Figure 6. Trial Design Schematic for Trials M16-045 and M18-891

Source: page 16 of the protocol for Trial M16-045.

Study product was administered orally (i.e., tablets) once daily (QD) for 16 weeks. At Week 16, subjects in the placebo group were re-randomize in a 1:1 ratio to receive either upadacitinib 30 mg or upadacitinib 15 mg. The protocols specified stratifying the re-randomization by EASI-50 status (yes/no), geographic region, and age (adolescent vs. adult). Subjects originally in the upadacitinib 30 mg group or upadacitinib 15 mg group were specified to continue their treatment up to the Week 136 visit. Subjects were scheduled to have the following study visits: screening, baseline (Day 1), and Weeks 1, 2, 4, 8, 12, 16, 20, 24, 32, 40, 52, and every 12 weeks until Week 136.

The protocols specified that rescue treatment for AD may be provided at the discretion of the investigator starting at Week 4, if medically necessary and the following specified parameters are met:

- Week 4 through Week 24: subjects with less than a 50% reduction in EASI (EASI-50) response at any two consecutive scheduled visits (e.g., at Week 2 and Week 4 with rescue at Week 4; or at Week 20 and Week 24 with rescue at Week 24)
- After Week 24: subjects with < EASI-50 response at any scheduled or unscheduled visit

The protocols specified that subjects who receive topical rescue treatment or oral corticosteroids during the study treatment period can continue study drug. If oral corticosteroids must be used, rescue treatment was specified to be limited to prednisone or prednisolone for up to 1 mg/kg for no more than 2 consecutive weeks. The protocols specified that any subject who receives oral corticosteroid for more than 2 consecutive weeks regardless of the dosage of corticosteroid should permanently discontinue study drug. If a subject needs rescue treatment with a non-corticosteroid systemic agent (including but not limited to cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, dupilumab) or with an injectable or parenteral corticosteroid, the protocols specified that study drug should be permanently discontinued prior to the initiation of rescue systemic agent. The protocols

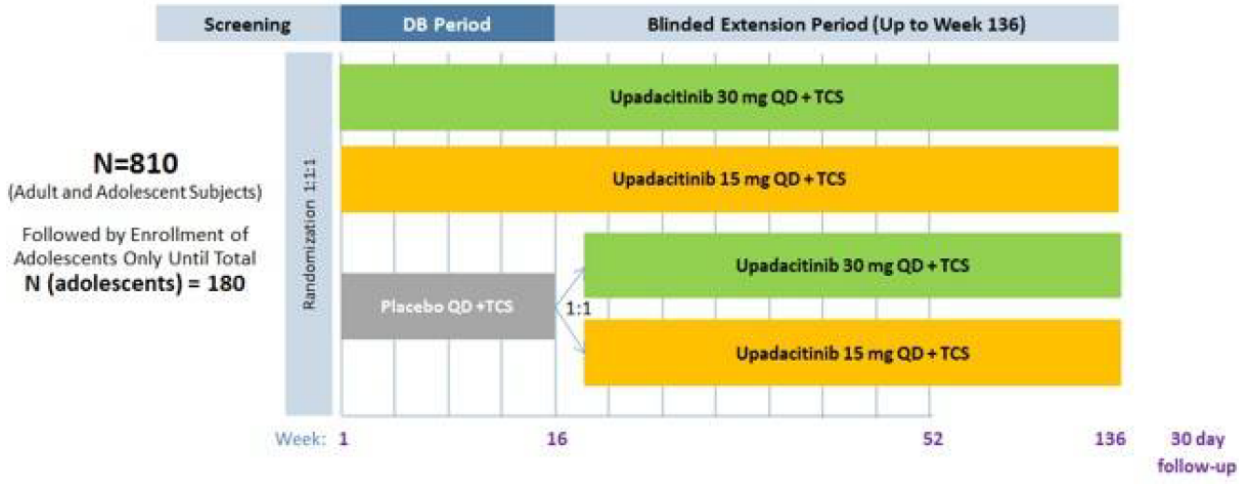
specified that subjects receiving rescue medications will be counted as nonresponders after the start of rescue medication for the primary analysis of the binary efficacy endpoints.

Phase 3 Combination Trial (M16-047)

Trial M16-047 was a randomized, multicenter, double-blind, placebo-controlled, Phase 3 trial to evaluate the safety and efficacy of two doses of upadacitinib (15 and 30 mg) in combination with TCS therapy. The trial design schematic for Trial M16-047 is presented in Figure 7. The trial consisted of a 35-day screening period, a 16-week double-blind treatment period, a long-term blinded extension period of up to Week 136, and a 30-day follow-up visit.

The trial was designed to enroll and randomize approximately 810 subjects from about 185 investigational sites. Subjects were randomized to one of the following treatment groups in a 1:1:1 ratio: upadacitinib 30 mg, upadacitinib 15 mg, and placebo. The randomization was stratified by baseline disease severity (vIGA-AD score), geographic region (US/Puerto Rico/Canada, Japan, China, and Other), and age (adolescent vs. adult). The protocol specified that a supplemental study will continue to enroll adolescent subjects (adolescent sub-study) until a total of 180 adolescent subjects are enrolled in the overall study (main study + adolescent sub-study). The protocol specified that the randomization for the adolescent sub-study will be stratified by baseline disease severity (vIGA-AD score) and geographic region (US/Puerto Rico/Canada and Other). The adolescent sub-study was ongoing at the time of sNDA submission.

Figure 7. Trial Design Schematic for Trial M16-047



Source: page 15 of the protocol for Trial M16-047.

Study product was administered orally QD for 16 weeks. At Week 16, subjects in the placebo group were re-randomize in a 1:1 ratio to receive either upadacitinib 30 mg or upadacitinib 15 mg. The protocols specified stratifying the re-randomization by EASI-50 status (yes/no), geographic region, and age (adolescent vs. adult). Subjects originally in the upadacitinib 30 mg group or upadacitinib 15 mg group were specified to continue their treatment up to the Week

136 visit. Subjects were scheduled to have the following study visits: screening, baseline (Day 1), and Weeks 1, 2, 4, 8, 12, 16, 20, 24, 32, 40, 52, and every 12 weeks until Week 136.

Starting at the baseline visit and continuing through the end of the trial, all subjects were to initiate treatment with TCS with the following step-down regimen:

- Apply medium potency TCS QD to areas with active lesions for a maximum of 3 consecutive weeks. Low potency TCS or TCI should be applied QD on areas of thin skin (face, neck, intertriginous and genital areas) or for areas where medium TCS are considered unsafe (e.g., areas of skin atrophy). See Table 15 for types and potency levels of recommended TCS.
- After lesions are under control (clear or almost clear) or after 3 consecutive weeks of medium potency TCS QD, switch from medium potency to low potency TCS and treat QD for 7 days, then stop. For sensitive skin locations, low-potency TCS, or TCI are to be tapered and stopped.
- If lesions return or persist, resume treatment with the step-down approach described above until lesion resolution as long as there is no sign of local or systemic TCS toxicity.
- The subject should be monitored for signs of local or systemic TCS toxicity and step down or stopping treatment should be performed as necessary. Topical therapy may be further limited in duration and potency if medically advisable (e.g., in subjects with extensive TCS pretreatment and clinical signs of TCS side effects such as striae, skin atrophy, or bruising).
- At or after Week 4, see also rescue therapy below for further details on rescue treatment options with higher potency TCS or systemic therapy.
- At or after Week 52, the use of any concomitant topical medication for AD can be administered per investigator discretion and is no longer required.

Table 15. Potency Levels of Recommended Topical Corticosteroids[1]

Potency[2]	Recommended Topical Steroids
Low[3]	Hydrocortisone 1% cream
Medium	Triamcinolone acetonide 0.1% cream Fluocinolone acetonide 0.025% ointment

[1] Potency levels are per U.S. guidelines.
[2] If the subject is intolerant to these TCS or they are not available, they may be substituted by a topical steroid with the same potency from the list provided in the protocol.
[3] Low potency steroids are to be applied to sensitive areas (e.g., face, intertriginous areas, groin).
Source: page 30 of the protocol for Trial M16-047.

The protocol specified that rescue treatment for AD may be provided at the discretion of the investigator starting at Week 4, if medically necessary and the following specified parameters are met:

- Week 4 through Week 24: subjects with < EASI-50 response at any two consecutive scheduled visits (e.g., at Week 2 and Week 4 with rescue at Week 4; or at Week 20 and Week 24 with rescue at Week 24)
- After Week 24: subjects with < EASI-50 response at any scheduled or unscheduled visit

The protocol specified that subjects who receive topical rescue treatment or oral corticosteroids during the study treatment period can continue study drug. If oral corticosteroids must be used, rescue treatment was to be limited to prednisone or prednisolone for up to 1 mg/kg for no more than 2 consecutive weeks. The protocol specified that any subject who receives oral corticosteroid for more than 2 consecutive weeks regardless of the dosage of corticosteroid should permanently discontinue study drug. If a subject needs rescue treatment with a non-corticosteroid systemic agent (including but not limited to cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, dupilumab) or with an injectable or parenteral corticosteroid, the protocol specified that study drug should be permanently discontinued prior to the initiation of rescue systemic agent. The protocol specified that subjects receiving rescue medications will be counted as nonresponders after the start of rescue medication for the primary analysis of the binary efficacy endpoints.

8.1.2. Efficacy Endpoints

For all three Phase 3 trials (i.e., M16-045, M18-891, and M16-047), the protocols specified the following coprimary efficacy endpoints:

- Proportion of subjects achieving an vIGA-AD score of 0 (“clear”) or 1 (“almost clear”) with at least a 2-grade reduction from baseline at Week 16
- Proportion of subjects achieving at least a 75% reduction from baseline in EASI score (EASI-75) at Week 16

The protocols specified separate sets of multiplicity-controlled key secondary efficacy endpoints for the European Union (EU)/European Medicines Agency (EMA) and for the U.S. Food and Drug Administration (FDA). This review will summarize only those specified for the FDA.

For the monotherapy Phase 3 trials (i.e., M16-045 and M18-891), the protocols specified the following key secondary efficacy endpoints:

- Proportion of subjects achieving an improvement (reduction) in WI-NRS ≥ 4 from baseline at Week 16 for subjects with WI-NRS ≥ 4 at baseline
- Proportion of subjects achieving EASI-90 at Week 16
- Proportion of subjects achieving an improvement (reduction) in WI-NRS ≥ 4 from baseline at Week 4 for subjects with WI-NRS ≥ 4 at baseline
- Proportion of subjects achieving EASI-75 at Week 2
- Proportion of subjects achieving an improvement (reduction) in WI-NRS ≥ 4 from baseline at Week 1 for subjects with WI-NRS ≥ 4 at baseline
- Proportion of subjects achieving an improvement (reduction) in WI-NRS ≥ 4 from baseline at Day 2 for subjects with WI-NRS ≥ 4 at baseline (only 30 mg vs. placebo)
- Proportion of subjects achieving an improvement (reduction) in WI-NRS ≥ 4 from baseline at Day 3 for subjects with WI-NRS ≥ 4 at baseline (only 15 mg vs. placebo)
- Proportion of subjects experiencing a flare, defined as an increase of EASI by ≥ 6.6 from baseline for subjects with EASI ≤ 65.4 at baseline, during double-blind period

- Proportion of subjects achieving an improvement (reduction) in Atopic Dermatitis Impact Scale (ADerm-IS) sleep domain score ≥ 12 from baseline at Week 16 for subjects with ADerm-IS sleep domain score ≥ 12 at baseline [*sleep domain score is the sum of items 1-3*]
- Proportion of subjects achieving an improvement (reduction) in Atopic Dermatitis Symptom Scale (ADerm-SS) skin pain score ≥ 4 from baseline at Week 16 for subjects with ADerm-SS skin pain score ≥ 4 at baseline [*skin pain score is item 3*]
- Proportion of subjects achieving an improvement (reduction) in ADerm-SS TSS-7 ≥ 28 from baseline at Week 16 for subjects with ADerm-SS TSS-7 ≥ 28 at baseline [*7-item total symptom score* (*TSS-7) is the sum of items 1-7*]
- Proportion of subjects achieving an improvement (reduction) in ADerm-IS emotional state domain score ≥ 11 from baseline at Week 16 for subjects with ADerm-IS emotional state domain score ≥ 11 at baseline [*emotional state domain score is the sum of items 8-10*]
- Proportion of subjects achieving an improvement (reduction) in ADerm-IS daily activities domain score ≥ 14 from baseline at Week 16 for subjects with ADerm-IS daily activities domain score ≥ 14 at baseline [*daily activities domain score is the sum of items 4-7*]
- Proportion of subjects achieving EASI-100 at Week 16

For the combination Phase 3 trial (i.e., M16-047), the protocol specified the following key secondary efficacy endpoints:

- Proportion of subjects achieving an improvement (reduction) in WI-NRS ≥ 4 from baseline at Week 16 for subjects with WI-NRS ≥ 4 at baseline
- Proportion of subjects achieving EASI-90 at Week 16
- Proportion of subjects achieving an improvement (reduction) in WI-NRS ≥ 4 from baseline at Week 4 for subjects with WI-NRS ≥ 4 at baseline
- Proportion of subjects achieving EASI-75 at Week 4
- Proportion of subjects achieving EASI-75 at Week 2
- Proportion of subjects achieving EASI-90 at Week 4
- Proportion of subjects achieving EASI-100 at Week 16 (only 30 mg vs. placebo)
- Proportion of subjects achieving an improvement (reduction) in WI-NRS ≥ 4 from baseline at Week 1 for subjects with WI-NRS ≥ 4 at baseline

Figure 33 and Figure 34 in Appendix 18.5.1 present the ADerm-IS and ADerm-SS, respectively.

8.1.3. Statistical Methdologies

The protocol-specified primary analysis population was the intent-to-treat (ITT) population, defined as all randomized subjects (adults and adolescents). The SAPs specified conducting supportive analyses using a per-protocol (PP) population. The SAPs specified that the PP population will exclude subjects who violate any of the following criteria:

- Receive 80% of planned study drug, per randomization, before Week 16

- Have EASI and vIGA-AD assessment post-baseline on or before Week 16
- Meet all the following disease activity criteria at baseline:
  - EASI score ≥ 16
  - vIGA-AD score ≥ 3
  - ≥ 10% BSA of AD involvement
- Must not have used the following AD treatments within the specified timeframe prior to baseline Visit, per assessment of eligibility criterion 16 in the protocol:
  - Systemic therapy for AD, including but not limited to corticosteroids, methotrexate, cyclosporine, azathioprine, phosphodiesterase type 4 (PDE4)-inhibitors, IFN-γ and mycophenolate mofetil within 4 weeks
  - Targeted biologic treatments (refer to within 5 half-lives [if known]) or within 12 weeks, whichever is longer
  - Phototherapy treatment, laser therapy, tanning booth, or extended sun exposure that could affect disease severity or interfere with disease assessments within 4 weeks
  - Oral or parenteral traditional Chinese medicine within 4 weeks
  - Marijuana use within 2 weeks
  - Topical treatments (with the exception of topical emollient treatments, described in Eligibility Criterion 8 in the protocol), including but not limited to TCS, TCIs, or topical PDE-4 inhibitors within 7 days

The protocols specified analyzing the categorical efficacy endpoints using the Cochran-Mantel-Haenszel (CMH) test stratified by baseline vIGA-AD score (3 vs. 4) and age (adolescent vs. adult). It should be noted that the coprimary and key secondary efficacy endpoints specified for the FDA are all binary endpoints.

The SAPs specified using a graphical multiplicity testing procedure to control the Type I error rate for testing multiple doses and efficacy endpoints (i.e., primary and key secondary efficacy endpoints). Figure 35 in Appendix 18.5.2 presents the graphical approach for the monotherapy Phase 3 trials (i.e., M16-045 and M18-891). Figure 36 in Appendix 18.5.2 presents the graphical approach for the combination Phase 3 trial (i.e., M16-047).

The SAPs specified that missing data for binary efficacy endpoints will be imputed using Non-Responder Imputation while incorporating multiple imputation (MI) to handle missing data due to COVID-19 (NRI-C). The NRI-C approach will impute missing data as non-responders except:

(1) When the subject is a responder both before and after the visit window, the subject will be imputed as a responder
(2) When missing data due to COVID-19 infection or logistical restriction, the missing data will be imputed using MI. The missing data will be imputed 30 times using the Markov Chain Monte Carlo (MCMC) method. The SAPs specified the seeds.

The SAPs specified the following sensitivity analyses for the handling of missing data:

- NRI-NC: missing data will be imputed as non-responders with No special data handling due to COVID-19 (i.e., missing data due to COVID-19 infection or logistical restriction will also be imputed as non-responders).

- Multiple Imputation (MI): the Markov chain Monte Carlo (MCMC) method will be used first to impute the non-monotonic missing data. The regression method will then be used to impute the monotonic missing data. The SAPs specified including treatment, baseline value, baseline IGA score (if not already included as baseline value), age (adolescent vs. adults), and measurements at each visit up to the end of the analysis period in the imputation regression model. The SAPs specified imputing 30 times. In addition, the SAPs stated: "regardless of MI imputed values, subjects after receiving rescue medications will be counted as non-responders."
- Tipping Point Analysis: the SAPs specified doing a tipping point analysis for the coprimary endpoints (both binary). The SAPs specified:

  "For each pair of (X1, X2), simulations will be used to randomly draw X1 subjects from the M1 subjects with missing values in placebo group and X2 subjects from the M2 subjects with missing values in upadacitinib group. These randomly selected X1 subjects in placebo and X2 subjects in upadacitinib missing EASI 75 status at Week 16 will be imputed as responders. The remaining subjects with missing EASI 75 status at Week 16 will be imputed as non-responders. Analysis of upadacitinib 15 mg vs. placebo will be conducted using the combined observed data and imputed data for each treatment group. A p-value will be calculated using the CMH test adjusted by Baseline vIGA-AD categories (< 4 vs. = 4) and age (adolescent vs. adult). The simulation will be repeated 50 times for each pair of (X1, X2) and the median p-value will be used for the conclusion. The random seed for simulation will be preset as specified in Section 9.0 Appendix. If one pair of parameters is found to just reverse the study conclusion (i.e., median p-value > 0.05 [tipping point analysis will be performed only if the primary analysis reached p-value ≤ 0.05]), then these parameters will be the tipping points. Note that subjects will be considered as non-responders after the use of rescue medication. The tipping point will be performed based on NRI-NC approach, since NRI-NC is a more conservative approach and it is more likely to find a tipping point under this approach (if any tipping point exists). Of note, an extreme case analysis will be checked first, where all missing data in placebo arms are considered as responders and all missing data in the upadacitinib arms are considered as non-responders. If the extreme case analysis does not reverse the conclusion based on the primary approach (NRI-C), complete tipping point analysis will not be performed."

M1:	Total number of subjects missing EASI 75 status at Week 16 in the placebo group
M2:	Total number of subjects missing EASI 75 status at Week 16 in the upadacitinib 15 mg group
X1:	Number of subjects who are imputed as responders, among the M1 subjects with missing EASI-75 status in the placebo group. X1 = 0,…, M1
X2:	Number of subjects who are imputed as responders among the M2 subjects with missing EASI-75 status in the upadacitinib 15 mg group. X1 = 0,…, M2

8.1.4. Subject Disposition, Demographics, and Baseline Disease Characteristics

Trial M16-045 enrolled and randomized a total of 847 subjects from 151 investigational sites located in 24 countries. Trial M18-891 enrolled and randomized a total of 836 subjects from 154 investigational sites located in 23 countries. Trial M16-047 enrolled and randomized a total of 901 subjects from 171 investigational sites located in 22 countries. Table 16 presents the disposition of subjects for Trials M16-045 and M18-891. Table 17 presents the disposition of subjects for Trial M16-047. In each trial, the trial discontinuation rate during Weeks 0 to 16 was higher in the placebo group compared to the two upadacitinib treatment groups. In addition, the discontinuation rates were similar between the two upadacitinib treatment groups. The overall rate of discontinuation during Weeks 0 to 16 in the combination Phase 3 trial (i.e., Trial M16-047) was smaller than the two monotherapy Phase 3 trials (i.e., Trials M16-045 and M18-891).

Table 16. Disposition of Subjects (Weeks 0 to 16) – Trials M16-045 and M18-891 (ITT[1])

	Trial M16-045			Trial M18-891		
		Upadacitinib			Upadacitinib	
	Placebo (N=281)	15 mg (N=281)	30 mg (N=285)	Placebo (N=278)	15 mg (N=276)	30 mg (N=282)
Discontinued, n (%)	33 (12)	8 (3)	11 (4)	33 (12)	12 (4)	12 (4)
Adverse events	5 (2)	1 (<1)	5 (2)	7 (3)	5 (2)	2 (1)
Lost to follow-up	2 (1)	3 (1)	1 (<1)	0	0	1 (<1)
Withdrawal by subject	17 (6)	2 (1)	4 (1)	12 (4)	3 (1)	6 (2)
Other	9 (3)	2 (1)	1 (<1)	14 (5)	4 (1)	3 (1)

[1] Intent-to-Treat (ITT) population: all randomized subjects.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADSL.xpt, ADDS.xpt

Table 17. Disposition of Subjects (Weeks 0 to 16) – Trial M16-047 (ITT[1])

	Trial M16-047		
		Upadacitinib	
	Placebo + TCS (N=304)	15 mg + TCS (N=300)	30 mg + TCS (N=297)
Discontinued, n (%)	18 (6)	10 (3)	8 (3)
Adverse events	3 (1)	2 (1)	1 (<1)
Lost to follow-up	5 (2)	2 (1)	2 (1)
Withdrawal by subject	7 (2)	5 (2)	2 (1)
Other	3 (1)	1 (<1)	3 (1)

[1] Intent-to-Treat (ITT) population: all randomized subjects.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADSL.xpt, ADDS.xpt

Table 18 and Table 19 present the demographics for the monotherapy trials (i.e., M16-045 and M18-891) and the combination trial (i.e., M16-047), respectively. The three trials were generally similar with respect to age, sex, and race. The monotherapy trials had a slightly higher proportion of subjects from the United States compared to the combination trial.

Table 18. Demographics – Trials M16-045 and M18-891 (ITT[1])

	Trial M16-045			Trial M18-891		
		Upadacitinib			Upadacitinib	
	Placebo (N=281)	15 mg (N=281)	30 mg (N=285)	Placebo (N=278)	15 mg (N=276)	30 mg (N=282)
Age (years)						
Mean (SD)	34 (15)	34 (16)	34 (16)	33 (15)	33 (16)	34 (16)
Median	31	30	29	29	28	30
Min, Max	12, 75	12, 74	12, 75	13, 71	12, 74	12, 75
Categories, n (%)						
12 to 17	40 (14)	42 (15)	42 (15)	36 (13)	33 (12)	35 (12)
18 to 64	230 (82)	226 (80)	228 (80)	231 (83)	228 (83)	228 (81)
≥ 65	11 (4)	13 (5)	15 (5)	11 (4)	15 (5)	19 (7)
Sex, n (%)						
Male	144 (51)	157 (56)	155 (54)	154 (55)	155 (56)	162 (57)
Female	137 (49)	124 (44)	130 (46)	124 (45)	121 (44)	120 (43)
Race, n (%)						
White	182 (65)	182 (65)	191 (67)	195 (70)	184 (67)	198 (70)
Asian	69 (25)	63 (22)	71 (25)	56 (20)	65 (24)	62 (22)
Black / African American	21 (7)	26 (9)	8 (3)	16 (6)	17 (6)	18 (6)
Other	9 (3)	10 (4)	15 (5)	11 (4)	10 (4)	4 (1)
Country, n (%)						
United States	76 (27)	84 (30)	71 (25)	76 (27)	78 (28)	82 (29)
Outside United States	205 (73)	197 (70)	214 (75)	202 (73)	198 (72)	200 (71)

[1] Intent-to-Treat (ITT) population: all randomized subjects.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADSL.xpt

Table 19. Demographics – Trial M16-047 (ITT[1])

	Trial M16-047		
		Upadacitinib	
	Placebo + TCS (N=304)	15 mg + TCS (N=300)	30 mg + TCS (N=297)
Age (years)			
Mean (SD)	34 (15)	33 (14)	35 (16)
Median	31	28	31
Min, Max	12, 75	13, 74	12, 72
Categories, n (%)			
12 to 17	40 (13)	39 (13)	37 (12)
18 to 64	250 (82)	256 (85)	243 (82)
≥ 65	14 (5)	5 (2)	17 (6)
Sex, n (%)			
Male	178 (59)	179 (60)	190 (64)
Female	126 (41)	121 (40)	107 (36)
Race, n (%)			
White	225 (74)	204 (68)	218 (73)
Asian	60 (20)	64 (21)	61 (21)
Black / African American	18 (6)	19 (6)	13 (4)
Other	1 (<1)	13 (4)	5 (2)
Country, n (%)			
United States	56 (18)	57 (19)	53 (18)
Outside United States	248 (82)	243 (81)	244 (82)

[1] Intent-to-Treat (ITT) population: all randomized subjects.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADSL.xpt

Table 20 and Table 21 present the key baseline disease characteristics for the monotherapy trials (i.e., M16-045 and M18-891) and the combination trial (i.e., M16-047), respectively. Overall, the proportion of subject that had prior systemic therapy for AD was lower in Trial M16-045 compared to Trials 18-891 and M16-047. The proportion of subjects with severe disease (i.e., IGA score = 4 [severe]) was also lower in Trial M16-045 compared to Trials M18-891 and M16-047. The three trials were generally similar with respect to EASI score, percent BSA involvement, and WI-NRS score at baseline. Table 110 and Table 111 in Appendix 18.5.3 present the baseline ADerm-IS and ADerm-SS information for the monotherapy trials and combination trial, respectively.

Table 20. Baseline Disease Characteristics – Trials M16-045 and M18-891 (ITT[1])

	Trial M16-045			Trial M18-891		
		Upadacitinib			Upadacitinib	
	Placebo (N=281)	15 mg (N=281)	30 mg (N=285)	Placebo (N=278)	15 mg (N=276)	30 mg (N=282)
Duration of AD Diagnosis (years)						
n	281	281	285	278	276	281
Mean (SD)	21.3 (15.3)	20.5 (15.9)	20.4 (14.3)	21.1 (13.6)	18.8 (13.3)	20.8 (14.3)
Median	18.7	16.8	17.8	19.5	17.2	19.0
Min, Max	0.04, 69.5	0.1, 72.1	0.1, 66.0	0.1, 67.8	0.3, 64.8	0.1, 74.3
Prior Systemic Therapy for AD, n (%)						
Yes	144 (51)	120 (43)	129 (45)	156 (56)	155 (56)	145 (51)
No	137 (49)	161 (57)	156 (55)	122 (44)	121 (44)	137 (49)
vIGA-AD, n (%)						
3 - Moderate	154 (55)	152 (54)	156 (55)	125 (45)	125 (45)	125 (44)
4 - Severe	127 (45)	129 (46)	129 (45)	153 (55)	151 (55)	157 (56)
EASI						
n	281	281	285	277	276	282
Mean (SD)	28.8 (12.6)	30.6 (12.8)	29.0 (11.1)	29.1 (12.1)	28.6 (11.7)	29.7 (12.2)
Median	24.4	26.3	26.6	25.5	26.2	26.4
Min, Max	16.0, 71.4	16.0, 67.2	16.0, 63.0	16.0, 72.0	16.0, 70.3	16.0, 72.0
Percent BSA						
n	281	281	285	277	276	282
Mean (SD)	45.7 (21.6)	48.5 (22.2)	47.0 (22.0)	47.6 (22.7)	45.1 (22.4)	47.0 (23.2)
Median	42	45	44.5	43	40	44.3
Min, Max	11.0, 98.0	10.0, 98.0	12.0, 99.0	12.0, 99.9	10.0, 99.0	11.0, 99.0
WI-NRS						
n	276	279	282	277	275	281
Mean (SD)	7.3 (1.7)	7.2 (1.6)	7.3 (1.5)	7.3 (1.6)	7.2 (1.6)	7.3 (1.6)
Median	7.4	7.2	7.4	7.3	7.3	7.4
Min, Max	0.3, 10.0	1.9, 10.0	2.1, 10.0	3.3, 10.0	2.9, 10.0	3.8, 10.0
Categories, n (%)						
< 4	4 (1)	5 (2)	2 (1)	3 (1)	5 (2)	1 (0)
≥ 4	272 (97)	274 (98)	280 (98)	274 (99)	270 (98)	280 (99)
Missing	5 (2)	2 (1)	3 (1)	1 (0)	1 (0)	1 (0)

[1] Intent-to-Treat (ITT) population: all randomized subjects.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADSL.xpt, ADEFNRS.xpt, ADEFADR.xpt

Table 21. Baseline Disease Characteristics – Trial M16-047 (ITT[1])

	Trial M16-047		
		Upadacitinib	
	Placebo + TCS (N=304)	15 mg + TCS (N=300)	30 mg + TCS (N=297)
Duration of AD Diagnosis (years)			
n	303	300	297
Mean (SD)	24.3 (15.2)	22.9 (13.9)	23.1 (16.1)
Median	21.9	20.7	20.4
Min, Max	0.1, 72.9	0.1, 65.8	0.1, 69.2
Prior Systemic Therapy for AD, n (%)			
Yes	157 (52)	171 (57)	172 (58)
No	147 (48)	129 (43)	125 (42)
vIGA-AD, n (%)			
3 - Moderate	143 (47)	141 (47)	140 (47)
4 - Severe	161 (53)	159 (53)	157 (53)
EASI			
Mean (SD)	30.3 (13.0)	29.2 (11.8)	29.7 (11.8)
Median	26.1	25.1	26.7
Min, Max	16.0, 69.6	16.0, 69.0	16.0, 67.8
Percent BSA			
Mean (SD)	48.6 (23.1)	46.7 (21.6)	48.5 (23.1)
Median	43.0	43.5	49
Min, Max	12.0, 99.0	12.0, 98.0	12.5, 99.9
WI-NRS			
n	301	299	295
Mean (SD)	7.1 (1.6)	7.1 (1.8)	7.4 (1.6)
Median	7.2	7.1	7.5
Min, Max	0.7, 10.0	0.0, 10.0	0.6, 10.0
Categories, n (%)			
< 4	7 (2)	11 (4)	4 (1)
≥ 4	294 (97)	288 (96)	291 (98)
Missing	3 (1)	1 (0)	2 (1)

[1] Intent-to-Treat (ITT) population: all randomized subjects.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADSL.xpt, ADEFNRS.xpt, ADEFADR.xpt

8.1.5. Rescue Medication Use

The use of rescue medication during Weeks 0 to 16 is summarized by treatment group in Table 22. In all three trials, the proportion of subjects who used rescue medication was higher in the placebo group compared to the upadacitinib groups. The proportion of subjects who used rescue medication was higher in the monotherapy trials (i.e., M16-045 and M18-891) compared to the combination trial (i.e., M16-047).

Table 22. Rescue Medication Use During Weeks 0 to 16 – Trials M16-045, M18-891, and M16-047 (ITT[1])

		Upadacitinib	
	Placebo	15 mg	30 mg
Trial M16-045 (Monotherapy)	N=281	N=281	N=285
Any Rescue, n (%)	133 (47)	32 (11)	19 (7)
Trial M18-891 (Monotherapy)	N=278	N=276	N=282
Any Rescue, n (%)	120 (43)	25 (9)	16 (6)
Trial M16-047 (Combination)	N=304	N=300	N=297

	Placebo	Upadacitinib 15 mg	Upadacitinib 30 mg
Any Rescue, n (%)	78 (26)	16 (5)	16 (5)

[1] Intent-to-Treat (ITT) population: all randomized subjects.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADSL.xpt

8.1.6. Results of the Coprimary Efficacy Endpoints

Table 23 and Table 24 present the results of the coprimary efficacy endpoints at Week 16 for the monotherapy trials (i.e., M16-045 and M18-891) and the combination trial (i.e., M16-047), respectively. In all three trials, both doses of upadacitinib were statistically superior to placebo on both coprimary efficacy endpoints (p-values < 0.001).

Table 23. Results of the Coprimary Efficacy Endpoints at Week 16 – Trials M16-045 and M18-891 (ITT[1])

	Trial M16-045			Trial M18-891		
		Upadacitinib			Upadacitinib	
	Placebo (N=281)	15 mg (N=281)	30 mg (N=285)	Placebo (N=278)	15 mg (N=276)	30 mg (N=282)
vIGA-AD Response[2]	8%	48%	62%	5%	39%	52%
Difference from Placebo (95% CI)[3]	-	40% (33%, 46%)	54% (47%, 60%)	-	34% (28%, 40%)	47% (41%, 54%)
P-value[3]	-	<0.001	<0.001	-	<0.001	<0.001
EASI-75	16%	70%	80%	13%	60%	73%
Difference from Placebo (95% CI)[3]	-	53% (46%, 60%)	63% (57%, 70%)	-	47% (40%, 54%)	60% (53%, 66%)
P-value[3]	-	<0.001	<0.001	-	<0.001	<0.001

[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data was imputed using NRI-C.
[2] Response was defined as a vIGA-AD score of 0 ("clear") or 1 ("almost clear") with at least a 2-grade reduction from baseline.
[3] Difference (95% CI) and p-value based on the CMH test stratified by baseline vIGA-AD score and age (adolescent vs. adults).
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADEFF.xpt

Table 24. Results of the Coprimary Efficacy Endpoints at Week 16 – Trial M16-047 (ITT[1])

	Trial M16-047		
		Upadacitinib	
	Placebo + TCS (N=304)	15 mg + TCS (N=300)	30 mg + TCS (N=297)
vIGA-AD Response[2]	11%	40%	59%
Difference from Placebo (95% CI)[3]	-	29% (22%, 35%)	48% (41%, 54%)
P-value[3]	-	<0.001	<0.001
EASI-75	26%	65%	77%
Difference from Placebo (95% CI)[3]	-	38% (31%, 45%)	51% (44%, 57%)
P-value[3]	-	<0.001	<0.001

[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data was imputed using NRI-C.
[2] Response was defined as a vIGA-AD score of 0 ("clear") or 1 ("almost clear") with at least a 2-grade reduction from baseline.
[3] Difference (95% CI) and p-value based on the CMH test stratified by baseline vIGA-AD score and age (adolescent vs. adults).
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADEFF.xpt

Table 25 presents the number and percentage of subjects who had missing data for the coprimary efficacy endpoints at Week 16 by treatment group for all three Phase 3 trials. In

addition, the table presents the number and percentage of subjects who had missing data but excludes the subjects with missing data who received rescue therapy during the double-blind period (i.e., Weeks 0 to 16). The percentage of subjects with missing data was higher in the placebo group compared to the upadacitinib groups in all three trials.

Table 25. Subjects with Missing Data for the Coprimary Efficacy Endpoints at Week 16 – Trials M16-045, M18-891, and M16-047 (ITT[1])

		Upadacitinib		
	Placebo	**15 mg**	**30 mg**	**Total**
Trial M16-045 (Enrolled)	N=281	N=281	N=285	N=847
All Missing Subjects, n (%)	38 (14)	9 (3)	13 (5)	60 (7)
Excluding Subjects who received Rescue Therapy, n (%)	21 (7)	6 (2)	10 (4)	37 (4)
Trial M18-891(Enrolled)	N=278	N=276	N=282	N=836
All Missing Subjects, n (%)	37 (13)	10 (4)	18 (6)	65 (8)
Excluding Subjects who received Rescue Therapy, n (%)	17 (6)	6 (2)	16 (6)	39 (5)
Trial M16-047 (Enrolled)	N=304	N=300	N=297	N=901
All Missing Subjects, n (%)	21 (7)	12 (4)	7 (2)	40 (4)
Excluding Subjects who received Rescue Therapy, n (%)	20 (7)	10 (3)	7 (2)	37 (4)

[1] Intent-to-Treat (ITT) population: all randomized subjects.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADEFF.xpt, ADSL.xpt

Table 26 presents the number and percentage of subjects that had missing visits due to the COVID-19 pandemic by treatment group and visit for all three Phase 3 trials. Approximately 1% of subjects in each trial had missed the Week 16 visit due to the COVID-19 pandemic.

Table 26. Subjects with Missing Visits due to COVID-19 Pandemic – Trials M16-045, M18-891, and M16-047 (ITT[1])

		Upadacitinib		
	Placebo	**15 mg**	**30 mg**	**Total**
Trial M16-045	N=281	N=281	N=285	N=847
Week 12, n (%)	0	0	1 (<1)	1 (<1)
Week 16, n (%)	4 (1)	1 (<1)	2 (1)	7 (1)
Trial M18-891	N=278	N=276	N=282	N=836
Week 12, n (%)	1 (<1)	1 (<1)	4 (1)	6 (1)
Week 16, n (%)	1 (<1)	0 (0)	4 (1)	5 (1)
Trial M16-047	N=304	N=300	N=297	N=901
Week 16, n (%)	2 (1)	2 (1)	2 (1)	6 (1)

[1] Intent-to-Treat (ITT) population: all randomized subjects.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADEFF.xpt

Table 27, Table 28, and Table 29 present the results for the coprimary efficacy endpoints at Week 16 using the primary method for handling missing data as well as the prespecified sensitivity analyses for handling missing data for Trials M16-045, M18-891, and Trial M16-047, respectively. For all three trials, the results were similar across of the various methods as the proportion of missing data was small. In the extreme case (i.e., worst-case scenario), both doses of upadacitinib remained significantly superior to placebo (p-values < 0.001) for both coprimary efficacy endpoints in all three trials.

Table 27. Results of the Coprimary Efficacy Endpoints at Week 16 by Various Methods to Impute Missing Data – Trial M16-045 (ITT[1])

		Upadacitinib		Difference (P-Value)[2]	
	Placebo (N=281)	15 mg (N=281)	30 mg (N=285)	15 mg vs. Placebo	30 mg vs. Placebo
vIGA-AD Response[3]					
NRI-C (Primary)	8%	48%	62%	40% (<0.001)	54% (<0.001)
NRI-NC	8%	48%	62%	40% (<0.001)	54% (<0.001)
MI	9%	49%	64%	40% (<0.001)	55% (<0.001)
Worst-case	16%	48%	62%	32% (<0.001)	46% (<0.001)
EASI-75					
NRI-C (Primary)	16%	70%	80%	53% (<0.001)	63% (<0.001)
NRI-NC	16%	69%	79%	54% (<0.001)	64% (<0.001)
MI	17%	70%	81%	53% (<0.001)	64% (<0.001)
Worst-case	23%	69%	79%	46% (<0.001)	56% (<0.001)

[1] Intent-to-Treat (ITT) population: all randomized subjects.
[2] Difference and p-value based on the CMH test stratified by baseline vIGA-AD score and age (adolescent vs. adults).
[3] Response was defined as a vIGA-AD score of 0 ("clear") or 1 ("almost clear") with at least a 2-grade reduction from baseline.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADEFF.xpt

Table 28. Results of the Coprimary Efficacy Endpoints at Week 16 by Various Methods to Impute Missing Data – Trial M18-891 (ITT[1])

		Upadacitinib		Difference (P-Value)[2]	
	Placebo (N=278)	15 mg (N=276)	30 mg (N=282)	15 mg vs. Placebo	30 mg vs. Placebo
vIGA-AD Response[3]					
NRI-C (Primary)	5%	39%	52%	34% (<0.001)	47% (<0.001)
NRI-NC	5%	39%	51%	34% (<0.001)	46% (<0.001)
MI	5%	39%	54%	34% (<0.001)	48% (<0.001)
Worst-case	11%	39%	51%	28% (<0.001)	40% (<0.001)
EASI-75					
NRI-C (Primary)	13%	60%	73%	47% (<0.001)	60% (<0.001)
NRI-NC	13%	60%	72%	47% (<0.001)	59% (<0.001)
MI	14%	61%	75%	47% (<0.001)	61% (<0.001)
Worst-case	19%	60%	72%	41% (<0.001)	53% (<0.001)

[1] Intent-to-Treat (ITT) population: all randomized subjects.
[2] Difference and p-value based on the CMH test stratified by baseline vIGA-AD score and age (adolescent vs. adults).
[3] Response was defined as a vIGA-AD score of 0 ("clear") or 1 ("almost clear") with at least a 2-grade reduction from baseline.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADEFF.xpt

Table 29. Results of the Coprimary Efficacy Endpoints at Week 16 by Various Methods to Impute Missing Data – Trial M16-047 (ITT[1])

		Upadacitinib		Difference (P-Value)[2]	
	Placebo + TCS (N=304)	15 mg + TCS (N=300)	30 mg + TCS (N=297)	15 mg vs. Placebo	30 mg vs. Placebo
vIGA-AD Response[3]					
NRI-C (Primary)	11%	40%	59%	29% (<0.001)	48% (<0.001)
NRI-NC	11%	39%	58%	28% (<0.001)	47% (<0.001)
MI	11%	41%	60%	29% (<0.001)	48% (<0.001)
Worst-case	17%	39%	58%	22% (<0.001)	41% (<0.001)
EASI-75					
NRI-C (Primary)	26%	65%	77%	38% (<0.001)	51% (<0.001)

		Upadacitinib		Difference (P-Value)[2]	
	Placebo + TCS (N=304)	15 mg + TCS (N=300)	30 mg + TCS (N=297)	15 mg vs. Placebo	30 mg vs. Placebo
NRI-NC	26%	64%	77%	38% (<0.001)	50% (<0.001)
MI	27%	66%	78%	38% (<0.001)	51% (<0.001)
Worst-case	33%	64%	77%	31% (<0.001)	44% (<0.001)

[1] Intent-to-Treat (ITT) population: all randomized subjects.
[2] Difference and p-value based on the CMH test stratified by baseline vIGA-AD score and age (adolescent vs. adults).
[3] Response was defined as a vIGA-AD score of 0 ("clear") or 1 ("almost clear") with at least a 2-grade reduction from baseline.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADEFF.xpt

8.1.7. Results of the Secondary Efficacy Endpoints

For all three trials, both doses of upadacitinib were statistically superior to placebo on all of the secondary efficacy endpoints (p-values < 0.001) in accordance with the multiplicity testing procedures (see Appendix 18.5.2). In this review, the secondary efficacy endpoints have been grouped for presentation to allow for ease of review. The secondary efficacy endpoints based on EASI are presented in Table 30 for Trials M16-045 and M18-891 and in Table 31 for Trial M16-047. The secondary efficacy endpoint based on the WI-NRS are present in Table 32 for Trials M16-045 and M18-891 and in Table 33 for Trial M16-047.

Table 30. Results of the Secondary Efficacy Endpoints based on EASI – Trials M16-045 and M18-891

	Trial M16-045			Trial M18-891		
		Upadacitinib			Upadacitinib	
	Placebo (N=281)	15 mg (N=281)	30 mg (N=285)	Placebo (N=278)	15 mg (N=276)	30 mg (N=282)
EASI-90 at Week 16[1]	8%	53%	66%	5%	42%	58%
Difference (95% CI)[2]	-	45% (39%, 52%)	58% (51%, 64%)	-	37% (31%, 43%)	53% (47%, 59%)
P-value[2]	-	<0.001	<0.001	-	<0.001	<0.001
EASI-100 at Week 16[1]	2%	17%	27%	1%	14%	19%
Difference (95% CI)[2]	-	15% (10%, 20%)	25% (20%, 31%)	-	13% (9%, 18%)	18% (13%, 23%)
P-value[2]	-	<0.001	<0.001	-	<0.001	<0.001
EASI-75 at Week 2[1]	4%	38%	47%	4%	33%	44%
Difference (95% CI)[2]	-	35% (28%, 41%)	44% (38%, 50%)	-	29% (23%, 35%)	40% (34%, 47%)
P-value[2]	-	<0.001	<0.001	-	<0.001	<0.001
	N=274[4]	N=279[4]	N=285[4]	N=269[4]	N=174[4]	N=277[4]
Flare During DB[3]	25%	1%	0%	25%	2%	1%
Difference (95% CI)[2]	-	-24% (-29%, -19%)	-25% (-30%, -20%)	-	-22% (-28%, -17%)	-23% (-28%, -18%)
P-value[2]	-	<0.001	<0.001	-	<0.001	<0.001

[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data was imputed using NRI-C.
[2] Difference (95% CI) and p-value based on the CMH test stratified by baseline vIGA-AD score and age (adolescent vs. adults).
[3] Flare was defined as an increase of EASI by ≥ 6.6 from baseline during the double-blind period (Weeks 0 to 16) and prior to use of rescue medication.
[4] Subjects with EASI ≤ 65.4 and at least one post baseline EASI assessment.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADEFF.xpt

Table 31. Results of the Secondary Efficacy Endpoints based on EASI – Trial M16-047 (ITT[1])

	Trial M16-045		
		Upadacitinib	
	Placebo + TCS (N=304)	15 mg + TCS (N=300)	30 mg + TCS (N=297)
EASI-90 at Week 16	13%	43%	63%
Difference (95% CI)[2]	-	30% (23%, 36%)	50% (43%, 56%)
P-value[2]	-	<0.001	<0.001
EASI-100 at Week 16	1%	12%	23%
Difference (95% CI)[2]	-	11% (7%, 15%)	21% (16%, 26%)
P-value[2]	-	NA[3]	<0.001
EASI-75 at Week 4	15%	59%	72%
Difference (95% CI)[2]	-	44% (37%, 51%)	58% (51%, 64%)
P-value[2]	-	<0.001	<0.001
EASI-75 at Week 2	7%	31%	44%
Difference (95% CI)[2]	-	24% (18%, 30%)	37% (31%, 43%)
P-value[2]	-	<0.001	<0.001

[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data was imputed using NRI-C.
[2] Difference (95% CI) and p-value based on the CMH test stratified by baseline vIGA-AD score and age (adolescent vs. adults).
[3] Endpoint not included in the multiplicity testing procedure.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADEFF.xpt

Table 32. Results of the Secondary Efficacy Endpoints based on Worst Itch NRS – Trials M16-045 and M18-891

	Trial M16-045			Trial M18-891		
		Upadacitinib			Upadacitinib	
	Placebo	15 mg	30 mg	Placebo	15 mg	30 mg
≥4-point improvement in WI-NRS at Week 16	N=272[1] 12%	N=274[1] 52%	N=280[1] 60%	N=274[1] 9%	N=270[1] 42%	N=280[1] 60%
Difference (95% CI)[2]	-	40% (33%, 48%)	48% (41%, 55%)	-	33% (26%, 39%)	50% (44%, 57%)
P-value[2]	-	<0.001	<0.001	-	<0.001	<0.001
≥4-point improvement in WI-NRS at Week 4	N=272[1] 4%	N=274[1] 51%	N=280[1] 67%	N=274[1] 4%	N=270[1] 49%	N=280[1] 61%
Difference (95% CI)[2]	-	47% (41%, 53%)	62% (56%, 68%)	-	45% (39%, 52%)	57% (51%, 63%)
P-value[2]	-	<0.001	<0.001	-	<0.001	<0.001
≥4-point improvement in WI-NRS at Week 1	N=272[1] 0%	N=274[1] 15%	N=280[1] 20%	N=274[1] 1%	N=270[1] 7%	N=280[1] 16%
Difference (95% CI)[2]	-	15% (10%, 19%)	19% (15%, 24%)	-	7% (3%, 10%)	15% (11%, 19%)
P-value[2]	-	<0.001	<0.001	-	<0.001	<0.001
≥4-point improvement in WI-NRS at Day 3	N=270[3] 3%	N=275[3] 16%	N=279[3] 21%	N=267[3] 3%	N=269[3] 12%	N=278[3] 17%
Difference (95% CI)[2]	-	13% (8%, 18%)	18% (13%, 23%)	-	9% (4%, 13%)	14% (9%, 19%)
P-value[2]	-	<0.001	NA[4]	-	<0.001	NA[4]

	Trial M16-045			Trial M18-891		
		Upadacitinib			Upadacitinib	
	Placebo	15 mg	30 mg	Placebo	15 mg	30 mg
	N=270[3]	N=275[3]	N=279[3]	N=267[3]	N=269[3]	N=278[3]
≥4-point improvement in WI-NRS at Day 2	4%	11%	12%	1%	7%	8%
Difference (95% CI)[2]	-	7% (3%, 11%)	8% (4%, 13%)	-	7% (3%, 10%)	7% (4%, 11%)
P-value[2]	-	NA[4]	<0.001	-	NA[4]	<0.001

[1] All randomized subjects with at least a WI-NRS score ≥ 4 at baseline. Baseline is defined as the average of the seven daily WI-NRS scores immediately prior to the first dose of study drug. Baseline is considered missing if 4 or more days of the 7-day period are missing, and subjects with missing baseline are not included in the analysis. Missing data after baseline was imputed using NRI-NC (i.e., there was no missing data due to the COVID-19 pandemic).
[2] Difference (95% CI) and p-value based on the CMH test stratified by baseline vIGA-AD score and age (adolescent vs. adults).
[3] All randomized subjects with at least a WI-NRS score ≥ 4 at baseline. Baseline for this endpoint was defined as the last non-missing daily WI-NRS score before the first dose of study drug. Subjects with missing baseline are not included in the analysis. Missing data after baseline was imputed using NRI-NC.
[4] Endpoint not included in the multiplicity testing procedure.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADEFNRS.xpt

Table 33. Results of the Secondary Efficacy Endpoints based on Worst Itch NRS – Trial M16-047

	Trial M16-047		
		Upadacitinib	
	Placebo + TCS (N=294)[1]	15 mg + TCS (N=288)[1]	30 mg + TCS (N=291)[1]
≥4-point improvement in WI-NRS at Week 16	15%	52%	64%
Difference (95% CI)[2]	-	37% (30%, 44%)	49% (42%, 56%)
P-value[2]	-	<0.001	<0.001
≥4-point improvement in WI-NRS at Week 4	15%	52%	66%
Difference (95% CI)[2]	-	37% (30%, 44%)	51% (44%, 57%)
P-value[2]	-	<0.001	<0.001
≥4-point improvement in WI-NRS at Week 1	3%	12%	19%
Difference (95% CI)[2]	-	9% (5%, 13%)	16% (11%, 21%)
P-value[2]	-	<0.001	<0.001

[1] All randomized subjects with at least a WI-NRS score ≥ 4 at baseline. Baseline is defined as the average of the seven daily WI-NRS scores immediately prior to the first dose of study drug. Baseline is considered missing if 4 or more days of the 7-day period are missing, and subjects with missing baseline are not included in the analysis. Missing data after baseline was imputed using NRI-NC (i.e., there was no missing data due to the COVID-19 pandemic).
[2] Difference (95% CI) and p-value based on the CMH test stratified by baseline vIGA-AD score and age (adolescent vs. adults).
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADEFNRS.xpt

For Trials M16-045 and M18-891, the protocol specified secondary efficacy endpoints based on the ADerm-IS and the ADerm-SS at Week 16. The results for these endpoints are presented in Table 34.

Table 34. Results of the Secondary Efficacy Endpoints based on ADerm-IS and ADerm-SS at Week 16 – Trials M16-045 and M18-891

	Trial M16-045			Trial M18-891		
		Upadacitinib			Upadacitinib	
	Placebo	15 mg	30 mg	Placebo	15 mg	30 mg
	N=233[1]	N=237[1]	N=249[1]	N=247[1]	N=237[1]	N=238[1]
≥4-point improvement in ADerm-SS Skin Pain	15%	54%	63%	13%	49%	65%
Difference (95% CI)[6]	-	39% (31%, 47%)	49% (41%, 56%)	-	36% (28%, 44%)	52% (44%, 59%)
P-value[6]	-	<0.001	<0.001	-	<0.001	<0.001
	N=226[2]	N=233[2]	N=246[2]	N=244[2]	N=230[2]	N=234[2]
≥28-point improvement in ADerm-IS TSS-7	15%	54%	68%	13%	53%	66%
Difference (95% CI) [6]	-	38% (30%, 46%)	53% (45%, 60%)	-	40% (33%, 48%)	53% (46%, 61%)
P-value[6]	-	<0.001	<0.001	-	<0.001	<0.001
	N=220[3]	N=218[3]	N=218[3]	N=233[3]	N=219[3]	N=228[3]
≥12-point improvement in ADerm-IS Sleep Domain	13%	55%	66%	12%	50%	62%
Difference (95% CI) [6]	-	42% (34%, 50%)	53% (45%, 61%)	-	38% (30%, 46%)	50% (42%, 57%)
P-value[6]	-	<0.001	<0.001	-	<0.001	<0.001
	N=212[4]	N=227[4]	N=226[4]	N=233[4]	N=228[4]	N=228[4]
≥11-point improvement in ADerm-IS Emotional State Domain	20%	63%	73%	17%	57%	71%
Difference (95% CI)[6]	-	43% (34%, 51%)	53% (45%, 60%)	-	40% (32%, 48%)	55% (47%, 62%)
P-value[6]	-	<0.001	<0.001	-	<0.001	<0.001
	N=197[5]	N=203[5]	N=205[5]	N=227[5]	N=207[5]	N=223[5]
≥14-point improvement in ADerm-IS Daily Activities Domain	20%	65%	73%	19%	57%	70%
Difference (95% CI)[6]	-	45% (36%, 53%)	53% (45%, 61%)	-	38% (29%, 46%)	51% (43%, 59%)
P-value[6]	-	<0.001	<0.001	-	<0.001	<0.001

[1] All randomized subjects with an ADerm-SS Skin Pain score ≥ 4 at baseline. Missing data after baseline was imputed using NRI-NC (i.e., there was no missing data due to the COVID-19 pandemic).
[2] All randomized subjects with an ADerm-SS TSS-7 ≥ 28 at baseline. Missing data after baseline was imputed using NRI-NC (i.e., there was no missing data due to the COVID-19 pandemic).
[3] All randomized subjects with an ADerm-IS Sleep Domain score ≥ 12 at baseline. Missing data after baseline was imputed using NRI-NC (i.e., there was no missing data due to the COVID-19 pandemic).
[4] All randomized subjects with an ADerm-IS Emotional State Domain score ≥ 11 at baseline. Missing data after baseline was imputed using NRI-NC (i.e., there was no missing data due to the COVID-19 pandemic).
[5] All randomized subjects with an ADerm-IS Daily Activity Domain score ≥ 14 at baseline. Missing data after baseline was imputed using NRI-NC (i.e., there was no missing data due to the COVID-19 pandemic).
[6] Difference (95% CI) and p-value based on the CMH test stratified by baseline vIGA-AD score and age (adolescent vs. adults).
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADEFADR.xpt

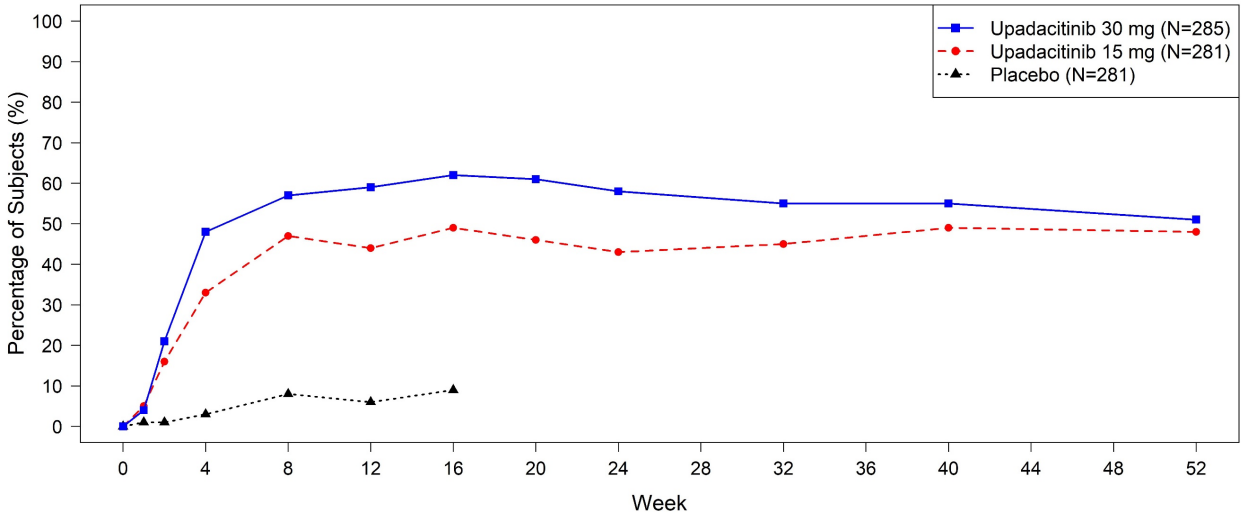
8.1.8. Efficacy Over Time

Figure 8, Figure 9, and Figure 10 present the results for the proportion of subjects with IGA response by visit (Weeks 0 to 52) for Trials M16-045, M18-891, and M16-047, respectively.

Figure 11, Figure 12, and Figure 13 present the results for the proportion of subjects with EASI-75 by visit (Weeks 0 to 52) for Trials M16-045, M18-891, and M16-047, respectively.

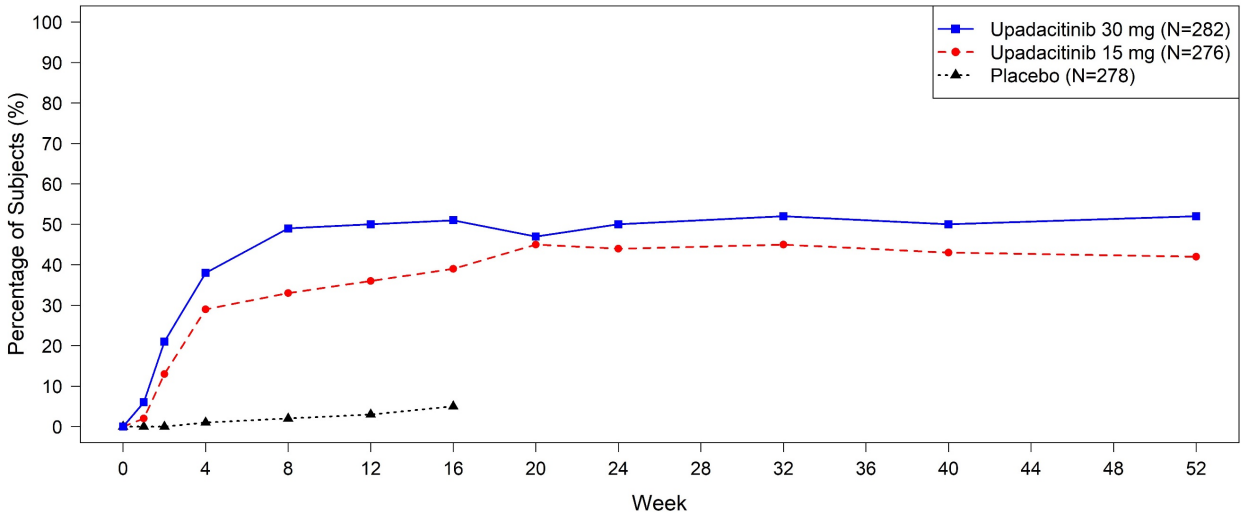
It should be noted that the original datasets (i.e., those submitted in the supplement on October 15, 2020) included data up to a specific cutoff date or a subject's Week 16 visit date, whichever was later. Therefore, in order evaluate efficacy up to Week 52, the Agency sent the Applicant an information request on June 17, 2021 for the data up to Week 52, as all subjects should have either completed their Week 52 visit or discontinued their respective trial by the date of the information request. The Applicant submitted the requested datasets on June 22, 2021 and the results presented below are based on these new datasets. It should be noted that the new datasets differ slightly from the original datasets in regard to designation of subjects who received rescue medication and visits designated as being missed because of the COVID-19 pandemic.

Figure 8. Proportion of Subjects with IGA Response[1] by Visit – Trial M16-045 (ITT[2])



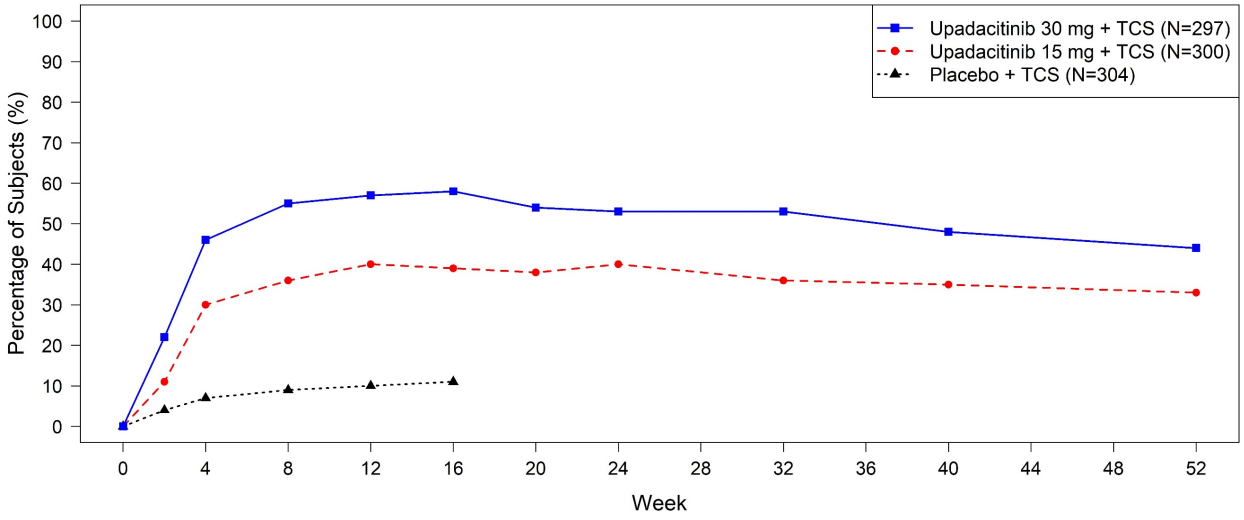
[1] Response was defined as a vIGA-AD score of 0 ("clear") or 1 ("almost clear") with at least a 2-grade reduction from baseline.
[2] ITT population: all randomized subjects. Missing data was imputed using NRI-NC.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADEFF.xpt (submitted on June 22, 2021)

Figure 9. Proportion of Subjects with IGA Response[1] by Visit – Trial M18-891 (ITT[2])



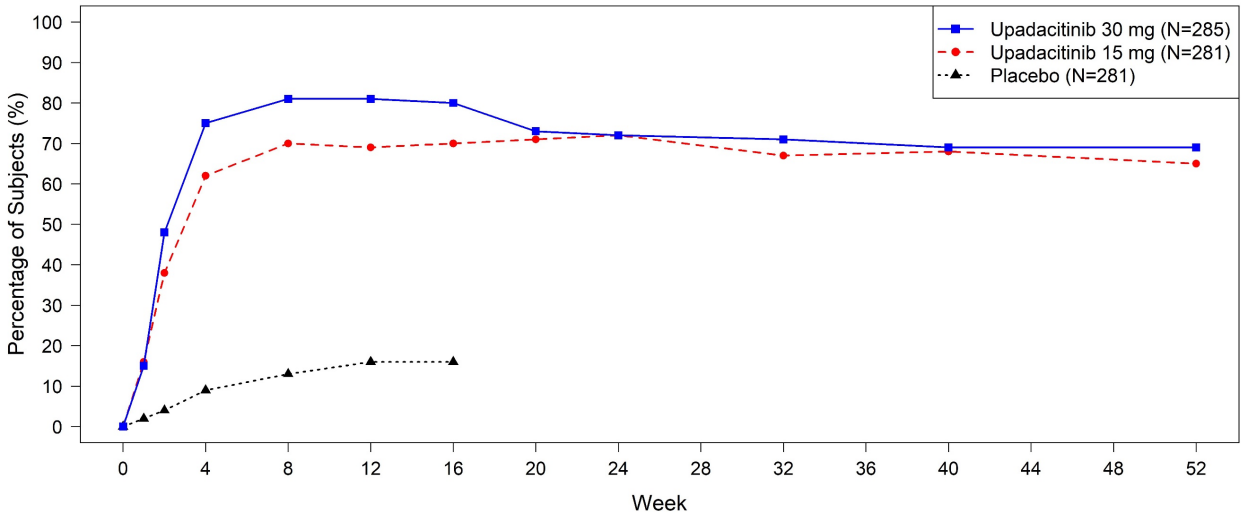
[1] Response was defined as a vIGA-AD score of 0 ("clear") or 1 ("almost clear") with at least a 2-grade reduction from baseline.
[2] ITT population: all randomized subjects. Missing data was imputed using NRI-NC.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADEFF.xpt (submitted on June 22, 2021)

Figure 10. Proportion of Subjects with IGA Response[1] by Visit – Trial M16-047 (ITT[2])



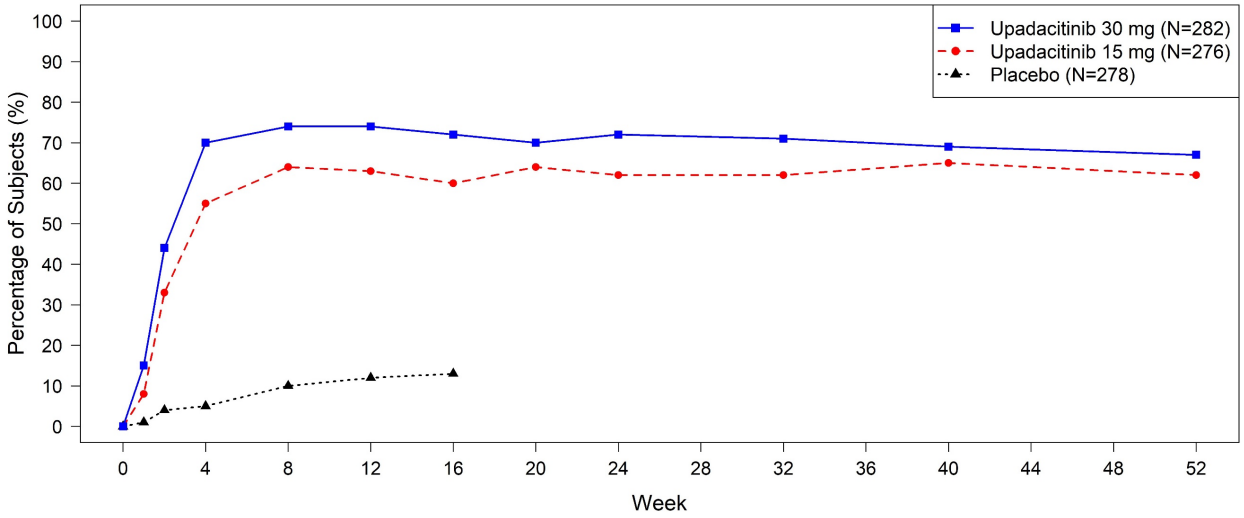
[1] Response was defined as a vIGA-AD score of 0 ("clear") or 1 ("almost clear") with at least a 2-grade reduction from baseline.
[2] ITT population: all randomized subjects. Missing data was imputed using NRI-NC.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADEFF.xpt (submitted on June 22, 2021)

Figure 11. Proportion of Subjects with EASI-75 by Visit – Trial M16-045 (ITT[1])



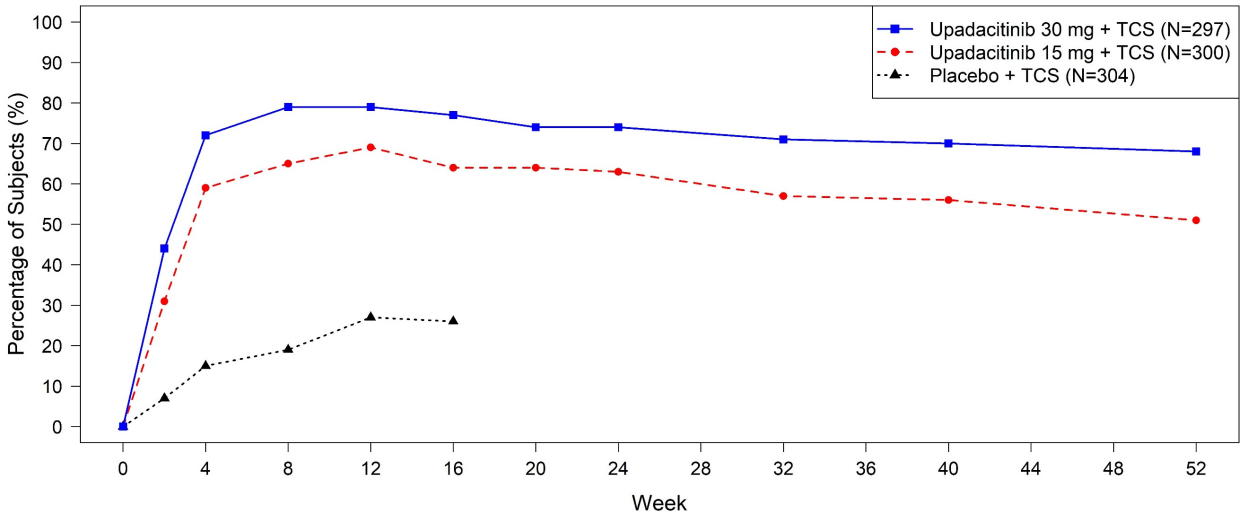
[1] ITT population: all randomized subjects. Missing data was imputed using NRI-NC.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADEFF.xpt (submitted on June 22, 2021)

Figure 12. Proportion of Subjects with EASI-75 by Visit – Trial M18-891 (ITT[1])



[1] ITT population: all randomized subjects. Missing data was imputed using NRI-NC.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADEFF.xpt (submitted on June 22, 2021)

Figure 13. Proportion of Subjects with EASI-75 by Visit – Trial M16-047 (ITT[1])



[1] ITT population: all randomized subjects. Missing data was imputed using NRI-NC.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADEFF.xpt (submitted on June 22, 2021)

8.1.9. Efficacy Results by Age (Adults vs. Adolescents)

Table 35 presents the results of the coprimary efficacy endpoints at Week 16 by age (i.e., adults vs. adolescents) for Trials M16-045, M18-891, and M16-047. Table 36 presents the results of the WI-NRS at Week 16 by age for Trials M16-045, M18-891, and M16-047. A generally large treatment effect for both doses of upadacitinib was observed in adults and adolescents for all three trials.

Table 35. Results of the Coprimary Efficacy Endpoints at Week 16 by Age (Adults vs. Adolescents) – Trials M16-045, M18-891, and M16-047 (ITT[1])

	Adults			**Adolescents**		
		Upadacitinib			**Upadacitinib**	
	Placebo	**15 mg**	**30 mg**	**Placebo**	**15 mg**	**30 mg**
Trial M16-045	N=241	N=239	N=243	N=40	N=42	N=42
vIGA-AD Response[2]	9%	50%	61%	8%	38%	69%
Difference (95% CI)	-	41% (34%, 49%)	52% (45%, 59%)	-	31% (14%, 47%)	62% (45%, 78%)
EASI-75	18%	69%	79%	8%	71%	83%
Difference (95% CI)	-	52% (44%, 59%)	61% (54%, 68%)	-	63% (47%, 79%)	75% (61%, 89%)
Trial M18-891	N=242	N=243	N=247	N=36	N=33	N=35
vIGA-AD Response[2]	5%	38%	51%	3%	42%	62%
Difference (95% CI)	-	33% (27%, 40%)	46% (39%, 52%)	-	40% (22%, 57%)	60% (42%, 77%)
EASI-75	13%	59%	73%	14%	67%	74%
Difference (95% CI)	-	46% (39%, 54%)	60% (52%, 67%)	-	53% (33%, 72%)	61% (42%, 79%)
Trial M16-047	N=264	N=261	N=260	N=40	N=39	N=37
vIGA-AD Response[2]	11%	41%	58%	8%	31%	65%
Difference (95% CI)	-	30%	46%	-	23%	57%

	Adults			Adolescents		
		Upadacitinib			Upadacitinib	
	Placebo	15 mg	30 mg	Placebo	15 mg	30 mg
		(22%, 37%)	(39%, 53%)		(7%, 40%)	(40%, 75%)
EASI-75	26%	66%	77%	30%	56%	76%
Difference (95% CI)	-	40%	51%	-	26%	46%
		(32%, 48%)	(44%, 59%)		(5%, 47%)	(26%, 65%)

[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data was imputed using NRI-C.
[2] Response was defined as a vIGA-AD score of 0 ("clear") or 1 ("almost clear") with at least a 2-grade reduction from baseline.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADEFF.xpt

Table 36. Results for Worst Itch NRS at Week 16 by Age (Adults vs. Adolescents) – Trials M16-045, M18-891, and M16-047 (ITT[1])

	Adults			Adolescents		
		Upadacitinib			Upadacitinib	
	Placebo	15 mg	30 mg	Placebo	15 mg	30 mg
Trial M16-045	N=233	N=234	N=238	N=39	N=40	N=42
≥4-point improvement in WI-NRS	11%	53%	61%	15%	45%	55%
Difference (95% CI)	-	42%	50%		30%	39%
		(35%, 50%)	(42%, 57%)	-	(10%, 49%)	(21%, 58%)
Trial M18-891	N=238	N=240	N=246	N=36	N=30	N=34
≥4-point improvement in WI-NRS	10%	43%	61%	3%	33%	50%
Difference (95% CI)	-	33%	51%		31%	47%
		(25%, 40%)	(44%, 58%)	-	(13%, 48%)	(30%, 65%)
Trial M16-047	N=256	N=252	N=258	N=38	N=36	N=33
≥4-point improvement in WI-NRS	15%	53%	65%	13%	42%	55%
Difference (95% CI)	-	38%	50%		29%	41%
		(30%, 46%)	(43%, 57%)	-	(9%, 48%)	(21%, 61%)

[1] All randomized subjects with at least a WI-NRS score ≥ 4 at baseline. Baseline is defined as the average of the seven daily WI-NRS scores immediately prior to the first dose of study drug. Baseline is considered missing if 4 or more days of the 7-day period are missing, and subjects with missing baseline are not included in the analysis. Missing data after baseline was imputed using NRI-NC (i.e., there was no missing data due to the COVID-19 pandemic).
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADEFNRS.xpt

8.1.10. Efficacy Results by Prior Use of Systemic Therapy for AD

Table 37 presents the results of the coprimary efficacy endpoints at Week 16 by prior use of systemic therapy for AD (yes/no) for Trials M16-045, M18-891, and M16-047. The treatment effect was generally consistent between those that had prior use of systemic therapy for AD and those that did not. Table 38 presents the results of the coprimary efficacy endpoints at Week 16 in subjects who reported having inadequate response, loss of response, or medical complication to prior systemic therapy for AD. The treatment effect in this subpopulation was generally similar to the treatment effect in the overall population (see Table 23 and Table 24).

Table 37. Results of the Coprimary Efficacy Endpoints at Week 16 by Prior Use of Systemic Therapy for AD – Trials M16-045, M18-891, and M16-047 (ITT[1])

	Prior Systemic Therapy - Yes			Prior Systemic Therapy - No		
		Upadacitinib			Upadacitinib	
	Placebo	15 mg	30 mg	Placebo	15 mg	30 mg
Trial M16-045	N=144	N=120	N=129	N=137	N=161	N=156

	Prior Systemic Therapy - Yes			Prior Systemic Therapy - No		
		Upadacitinib			Upadacitinib	
	Placebo	15 mg	30 mg	Placebo	15 mg	30 mg
vIGA-AD Response[2]	6%	48%	61%	11%	48%	63%
Difference (95% CI)	-	42%	55%	-	37%	52%
		(33%, 52%)	(46%, 64%)		(28%, 46%)	(42%, 61%)
EASI-75	14%	68%	81%	19%	71%	78%
Difference (95% CI)	-	54%	67%	-	52%	59%
		(43%, 64%)	(59%, 76%)		(43%, 62%)	(50%, 69%)
Trial M18-891	N=156	N=155	N=145	N=122	N=121	N=137
vIGA-AD Response[2]	5%	39%	48%	4%	39%	56%
Difference (95% CI)	-	34%	43%	-	35%	52%
		(25%, 42%)	(34%, 52%)		(25%, 44%)	(43%, 61%)
EASI-75	11%	61%	73%	16%	59%	73%
Difference (95% CI)	-	50%	62%	-	42%	57%
		(41%, 59%)	(53%, 71%)		(31%, 53%)	(47%, 67%)
Trial M16-047	N=157	N=171	N=172	N=147	N=129	N=125
vIGA-AD Response[2]	11%	36%	54%	10%	45%	65%
Difference (95% CI)	-	24%	42%	-	34%	55%
		(16%, 33%)	(33%, 51%)		(24%, 44%)	(45%, 64%)
EASI-75	22%	63%	74%	31%	67%	81%
Difference (95% CI)	-	40%	52%	-	36%	50%
		(31%, 50%)	(43%, 61%)		(25%, 47%)	(40%, 60%)

[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data was imputed using NRI-C.
[2] Response was defined as a vIGA-AD score of 0 ("clear") or 1 ("almost clear") with at least a 2-grade reduction from baseline.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADEFF.xpt, ADSL.xpt

Table 38. Results of the Coprimary Efficacy Endpoints at Week 16 in Subjects who had Inadequate Response, Loss of Response, or Medical Complication to Prior Systemic Therapy for AD – Trials M16-045, M18-891, and M16-047 (ITT[1])

	IGA Response[2] at Week 16			EASI-75 at Week 16		
		Upadacitinib			Upadacitinib	
	Placebo	15 mg	30 mg	Placebo	15 mg	30 mg
Trial M16-045	N=86	N=86	N=78	N=86	N=86	N=78
Proportion	4%	51%	60%	11%	64%	85%
Difference (95% CI)	-	47%	56%	-	53%	73%
		(35%, 58%)	(44%, 68%)		(41%, 65%)	(63%, 84%)
Trial M18-891	N=108	N=110	N=100	N=108	N=110	N=100
Proportion	6%	35%	49%	11%	60%	74%
Difference (95% CI)		30%	43%	-	49%	63%
	-	(20%, 40%)	(33%, 54%)		(38%, 60%)	(52%, 73%)
Trial M16-047	N=108	N=117	N=107	N=108	N=117	N=107
Proportion	11%	35%	56%	22%	58%	76%
Difference (95% CI)	-	24%	45%	-	36%	54%
		(14%, 35%)	(34%, 56%)		(24%, 48%)	(43%, 65%)

[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data was imputed using NRI-C.
[2] Response was defined as a vIGA-AD score of 0 ("clear") or 1 ("almost clear") with at least a 2-grade reduction from baseline.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADEFF.xpt, ADSL.xpt, ADCM.xpt

8.1.11. Findings in Additional Subgroup Populations

The results of the coprimary efficacy endpoints at Week 16 by sex, race, weight (<70, 70-100, and >100 kg), country (United States and outside United States), and baseline IGA score are

presented in Table 112 through Table 117 in Appendix 18.5.4. For all of these subgroups, the treatment effect consistently favored both doses of upadacitinib compared to placebo. In addition, the treatment effects were generally comparable for sex, race, baseline body weight, and country. For race, the sample size in the subgroups of subjects who identify as Black or African American and Other was small; therefore, it would be difficult to detect any difference in efficacy between these subgroups. The treatment effect tended to be higher in subjects with a baseline IGA score of 3 (moderate) compared to those with a baseline IGA score of 4 (severe); however, this was not completely consistent across the trials and endpoints.

8.2. Review of Safety

8.2.1. Safety Review Approach

The primary focus of this safety review is on the data from 3 Phase 3 studies (M16-045, M18-891 and M16-0470), and those from the placebo-controlled period in the Phase 2b study M16-048 (placebo, upadacitinib 15 mg, and upadacitinib 30 mg doses only). Safety data from the Phase 2b study are integrated with those from the 3 Phase 3 studies for the Placebo-Controlled Analysis Set to compare incidences of adverse events (AEs), because these studies had similar designs (placebo-control) and study populations, and studied the doses that reflect anticipated use. Data obtained from these studies will allow the direct comparison of AE rates in upadacitinib-treated subjects to rates of AEs in placebo treated subjects.

Data from the long-term BE periods of the 3 Phase 3 studies will be used to assess potential safety signals that may occur following long term administration of upadacitinib. However, data from this study may be difficult to interpret due to lack of a placebo arm.

Because of differences in the study design following the placebo-controlled period of the Phase 2b clinical trial compared to the Phase 3 studies, the longer-term Phase 2b safety data are not integrated with the global Phase 3 studies for the long-term analysis set.

The Japan regional study (M17-377) and the longer-term Phase 2b safety data will be analyzed separately for counts of rare events and AEs of special interest only.

8.2.2. Review of the Safety Database

Overall Exposure

The development program for upadacitinib included a total of 2898 subjects who received at least 1 dose of upadacitinib in the All Upadacitinib AD Analysis Set (Table 39). Of these subjects, 931 (67.4%) and 895 (65.2%) had exposure to upadacitinib 30 mg and 15 mg, respectively, for at least 12 months as of the data cutoff for 90 day safety update report (SUR).

A total of 333 out of the 2485 subjects from the Phase 3 studies were adolescents, of which 113 subjects (68.1%) and 110 subjects (65.9%) in the upadacitinib 30 mg and 15 mg groups, respectively, had been exposed to upadacitinib for at least 52 weeks as of the SUR data cutoff.

Table 39. Number and Percentages of Subjects Exposed to Study Drug by Duration Intervals (Long-term Upadacitinib Phase 3 AD Analysis Set)

	Overall		Adolescents	
Days	UPA 15 mg n (%) (N = 1239)	UPA 30 mg n (%) (N = 1246)	UPA 15 mg n (%) (N = 167)	UPA 30 mg n (%) (N = 166)
≥ 4 weeks	1230 (99.3)	1240 (99.5)	167 (100)	165 (99.4)
≥ 12 weeks	1203 (97.1)	1215 (97.5)	164 (98.2)	164 (98.8)
≥ 24 weeks	1155 (93.2)	1171 (94.0)	158 (94.6)	160 (96.4)
≥ 36 weeks	1072 (86.5)	1098 (88.1)	147 (88.0)	148 (89.2)
≥ 48 weeks	897 (72.4)	938 (75.3)	128 (76.6)	130 (78.3)
≥ 52 weeks	791 (63.8)	826 (66.3)	110 (65.9)	113 (68.1)
≥ 72 weeks	298 (24.1)	326 (26.2)	49 (29.3)	53 (31.9)
≥ 104 weeks	18 (1.5)	14 (1.1)	2 (1.2)	2 (1.2)
Mean duration (days)	404.9	414.6	419.4	431.1

Abbreviations: QD = once daily; UPA = upadacitin b
Source: Table 2. Safety Update Report.

As shown in Table 40, each integrated analysis set included all subjects who received at least one dose of study drug. For the safety analysis set, subjects were assigned to a treatment group based on the "as treated" treatment group regardless of the treatment randomized.

Table 40. Integrated Safety Analysis Sets

Analysis Set	Analysis Set Rationale and Description	Analyses	Pooled Studies	Summarized Treatment Group(s)	Treatment Comparison(s)[b]
PBO-controlled AD Analysis Set	This analysis set assesses short-term safety through 16 weeks of upadacitinib 15 mg QD and upadacitinib 30 mg QD versus placebo. It includes subjects who received upadacitinib 15 mg QD, upadacitinib 30 mg QD, and placebo during the 16-week placebo-controlled period in Studies M16-048, M16-045 (Main Study), M16-047 (Main Study), and M18-891 (Main Study).	Short-Term (16 weeks)	M16-048 M16-045 M16-047 M18-891	- Upadacitinib 15 mg QD - Upadacitinib 30 mg QD - Placebo	Upadacitinib 15 mg QD versus placebo Upadacitinib 30 mg QD versus placebo
Long-term Upadacitinib Phase 3 AD Analysis Set[a]	This analysis set is to assess long-term safety of upadacitinib 15 mg QD, upadacitinib 30 mg QD, as well as all upadacitinib dosing regimens. It includes all subjects who received upadacitinib 15 mg QD or upadacitinib 30 mg QD from Studies M16-045(Main Study), M16-047 (Main Study), and M18-891 (Main Study). This analysis set was based on all cumulative exposure.	Long-term (All exposure)	M16-045 M16-047 M18-891	- Upadacitinib 15 mg QD - Upadacitinib 30 mg QD	NA
All Upadacitinib AD Analysis Set[a]	This is a supplemental analysis set that is used to provide counts of rare events (e.g., death) and AEs of special interest in the entire AD program including regional studies. This analysis set includes all subjects who received upadacitinib from the following Phase 2 and 3 studies: M16-048, M16-045 (Main Study), M16-047 (Main Study), M18-891 (Main Study) and M17-377. This analysis set will be based on all cumulative upadacitinib exposure.	Supplemental Long-term (AE only)	M16-045 M16-048 M16-047 M18-891 M17-377	- Upadacitinib 15 mg QD (Phase 3 global and Japan only) - Upadacitinib 30 mg QD (Phase 3 global and Japan only) - Phase 2 All Upadacitinib Doses[c] - Total	NA

Abbreviations: AD = atopic dermatitis; AE = adverse event; NA = not applicable; PBO = placebo; QD = once daily
a. All subjects who received at least one dose of upadacitinib.
b. Treatment comparison for overview of treatment-emergent adverse event (TEAE), overview of treatment-emergent adverse event of special interest (AESI), and potentially clinically significant (PCS) laboratory values.
c. All upadacitinib doses in the Phase 2 study were combined and data are presented as one All Doses group.
Source: Table 3. Clinical Summary of Safety (CSS).

Table 41 shows the Phase 2 and 3 AD studies included in safety analysis sets.

Table 41. Phase 2 and Phase 3 AD Studies Included in Safety Analysis Sets

	M16-045	M16-047	M18-891	M16-048	M17-377
Population	monotherapy	combo with TCS	monotherapy	monotherapy	combo with TCS in Japanese subjects
Treatment Groups (N)	UPA 15 mg QD (281) UPA 30 mg QD (285) Placebo (281)	UPA 15 mg QD (300) UPA 30 mg QD (297) Placebo (303)	UPA 15 mg QD (276) UPA 30 mg QD (282) Placebo (278)	UPA 7.5 mg (42)* UPA 15 mg QD (42) UPA 30 mg QD (42) Placebo (40)	UPA 15 mg QD (91) UPA 30 mg QD (91) Placebo (90)
Placebo Duration (Weeks)	16	16	16	16	16
Included in					
Placebo-Controlled AD Analysis Set	X	X	X	X	
Long-term Upadacitinib Phase 3 AD Analysis Set‡	X	X	X		
All Upadacitinib AD Analysis Set ‡	X	X	X	X†	X

Abbreviations: AD = atopic dermatitis; QD = once daily; TCS = topical corticosteroids; UPA = upadacitinib
* Not included as part of the integrated Placebo-controlled AD Analysis Set.
‡ All subjects who received at least 1 dose of upadacitin b.
† All upadacitinib doses in the Phase 2b study were combined and data are presented as one All Doses group.
Source: CSS Table 1.

Adequacy of the safety database:

The safety database submitted by the Applicant is sufficient to characterize the safety profile of upadacitinib for the treatment of moderate-to-severe AD.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of the data submitted is adequate to characterize the safety and efficacy of upadacitinib.

Categorization of Adverse Events

The adverse events (AEs) were categorized as follows:

- Deaths
- Other Serious Adverse Events (SAEs)
- Adverse events that led to study drug discontinuation
- Other significant adverse events, including
  - Adverse Events of Special Interest (AESI)
  - Acne
- Treatment Emergent Adverse Events and Adverse Reactions
  - Severe Treatment Emergent Adverse Events (TEAEs)
  - Common Treatment Emergent Adverse Events
  - Adverse Drug Reactions (ADRs)
  - Suicidal Ideation and Behavior (SIB)

According to the Applicant, the criteria for potentially clinically significant (PCS) laboratory values was determined by Common Terminology Criteria for Adverse Events (CTCAE) criteria of Grade 2, Grade 3, Grade 4, and ≥ Grade 3 (if applicable), with a grade worsening compared to baseline. Toxicity grading scale was based on National Cancer Institute (NCI) CTCAE version 4.03.

Adverse Event

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

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a

pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study drug, necessitate therapeutic medical intervention, meets protocol specific criteria and/or if the investigator considers them to be AEs.

Treatment Emergent Adverse Event

According to the Applicant, for the Placebo-controlled AD Analysis Set a treatment-emergent adverse event (TEAE) is defined as an AE with an onset date that is on or after the first dose of oral study drug, and no more than 30 days after the last dose of upadacitinib and placebo in the placebo-controlled period. For the long-term analysis sets, a TEAE is defined as an AE with an onset date that is on or after the first dose of upadacitinib and no more than 30 days after the last dose of upadacitinib.

Severity of Adverse Event

According to the Applicant, adverse events were graded based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Toxicity grading scale for laboratory data was based on NCI CTCAE v4.03 instead of v5.0, as some laboratory parameters in v5.0 are provided with only qualitative descriptions of the severity grade, which does not allow for quantitative statistical programming.

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

Mild (Grade 1): Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Moderate (Grade 2): Minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL)

Severe (Grade 3 - 5)

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (Self-care ADL refers to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden)
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Adverse Drug Reaction

In this review, the Adverse Drug Reactions (ADRs) are defined as the TEAEs that are considered by the investigator to have a reasonable possibility of being study drug related.

The Relationship of an AE to the Study Drug

According to the Applicant, the investigators use the following definitions to assess the relationship of the AE to the use of study drug:

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

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

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug are considered "associated." Events assessed as having no reasonable possibility of being related to study drug are considered "not associated." In addition, when the investigator has not reported a causality or deemed it not assessable, the Applicant considers the event associated. If an investigator's opinion of no reasonable possibility of being related to study drug is given, another cause of event must be provided by the investigator for the SAE.

Serious Adverse Events

An SAE was defined as any untoward medical occurrence that results in any of the following outcomes:

- Death
- Life-threatening
- Persistent or significant disability/incapacity
- Hospitalization or prolongation of hospitalization
- Congenital anomaly
- Important medical event requiring medical or surgical intervention to prevent serious outcome

Adverse Events of Special Interest

The safety evaluation plan considered the safety concerns associated with the JAK inhibitor drug class, safety concerns identified from upadacitinib preclinical studies, as well as those of customary regulatory interest for novel small molecule immunomodulatory products. According to this reasoning, the AESIs were:

- serious infection;
- opportunistic infections (excluding TB and herpes zoster);
- herpes zoster;
- active TB;
- malignancy (including NMSC, malignant tumors excluding NMSC, and lymphoma);
- hepatic disorders;
- adjudicated gastrointestinal (GI) perforation;
- adjudicated major adverse cardiovascular event (MACE), defined as cardiovascular (CV) death, non-fatal myocardial infarction [MI] and non-fatal stroke;

- adjudicated venous thromboembolic events (VTE), defined as pulmonary embolism (PE) and deep vein thrombosis (DVT) and other venous and arterial thromboembolic events (non-cardiac, non-neurologic, fatal and non-fatal);
- anemia;
- neutropenia;
- lymphopenia;
- renal dysfunction, and
- creatine phosphokinase (CPK) elevation.

Routine Clinical Tests

During the placebo-controlled and long term studies, the investigators performed safety assessments. The safety data from the placebo-controlled period in the Phase 2b study M16-048 (placebo and upadacitinib 15 mg and 30 mg doses only) and the 3 Phase 3 studies (M16-045, M16-047, M18-891) were pooled for analysis.

The following safety assessments were performed :

- Hematology, clinical chemistry, urinalysis, hsCRP, prothrombin time (PT)
- Urine and serum pregnancy tests for all female subjects of childbearing age
- TB Test (QuantiFERON TB Gold test [or interferon gamma release assay equivalent such as T-SPOT test] and/or local PPD skin test, if required) at screening
- Chest X-ray for TB assessment at screening
- Drug and alcohol screen at screening
- HIV, hepatitis B (HBV), and hepatitis C (HCV) at screening
- Total Serum IgE
- 12-lead electrocardiogram (ECG) at screening
- Vital signs, weight, height
- Physical examination

The safety assessments allowed adequate characterization of safety of upadacitinib.

8.2.4. Safety Results

8.2.4.1. Deaths

There were 2 deaths in the Phase 2b study (Subject (b) (6) and Subject (b) (6)) and one in Phase 3 study M16-045 (Subject (b) (6)). All 3 subjects were treated with upadacitinib 30 mg.

- Subject (b) (6) in Study M16-048, a 63-year-old female with a history of hypertension and asthma who received the following treatment sequence: upadacitinib 30 mg /placebo/rescue upadacitinib 30 mg, had cardiopulmonary arrest and died at home 2

days after the last dose of upadacitinib. No autopsy was performed, and no further information was available.

- Subject (b) (6) in Study M16-048, a 71-year-old male, died approximately 4.5 months after the last dose of upadacitinib due to complications following a cardiac ablation procedure to treat atrial fibrillation. This was considered a non-treatment-emergent death.

- Subject (b) (6) in Study M16-045, a 67-year-old male on upadacitinib 30 mg, died from COVID-19 infection.

8.2.4.2. Serious Adverse Events

PBO-controlled AD Analysis Set (16-Week Mono- and Combination Therapy)

As shown in Table 42, in the PBO-controlled AD Analysis Set, the percentages of subjects with SAEs were similar between the treatment groups. The majority of SAEs were reported in only one subject in each of the treatment groups.

The Applicant reported 5 adult subjects who experienced serious hypersensitivity reactions across the treatment groups, which were reported as anaphylactic reaction and anaphylactic shock (placebo group), hypersensitivity (upadacitinib 15 mg group), and anaphylactic reaction (2 events on upadacitinib 30 mg). None of these events were considered by the investigator to have a reasonable possibility of being related to study drug.

- Subject (b) (6) in Study M16-045 (placebo): a 22-year-old female reported a serious event of anaphylactic shock on Study Day 13. The event was considered by the investigator to have no reasonable possibility of being related to study drug and was due to an allergy to nuts.

- Subject (b) (6) in Study M16-047 (placebo): a 28-year-old male with a medical history of peanut allergy reported a serious event of anaphylactic reaction on Study Day 18. The event was considered by the investigator to have no reasonable possibility of being related to study drug and was due to ingestion of peanuts.

- Subject (b) (6) in Study M16-045 (upadacitinib 15 mg): a 38-year-old male reported a SAE of hypersensitivity on Study Day 9. The event was considered by the investigator to have no reasonable possibility of being related to study drug and was a reaction to an allergen given by his allergy specialist.

- Subject (b) (6) in Study M16-045 (upadacitinib 30 mg): a 23-year-old male with a medical history of anaphylaxis to tree nuts reported a SAE of anaphylactic reaction on Study Day 14. The event was considered by the investigator to have no reasonable

possibility of being related to study drug and was due to accidental ingestion of pesto sauce.

- Subject (b) (6) in Study M16-047 (upadacitinib 30 mg): a 28-year-old female with a medical history of peanut allergy reported a SAE of anaphylactic reaction on Study Day 12 following an exposure to peanuts. The event was considered by the investigator to have no reasonable possibility of being related to study drug.

Additionally, there were 2 subjects in the placebo group who experienced SAE of dermatitis exfoliative generalised.

There were 3 adult subjects who experienced retinal detachment (one in the placebo group and 2 in the upadacitinib 15 mg group). These AEs were reviewed by ophthalmology consultant Dr. Wiley Chambers. Please see further discussion on these AEs later in this review (Section 8.2.5 Analysis of Submission-Specific Safety Issues).

In the adolescent PBO-controlled AD Analysis Set, all SAEs were reported in 1 subject each, with exception of dermatitis atopic.

Table 42. Proportion of Subjects with Serious Adverse Events (PBO-controlled AD Analysis Set)

	Overall Population			Adolescent Population		
Adverse Event	Placebo (N=902) n (%)	UPA 15 mg (N=899) n (%)	UPA 30 mg (N=906) n (%)	Placebo (N=115) n (%)	UPA 15 mg (N=114) n (%)	UPA 30 mg (N=114) n (%)
Any adverse event	26 (2.9)	19 (2.1)	19 (2.1)	3 (2.6)	3 (2.7)	0
Dermatitis atopic	6 (0.7)	1 (0.1)	0	2 (1.7)	1 (0.9)	0
Hypersensitivity[a]	4 (0.4)	1 (0.1)	2 (0.2)	0	0	0
Pneumonia[b]	1 (0.1)	0	2 (0.2)	0	0	0
Retinal detachment[c]	1 (0.1)	2 (0.2)	0	0	0	0
Suicide attempt	1 (0.1)	1 (0.1)	1 (0.1)	0	1 (0.9)	0
Appendicitis	0	3 (0.3)	0	0	0	0
Upper respiratory tract infection[d]	0	2 (0.2)	1 (0.1)	0	0	0
Eczema	2 (0.2)	0	0	0	0	0
Impetigo	1 (0.1)	1 (0.1)	0	0	1 (0.9)	0
Cellulitis	1 (0.1)	0	0	1 (0.9)	0	0
Subcutaneous abscess	1 (0.1)	0	0	1 (0.9)	0	0
Pneumomediastinum	0	1 (0.1)	0	0	1 (0.9)	0

This table lists the AEs that occurred in more than one subject in any treatment group in the overall population, and all AEs occurred in the adolescent population.
a. Includes anaphylactic reaction, anaphylactic shock, dermatitis exfoliative generalised, and hypersensitivity.
b. Includes pneumonia and pneumonia staphylococcal.
c. Includes retinal detachment, retinal tear, and rhegmatogenous retinal detachment.
d. Includes Oropharyngeal pain, Pharyngeal abscess, and Pharyngitis streptococcal.
Source: Tables 1_1.2.2 and 1_1.9.1 in the Applicant's IR Response on 5/3/2021.

Long-term Upadacitinib Phase 3 AD Analysis Set

In the Long-term Upadacitinib Phase 3 AD Analysis Set, the most common SAEs are presented in Table 43. SAEs with the highest Study Size Adjusted Incidence Rate (SSA IR) per 100 Patient Years (PY) were pneumonia and coronavirus infection (30 mg) and dermatitis atopic (15 mg).

Table 43. Serious Adverse Events in Exposure-Adjusted Incidence Rate per 100 Patient Years (Long-term Upadacitinib Phase 3 AD Analysis Set)

	Overall Population		Adolescent Population	
Study Size Adjusted Incidence Rate	**UPA 15 mg (N=1239) [total PY=1373.4] n (SSA IR/100PY)**	**UPA 30 mg (N=1246) [total PY=1414.2] n (SSA IR/100PY)**	**UPA 15 mg (N=167) [total PY=191.7] n (SSA IR/100PY)**	**UPA 30 mg (N=166) [total PY=195.9] n (SSA IR/100PY)**
Any adverse event	71 (5.3)	76 (5.5)	10 (5.3)	6 (3.1)
Dermatitis atopic	7 (0.5)	2 (0.1)	3 (1.6)	1 (0.5)
Pneumonia[a]	2 (0.1)	7 (0.5)	0	1 (0.5)
Herpes zoster[b]	4 (0.3)	2 (0.1)	0	0
Corona virus infection[c]	1 (<0.1)	5 (0.4)	0	0
Hypersensitivity[d]	2 (0.1)	3 (0.2)	0	0
Eczema herpeticum	4 (0.3)	1 (<0.1)	0	0
Depression and suicidality[e]	4 (0.3)	1 (<0.1)	3 (1.6)	0
Retinal detachment[f]	3 (0.2)	1 (<0.1)	0	0
Abortion induced	2 (0.1)	2 (0.1)	0	0
Asthma	2 (0.1)	2 (0.1)	0	0
Upper respiratory tract infection[g]	2 (0.1)	2 (0.1)	0	0
Appendicitis	3 (0.2)	0	0	0
Chest pain	2 (0.1)	1 (<0.1)	0	0
Cerebrovascular accident[h]	2 (0.1)	1 (<0.1)	0	0
Sepsis[i]	0	2 (0.1)	0	1 (0.5)
Herpes simplex[j]	0	2 (0.1)	0	0
Pancreatitis	0	2 (0.1)	0	0
Pyelonephritis	0	2 (0.1)	0	1 (0.5)
Impetigo	2 (0.1)	0	2 (1.0)	0
Eczema infected	1 (<0.1)	1 (<0.1)	1 (0.5)	1 (0.5)
Cataract	0	1 (<0.1)	0	1 (0.5)
Osteomyelitis	0	1 (<0.1)	0	1 (0.5)
Blood creatine phosphokinase (CPK) increased	1 (<0.1)	0	1 (0.5)	0
Cat scratch disease	1 (<0.1)	0	1 (0.5)	0
Bacterial infection	1 (<0.1)	0	1 (0.5)	0
Ovarian cyst	1 (<0.1)	0	1 (0.5)	0
Periorbital cellulitis	1 (<0.1)	0	1 (0.5)	0
Pneumomediastinum	1 (<0.1)	0	1 (0.5)	0

This table lists the AEs that occurred in more than one subject in any treatment group in the overall population, and all AEs occurred in the adolescent population.
a. Includes pneumonia, pneumonia staphylococcal, and pneumonia bacterial.
b. Includes herpes zoster, herpes zoster cutaneous disseminated, and herpes zoster disseminated.
c. Includes corona virus infection and 1 case of “not coded” (PE in the setting of COVID-19 infection).
d. Includes anaphylactic reaction, drug hypersensitivity, hypersensitivity, and toxic epidermal necrolysis.
e. Includes suicidal ideation and suicide attempt.
f. Includes retinal detachment, retinal tear, and rhegmatogenous retinal detachment
g. Includes oropharyngeal pain, pharyngeal abscess, pharyngitis streptococcal and respiratory tract infection viral.
h. Includes cerebrovascular accident, ischaemic stroke, and subarachnoid haemorrhage.

i. Includes sepsis and staphylococcal sepsis.
j. Includes herpes simplex and herpes ophthalmic.
Source: Tables 1_2.2.2 and 1_2.9.1 in the Applicant's IR Response on 5/3/2021.

- Subject (b) (6) in Study M16-045, a 50-year-old female on upadacitinib 15 mg treatment, developed pyodermatitis on Study Day 135. Upadacitinib was stopped, and she was treated with cefadroxyl on Day 135 to 139. On Study Day 140, she developed a SAE of toxic epidermal necrolysis. The event of toxic epidermal necrolysis was not considered to be related to study drug with an alternative etiology of cefadroxyl administration.

- Subject (b) (6) in Study M18-891, a 59-year-old female with a history of AD, hay fever, asthma, and eosinophilic esophagitis, had a SAE of drug hypersensitivity reaction on Day 354-361 of treatment with upadacitinib 30 mg, which resolved with steroid treatment. This event was considered by the investigator to be related to the study drug and the subject was withdrawn from the study.

8.2.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

PBO-controlled AD Analysis Set

Table 44 lists the percentages of subjects with TEAEs leading to discontinuation of study drug in the PBO-controlled AD Analysis Set. The most common TEAEs leading to discontinuation was atopic dermatitis, occurring more frequently in the placebo treatment group than the upadacitinib 15 mg, or 30 mg group.

In the adolescent PBO-controlled AD Analysis Set, TEAEs leading to discontinuation of study drug were rare and mostly occurred in one subject except dermatitis atopic. There were no TEAEs that led to discontinuation in the upadacitinib 30 mg group.

Table 44. Proportion of Subjects with AE that Led to Discontinue of Study Drug (PBO-controlled AD Analysis Set)

	Overall Population			Adolescent Population		
Adverse Event	**Placebo (N=902) n (%)**	**UPA 15 mg (N=899) n (%)**	**UPA 30 mg (N=906) n (%)**	**Placebo (N=115) n (%)**	**UPA 15 mg (N=114) n (%)**	**UPA 30 mg (N=114) n (%)**
Any adverse event	34 (3.8)	21 (2.3)	26 (2.9)	3 (2.6)	3 (2.7)	0
Dermatitis atopic	15 (1.7)	7 (0.8)	3 (0.3)	2 (1.8)	0	0
Hypersensitivity[a]	4 (0.4)	1 (<0.1)	2 (0.2)	1 (0.9)	0	0
Eczema	2 (0.2)	0	1 (<0.1)	0	0	0
Depression and suicidal activity[b]	0	0	2 (0.2)	0	0	0
Neutropenia	0	0	2 (0.2)	0	0	0
Asthma	0	1 (<0.1)	0	0	1 (0.9)	0
Hepatic function abnormal	0	1 (<0.1)	0	0	1 (0.9)	0
Pruritus	0	1 (<0.1)	0	0	1 (0.9)	0

This table lists the AEs that occurred in more than one subject in any treatment group in the overall population, and all AEs occurred in the adolescent population.
a. Includes dermatitis exfoliative generalised, drug hypersensitivity, face oedema, and urticaria.
b. Includes mixed anxiety and depressive disorder and suicide attempt.
Source: Tables 1 _1.3.2 and 1_1.9.2 in the Applicant's IR Response on 5/3/2021.

Long-term Upadacitinib Phase 3 AD Analysis Set

In the Long-term Upadacitinib Phase 3 AD Analysis Set, the TEAE leading to discontinuation of study drug with the highest SSA IR was dermatitis atopic in both the upadacitinib 15 mg (0.5) and 30 mg (1.0) groups. The most common TEAEs leading to discontinuation of study drug are presented in Table 45.

In the adolescent Long-term Upadacitinib Phase 3 AD Analysis Set, TEAEs leading to discontinuation of study drug were rare and mostly occurred in one subject except for dermatitis atopic.

Table 45. TEAE Leading to Discontinuation of Study Drug in Exposure-Adjusted Rate per 100 Patient Years (Long-term Upadacitinib Phase 3 AD Analysis Set)

	Overall Population		Adolescent Population	
Study Size Adjusted Incidence Rate	**UPA 15 mg (N=1239) [total PY=1373.4] n (SSA IR/100PY)**	**UPA 30 mg (N=1246) [total PY=1414.2] n (SSA IR/100PY)**	**UPA 15 mg (N=167) [total PY=191.7] n (SSA IR/100PY)**	**UPA 30 mg (N=166) [total PY=195.9] n (SSA IR/100PY)**
Any Adverse Event	53 (3.9)	67 (4.8)	8 (4.2)	4 (2.0)
Dermatitis atopic	14 (1.0)	7 (0.5)	2 (1.0)	1 (0.5)
Herpes simplex[a]	1 (< 0.1)	4 (0.3)	0	0
Liver function test abnormal[b]	2 (0.1)	3 (0.2)	1 (0.5)	0
Weight increased	2 (0.1)	2 (0.1)	0	0
Hypersensitivity[c]	2 (0.1)	2 (0.1)	0	0
Neutropenia	0	3 (0.2)	0	0
Acne	1 (< 0.1)	2 (0.1)	0	0
Blood CPK increased	1 (< 0.1)	2 (0.1)	0	0
Depression and suicidal activity[d]	1 (< 0.1)	2 (0.1)	1 (0.5)	0
Cerebrovascular accident[e]	2 (0.1)	1 (< 0.1)	0	0
Upper respiratory tract infection[f]	2 (0.1)	1 (< 0.1)	1 (0.5)	0
Corona virus infection[g]	0	2 (0.1)	0	0
Eczema	0	2 (0.1)	0	0
Haemoglobin decreased	0	2 (0.1)	0	0
Asthma	2 (0.1)	0	1 (0.5)	0
Electrocardiogram QT interval abnormal	2 (0.1)	0	1 (0.5)	0
Impetigo	2 (0.1)	0	0	0
Pruritus	2 (0.1)	0	1 (0.5)	0
Pneumonia	1 (< 0.1)	1 (< 0.1)	0	1 (0.5)
Sepsis	0	1 (< 0.1)	0	1 (1.0)
Cardiac murmur	0	1 (< 0.1)	0	1 (0.5)
Osteomyelitis	0	1 (< 0.1)	0	1 (0.5)
Pyoderma	0	1 (< 0.1)	0	1 (0.5)
Pharyngotonsillitis	1 (< 0.1)	0	1 (0.5)	0
Pyrexia	1 (< 0.1)	0	1 (0.5)	0

This table lists the AEs that occurred in more than one subject in any treatment group in the overall population, and all AEs occurred in the adolescent population.
a. Includes herpes ophthalmic and herpes simplex.
b. Includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic function abnormal, and transaminases increased.
c. Includes drug hypersensitivity, face oedema, toxic epidermal necrolysis, and urticaria.
d. Includes depression and mixed anxiety and depressive disorder.
e. Includes cerebrovascular accident, ischaemic stroke, and subarachnoid haemorrhage.
f. Includes pharyngeal abscess, pharyngotonsillitis, and sinusitis
g. Includes corona virus infection and 1 case of "not coded" (PE in the setting of COVID-19 infection).
Source: Tables 1 _2.3.2 and 1_2.9.2 in the Applicant's IR Response on 5/3/2021.

Two events of ECG QT interval abnormal leading to discontinuation were reported in 2 subjects in the upadacitinib 15 mg group:

- Subject (b) (6)/Study M16-047: After database lock, the site confirmed that the QT prolongation reported in this subject was a data entry error.

- Subject (b) (6)/M16-045: A 28-year-old male had QTc Prolongation (QTcF = 420.11 msec vs 350.76 msec at screening), sinus arrhythmia and chest pain on Study Day 366. His chest pain resolved in 3 days. A repeat ECG on Study Day 373 was normal with QTc of 390.26 msec. Study treatment was discontinued on Study Day 382. This event was considered possibly related to the study drug. A repeat ECG after study drug discontinuation was normal. A cardiology evaluation did not reveal any clinically significant findings that required further treatment or evaluation.

8.2.4.4. Other Significant Adverse Events

8.2.4.4.1. Adverse Events of Special Interest

PBO-controlled AD Analysis Set

The Adverse Events of Special Interest are presented in Table 46 for the PBO-controlled AD Analysis Set.

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Table 46. Proportion of Subjects with AESIs (PBO-controlled AD Analysis Set)

	Overall Population			Adolescent Population		
	Placebo (N=902) n (%)	UPA 15 mg (N=899) n (%)	UPA 30 mg (N=906) n (%)	Placebo (N=115) n (%)	UPA 15 mg (N=114) n (%)	UPA 30 mg (N=114) n (%)
MACE, VTE and GI Perforation						
Adjudicated MACE	0	0	0	0	0	0
Adjudicated VTE	1 (0.1)	0	0	0	0	0
Adjudicated gastrointestinal perforation	0	0	0	0	0	0
Malignancies						
All Malignancies	0	3 (0.3)	6 (0.7)	0	0	0
Non-melanoma skin cancer (NMSC)	0	3 (0.3)	2 (0.2)	0	0	0
Malignancy excluding NMSC	0	0	4 (0.4)	0	0	0
Lymphoma	0	0	0	0	0	0
Infections						
All Infections	271 (30.0)	348 (38.7)	390 (43.1)	27 (23.5)	47 (41.3)	54 (47.5)
Opportunistic infection excluding tuberculosis and herpes zoster	4 (0.4)	7 (0.8)	12 (1.3)	0	0	0
Serious infection	5 (0.6)	7 (0.8)	4 (0.4)	1 (0.9)	1 (0.9)	0
Herpes zoster	5 (0.6)	14 (1.6)	14 (1.5)	0	1 (0.9)	3 (2.6)
Active tuberculosis	0	0	0	0	0	0
Abnormal Laboratory Values						
Anemia	4 (0.4)	3 (0.3)	13 (1.4)	0	1 (0.9)	0
Neutropenia	3 (0.3)	10 (1.1)	26 (2.9)	1 (0.9)	2 (1.8)	6 (5.3)
Lymphopenia	3 (0.3)	2 (0.2)	3 (0.3)	0	0	0
Creatine phosphokinase (CPK) elevation	21 (2.3)	41 (4.6)	50 (5.5)	3 (2.6)	6 (5.3)	9 (7.9)
Renal dysfunction	0	1 (0.1)	0	0	0	0
Liver function test abnormal	12 (1.3)	14 (1.6)	12 (1.3)	0	5 (4.3)	0

Opportunistic infection includes oral candidiasis.
Source: Integrated Summary of Safety (ISS) Table 2.4__1.2.1 and 2.4__1.6.3.1.

Long-term Upadacitinib Phase 3 AD Analysis Set

Adverse Events of Special Interest are presented in Table 47 for the Long-term Upadacitinib Phase 3 AD Analysis Set in Study Size Adjusted Incidence Rate (SSA IR).

Table 47. AESI in Exposure-Adjusted Rate per 100 Patient Years (Long-term Upadacitinib Phase 3 AD Analysis Set)

	Overall Population		Adolescent Population	
Study Size Adjusted Incidence Rate	**UPA 15 mg (N=1239) [total PY=1373.4] n (SSA IR/100PY)**	**UPA 30 mg (N=1246) [total PY=1414.2] n (SSA IR/100PY))**	**UPA 15 mg (N=167) [total PY=191.7] n (SSA IR/100PY)**	**UPA 30 mg (N=166) [total PY=195.9] n (SSA IR/100PY)**
MACE, VTE and GI Perforation				
Adjudicated MACE	2 (0.1)	1 (<0.1)	0	0
Adjudicated VTE	1 (<0.1)	1 (<0.1)	0	0
Adjudicated gastrointestinal perforation	0	0	0	0
Malignancies				
All Malignancies	7 (0.5)	12 (0.9)	0	0
Malignancy excluding NMSC	3 (0.2)	7 (0.5)	0	0
Non-melanoma skin cancer (NMSC)	4 (0.3)	5 (0.4)	0	0
Lymphoma	0	1 (<0.1)	0	0
Infections				
All Infections	642 (80.2)	711 (94.3)	84 (73.3)	99 (100.7)
Serious infection	26 (1.9)	30 (2.1)	4 (2.1)	4 (2.1)
Opportunistic infection excluding tuberculosis and herpes zoster	23 (1.7)	27 (1.9)	1 (0.5)	1 (0.5)
Herpes zoster	46 (3.4)	69 (5.0)	2 (1.1)	7 (3.7)
Active tuberculosis	1 (<0.1)	1 (<0.1)	0	0
Abnormal Laboratory Values				
Anemia	14 (1.0)	34 (2.4)	4 (2.1)	2 (1.0)
Neutropenia	21 (1.5)	32 (2.3)	5 (2.6)	9 (4.9)
Lymphopenia	3 (0.2)	8 (0.6)	0	0
Creatine phosphokinase (CPK) elevation	74 (5.7)	123 (9.3)	10 (5.6)	20 (11.2)
Renal dysfunction	1 (<0.1)	2 (0.1)	0	0
Liver function test abnormal	48 (3.6)	58 (4.2)	9 (5.0)	3 (1.6)

Opportunistic infection includes oral candidiasis.
Source: Table 2 in the Applicant's IR Response on 4/7/2021.

Reviewer's comments:

The SSA IRs were significantly higher (difference >1) in the upadacitinib 30mg group than the 15mg group for infection for herpes zoster, hepatic disorder, anemia, and CPK elevation. We recommend periodic laboratory testing for close safety monitoring during treatment with upadacitinib.

8.2.4.4.1.1. Infection

Overall, treatment with upadacitinib was associated with an increase in the rate of infections in a dose-dependent pattern, in both the PBO-controlled and Long-term Upadacitinib Phase 3 AD Analysis Sets, which was consistent with the findings from the rheumatoid arthritis studies.

8.2.4.4.1.2. Serious infection

As shown in Table 48, the PBO-controlled AD Analysis Set, the percentages of subjects who experienced serious infections were similar across the upadacitinib 30 mg, upadacitinib 15 mg, and placebo groups. Appendicitis was the only serious infection reported in > 1 subjects in any treatment group [upadacitinib 15 mg group (n = 3)].

In the adolescent population, one subject experienced serious infection in the placebo group and upadacitinib 15mg group, none in the 30 mg group.

Table 48. Number and Percentage of Subjects with Serious Infections (PBO-controlled AD Analysis Set)

	Overall Population			Adolescent Population		
Adverse Event	**PBO (N = 902) n (%)**	**UPA 15 mg (N = 899) n (%)**	**UPA 30 mg (N = 906) n (%)**	**PBO (N = 115) n (%)**	**UPA 15 mg (N = 114) n (%)**	**UPA 30 mg (N = 114) n (%)**
Any adverse event	5 (0.6)	7 (0.8)	4 (0.4)	1 (0.9)	1 (0.9)	0
Anal abscess	1 (0.1)	0	0	0	0	0
Appendicitis	0	3 (0.3)	0	0	0	0
Cellulitis	1 (0.1)	0	0	1 (0.9)	0	0
Eczema herpeticum	0	1 (0.1)	0	0	0	0
Impetigo	1 (0.1)	1 (0.1)	0	0	1 (0.9)	0
Orchitis	0	0	1 (0.1)	0	0	0
Peritonsillar abscess	0	1 (0.1)	0	0	0	0
Pharyngeal abscess	0	0	1 (0.1)	0	0	0
Pharyngitis streptococcal	0	1 (0.1)	0	0	0	0
Pneumonia	1 (0.1)	0	1 (0.1)	0	0	0
Pneumonia staphylococcal	0	0	1 (0.1)	0	0	0
Staphylococcal sepsis	1 (0.1)	0	0	0	0	0
Subcutaneous abscess	1 (0.1)	0	0	1 (0.9)	0	0
Urinary tract infection	1 (0.1)	0	0	0	0	0

Source: CSS Table 33.

In the Long-term Upadacitinib Phase 3 AD Analysis Set (Table 49), most of the serious infections were reported in 1 or 2 subjects in each treatment group. The SSA IRs were similar between the upadacitinib 15 mg and 30 mg groups for the overall and adolescent populations.

Table 49. Serious Infection in Exposure-Adjusted Rate per 100 Patient Years (Long-term Upadacitinib Phase 3 AD Analysis Set)

	Overall Population		Adolescent Population	
Study Size Adjusted Incidence Rate	**UPA 15 mg (N=1239) [total PY=1373.4] n (SSA IR/100PY)**	**UPA 30 mg (N=1246) [total PY=1414.2] n (SSA IR/100PY))**	**UPA 15 mg (N=167) [Total PYR=191.7] n (SSA IR/100PY)**	**UPA 30 mg (N=166) [Total PYR=195.9] n (SSA IR/100PY)**
Any adverse event	26 (1.9)	30 (2.1)	4 (2.1)	4 (2.1)
Corona virus infection	1 (<0.1)	5 (0.4)	0	0
Pneumonia	2 (0.1)	5 (0.4)	0	1 (0.5)
Herpes zoster[a]	4 (0.3)	2 (0.1)	0	0
Herpes simplex	0	2 (0.1)	0	0
Pyelonephritis	0	2 (0.1)	0	1 (0.5)
Eczema herpeticum	4 (0.3)	1 (<0.1)	0	0
Eczema infected	1 (<0.1)	1 (<0.1)	1 (0.5)	1 (0.5)
Osteomyelitis	0	1 (<0.1)	0	1 (0.5)
Staphylococcal sepsis	0	1 (<0.1)	0	1 (0.5)
Appendicitis	3 (0.2)	0	0	0
Impetigo	2 (0.1)	0	2 (1.0)	0
Periorbital cellulitis	1 (<0.1)	0	1 (0.5)	0

This table lists the AEs that occurred in more than one subject in any treatment group in the overall population, and all AEs occurred in the adolescent population.
a. Includes herpes zoster, herpes zoster disseminated, and herpes zoster cutaneous disseminated.
Source: Table 1__2.1.2.2 in the Applicant's IR Response on 4/7/2021.

8.2.4.4.1.3. Opportunistic Infections:

In the PBO-controlled AD Analysis Set, all treatment-emergent opportunistic infections (TEOIs) excluding TB and herpes zoster were oral candidiasis and eczema herpeticum or the synonymous Kaposi's varicelliform eruption (KVE), none of which occurred in the adolescent population, as is shown in Table 50.

Table 50. Proportion of Subjects with Opportunistic Infections in the PBO-controlled AD Analysis Set

	Overall Population			Adolescent Population		
	Placebo (N=902) n (%)	**UPA 15 mg (N=899) n (%)**	**UPA 30 mg (N=906) n (%)**	**Placebo (N=115) n (%)**	**UPA 15 mg (N=114) n (%)**	**UPA 30 mg (N=114) n (%)**
Opportunistic infection, excluding tuberculosis and herpes zoster	4 (0.4)	7 (0.8)	12 (1.3)	0	0	0
Oral candidiasis	0	1 (0.1)	5 (0.6)	0	0	0
Eczema herpeticum	4 (0.4)	6 (0.7)	7 (0.8)	0	0	0

Source: Created from the submitted data.

In the Long-term Upadacitinib Phase 3 AD Analysis Set (Table 51), most of the TEOIs excluding TB and herpes zoster were oral candidiasis and eczema herpeticum, with an additional event of oesophageal candidiasis.

In the adolescent Long-term Upadacitinib Phase 3 AD Analysis Set, one incidence of TEOI occurred in 15 mg group and 30 mg group, respectively.

Table 51. Opportunistic Infection in Exposure-Adjusted Rate per 100 Patient Years in Long-term Upadacitinib Phase 3 AD Analysis Set

	Overall Population		Adolescent Population	
Study Size Adjusted Incidence Rate	**UPA 15 mg (N=1239) [total PY=1373.4] n (SSA IR/100PY)**	**UPA 30 mg (N=1246) [total PY=1414.2] n (SSA IR/100PY)**	**UPA 15 mg (N=167) [Total PYR=191.7] n (SSA IR/100PY)**	**UPA 30 mg (N=166) [Total PYR=195.9] n (SSA IR/100PY)**
Opportunistic infection, excluding tuberculosis and herpes zoster	23 (1.7)	27 (1.9)	1 (0.5)	1 (0.5)
Oral candidiasis	3 (0.2)	7 (0.5)	0	0
Eczema herpeticum	20 (1.4)	19 (1.4)	1 (0.5)	1 (0.5)
Oesophageal candidiasis	0	1 (<0.1)	0	0

Source: Table 1__2.1.3.2 in the Applicant's IR Response on 4/7/2021

8.2.4.4.1.4. Herpes Zoster

The rates of herpes zoster (HZ) in the PBO-controlled AD Analysis Set are shown in Table 52. Upadacitinib treatment was associated with increased rates of HZ. No serious TEAEs of herpes zoster were reported. Most events of herpes zoster were mild or moderate in severity, and were considered by the investigator to have a reasonable possibility of being related to study drug. No subjects discontinued study drug due to a treatment-emergent event of HZ.

Table 52. Proportion of Subjects with Herpes Zoster (PBO-controlled AD Analysis Set)

	Overall Population			Adolescent		
	Placebo (N=902) n (%)	**UPA 15 mg (N=899) n (%)**	**UPA 30 mg (N=906) n (%)**	**Placebo (N=115) n (%)**	**UPA 15 mg (N=114) n (%)**	**UPA 30 mg (N=114) n (%)**
Herpes zoster	5 (0.6)	14 (1.6)	14 (1.5)	0	1 (0.9)	3 (2.6)

Source: Table 1__1.1.7.2 in the Applicant's IR Response on 4/7/2021

The rates of herpes zoster in the Long-term Upadacitinib Phase 3 AD Analysis Set are shown in Table 53. Higher rate of HZ occurred in the upadacitinib 30mg group.

Table 53. Herpes Zoster in Exposure-Adjusted Rate per 100 Patient Years (Long-term Upadacitinib Phase 3 AD Analysis Set)

	Overall Population		Adolescent Population	
Study Size Adjusted Incidence Rate	**UPA 15 mg (N=1239) [total PY=1373.4] n (SSA IR/100PY)**	**UPA 30 mg (N=1246) [total PY=1414.2] n (SSA IR/100PY)**	**UPA 15 mg (N=167) [Total PYR=191.7] n (SSA IR/100PY)**	**UPA 30 mg (N=166) [Total PYR=195.9] n (SSA IR/100PY)**
Any adverse event	46 (3.4)	69 (5.0)	2 (1.1)	7 (3.7)
Herpes zoster	44 (3.3)	62 (4.5)	2 (1.1)	6 (3.1)
Ophthalmic herpes zoster	0	4 (0.3)	0	1 (0.5)
Herpes zoster cutaneous disseminated	1 (<0.1)	2 (0.1)	0	0
Post herpetic neuralgia	2 (0.1)	1 (<0.1)	0	0
Herpes zoster disseminated	1 (<0.1)	1 (<0.1)	0	0
Herpes zoster oticus	0	1 (<0.1)	0	0

Source: Table 1__2.1.7.2 in the Applicant's IR Response on 4/7/2021

8.2.4.4.1.5. Active TB

In the PBO-controlled AD Analysis Set, there were no reports of active TB.

In the Long-term Upadacitinib Phase 3 AD Analysis Set, two cases of active TB were reported, one in each upadacitinib treatment groups.

No adolescent subjects developed active TB during upadacitinib AD program.

8.2.4.4.1.6. Malignancy

In the PBO-controlled Analysis Set, all malignancies excluding NMSC were reported in the upadacitinib 30 mg group (4 subjects, 0.4%). One of the NMSC in the upadacitinib 30 mg group was reported as mycosis fungoides (cutaneous T-cell lymphoma - CTCL). However, after database lock, the study site confirmed the event term was entered in error and the actual event was a fungal infection – mycosis inguinalis.

The specific malignancies excluding NMSC are listed in Table 54. None of the malignancies were assessed by the investigator as having a reasonable possibility of being related to study drug.

Table 54. Number and Percentage of Subjects with Treatment-Emergent Malignancy Excluding NMSC (PBO-controlled AD Analysis Set)

	Overall Population			Adolescent		
	PBO (N = 902) n (%)	UPA 15 mg (N = 899) n (%)	UPA 30 mg (N = 906) n (%)	PBO (N = 115) n (%)	UPA 15 mg (N = 114) n (%)	UPA 30 mg (N = 114) n (%)
Any adverse event	0	0	4 (0.4)	0	0	0
Adenocarcinoma of colon	0	0	1 (0.1)	0	0	0
Anal squamous cell carcinoma	0	0	1 (0.1)	0	0	0
Gastric cancer	0	0	1 (0.1)	0	0	0
Invasive ductal breast carcinoma	0	0	1 (0.1)	0	0	0

Source: Modified from CSS Table 41

The malignancies diagnosed in the Long-term Upadacitinib Phase 3 AD Analysis Set are listed in Table 55.

Table 55. Treatment-Emergent Malignancy EAIR Per 100 PY in the Overall Population and Day of Upadacitinib Exposure at Diagnosis (Long-term Upadacitinib Phase 3 AD Analysis Set)

	UPA 15 mg (N = 1239) n (n/100PY) (Day of UPA Exposure)	UPA 30 mg (N = 1246) n (n/100PY) (Day of UPA Exposure)
Malignancy Excluding NMSC		
Any Adverse Events	3 (0.2)	7 (0.5)
Adenocarcinoma of colon	0	1 (< 0.1) (Day 7)
Anal squamous cell carcinoma	0	1 (< 0.1) (Day 64)
Gastric cancer	0	1 (< 0.1) (Day 36)
Invasive ductal breast carcinoma	0	1 (< 0.1) (Day 25)
Clear cell renal cell carcinoma	0	1 (< 0.1) (Day 205)
Endometrial adenocarcinoma	0	1 (< 0.1) (Day 515)
Malignant melanoma in situ	0	1 (< 0.1) (Day 233- present prior to study entry)
Squamous cell carcinoma of the oral cavity	1 (< 0.1) (Day 319)	0
Breast cancer	1 (< 0.1) (Day 407)	0
Adenocarcinoma of colon	1 (< 0.1) (Day 437)	0
NMSC		
Cutaneous T-cell lymphoma	0	1 (< 0.1) (Day 194)
Keratoacanthoma	0	1 (<0.1) (Day 45)
Basal cell carcinoma	1 (< 0.1) (Day 22)	1 (<0.1) (Day 610)
Squamous cell carcinoma of skin	2 (0.1) (Day 21/113)	2 (0.1) (Day 322/218)
Bowen's disease	1 (< 0.1) (Day 7)	0

Source: Modified from SUR Tables 17 and 34.

In the Long-term Upadacitinib Phase 3 AD Analysis Set, Subject (b) (6) in Study M18-891, a 52-year-old female had confirmed cutaneous T cell lymphoma (CTCL) on Day 194 of treatment with upadacitinib 30 mg. The study drug was discontinued. The Applicant stated that medical review of this case indicates that the subject likely had CTCL at baseline based on the clinical history and histological findings. The event was assessed by the investigator as having no reasonable possibility of being related to study drug.

In addition to the case in the Phase 3 studies, there was an additional event of CTCL (mycosis fungoides) reported in the Phase 2b study: Subject (b) (6) in Study M16-048, a 38-year-old male, was diagnosed with CTCL on Study Day 574. The subject was initially on upadacitinib 15

mg until Study Day 146, followed by upadacitinib 30 mg until Study Day 574 when the study drug was permanently discontinued. The event was assessed by the investigator as having no reasonable possibility of being related to study drug. However, this reviewer considers this case of CTCL as possibly associated with the study drug treatment considering the duration of drug exposure before the diagnosis of CTCL.

No events of malignancies were reported in adolescent subjects.

Reviewer's Comments:
Cases of adenocarcinoma of colon, anal squamous cell carcinoma, gastric cancer, and invasive ductal breast carcinoma were diagnosed within 64 days of study drug exposure. Due to the short duration of exposure, it is unlikely that these cases were associated with the study drug treatment.

8.2.4.4.1.7. Hepatic Disorders

In both PBO-controlled and the Long-term Upadacitinib Phase 3 AD Analysis sets, transaminase elevations usually resolved or were resolving with study drug ongoing or temporary interruption. No hepatic events were reported as serious. Study drug discontinuation due to abnormal liver function tests occurred in one subject in the 15 mg treatment group in the PBO-controlled Upadacitinib Phase 3 AD Analysis set; two subjects in the 15 mg treatment group and 3 subjects in the 30 mg treatment group in the Long-term Upadacitinib Phase 3 AD Analysis set. No subjects were identified as meeting biochemical criteria for Hy's Law in the PBO-controlled AD Analysis set.

As shown in Table 56, the percentages of subjects with ALT or AST ≥ 5 × ULN were less than 1% in both upadacitinib treatment groups.

In the PBO-controlled Upadacitinib Phase 3 AD Analysis set, the percentages of subjects with transaminase elevations were similar across the treatment groups.

Table 56. Number and Percentage of Subjects Meeting Criteria for Liver-Related Elevations (PBO-controlled AD Analysis Set)

	Overall Population			Adolescent Population		
	PBO (N = 902) n/N_OBS (%)	UPA 15 mg (N = 899) n/N_OBS (%)	UPA 30 mg (N = 906) n/N_OBS (%)	PBO (N = 115) n/N_OBS (%)	UPA 15 mg (N = 114) n/N_OBS (%)	UPA 30 mg (N = 114) n/N_OBS (%)
ALT ≥ 3 × ULN	10/897 (1.1)	6/896 (0.7)	13/904 (1.4)	1/114 (0.9)	1/114 (0.9)	0
ALT ≥ 5 × ULN	2/897 (0.2)	2/896 (0.2)	2/904 (0.2)	0	1/114 (0.9)	0
ALT ≥ 10 × ULN	0	0	0	0	0	0
ALT ≥ 20 × ULN	0	0	0	0	0	0
AST ≥ 3 × ULN	8/897 (0.9)	11/895 (1.2)	10/904 (1.1)	0	2/114 (1.8)	1/114 (0.9)
AST ≥ 5 × ULN	3/897 (0.3)	4/895 (0.4)	5/904 (0.6)	0	0	0
AST ≥ 10 × ULN	3/897 (0.3)	1/895 (0.1)	3/904 (0.3)	0	0	0
AST ≥ 20 × ULN	0	0	1/904 (0.1)	0	0	0
TBL ≥ 2 × ULN	0	8/896 (0.9)	8/904 (0.9)	0	2/114 (1.8)	1/114 (0.9)
ALP ≥ 1.5 × ULN	1/897 (0.1)	0	3/904 (0.3)	1/114 (0.9)	0	1/114 (0.9)
ALT and/or AST ≥ 3 × ULN and concurrent TBL ≥ 1.5 × ULN	0	0	1/904 (0.1)	0	0	0
ALT and/or AST ≥ 3 × ULN and concurrent TBL ≥ 2 × ULN	0	0	0	0	0	0

Source: CSS Table 44.

In the Long-term Upadacitinib Phase 3 AD Analysis set, transient transaminase elevations were observed in subjects treated with upadacitinib (Table 57). In the overall population, the proportion of subjects with transaminase elevation ≥ 3 × ULN was higher in the upadacitinib 30 mg group compared to 15mg group.

Table 57. Number and Percentage of Subjects Meeting Criteria for Liver-Related Elevations (Long-term Upadacitinib Phase 3 AD Analysis Set)

	Overall Population		Adolescent Population	
	UPA 15 mg (N = 1239) n/N_OBS (%)	UPA 30 mg (N = 1246) n/N_OBS (%)	UPA 15 mg (N = 167) n/N_OBS (%)	UPA 30 mg (N = 166) n/N_OBS (%)
ALT ≥ 3 × ULN	25/1232 (2.0)	38/1241 (3.1)	2/166 (1.2)	0
ALT ≥ 5 × ULN	5/1232 (0.4)	9/1241 (0.7)	1/166 (0.6)	0
ALT ≥ 10 × ULN	0	1/1241 (< 0.1)	0	0
ALT ≥ 20 × ULN	0	1/1241 (< 0.1)	0	0
AST ≥ 3 × ULN	19/1231 (1.5)	35/1241 (2.8)	5/166 (3.0)	3/165 (1.8)
AST ≥ 5 × ULN	8/1231 (0.6)	16/1241 (1.3)	1/166 (0.6)	0
AST ≥ 10 × ULN	2/1231 (0.2)	7/1241 (0.6)	0	0
AST ≥ 20 × ULN	1/1231 (<0.1)	2/1241 (0.2)	0	0
TBL ≥ 2 × ULN	13/1232 (1)	16/1241 (1.3)	5/166 (1.2)	2/165 (1.2)
ALP ≥ 1.5 × ULN	4/1233 (0.3)	8/1242 (0.6)	2/166 (1.2)	4/166 (2.4)
ALT and/or AST ≥ 3 × ULN and concurrent TBL ≥ 1.5 × ULN	0	2/1241 (0.2)	0	0
ALT and/or AST ≥ 3 × ULN and concurrent TBL ≥ 2 × ULN	0	0	0	0

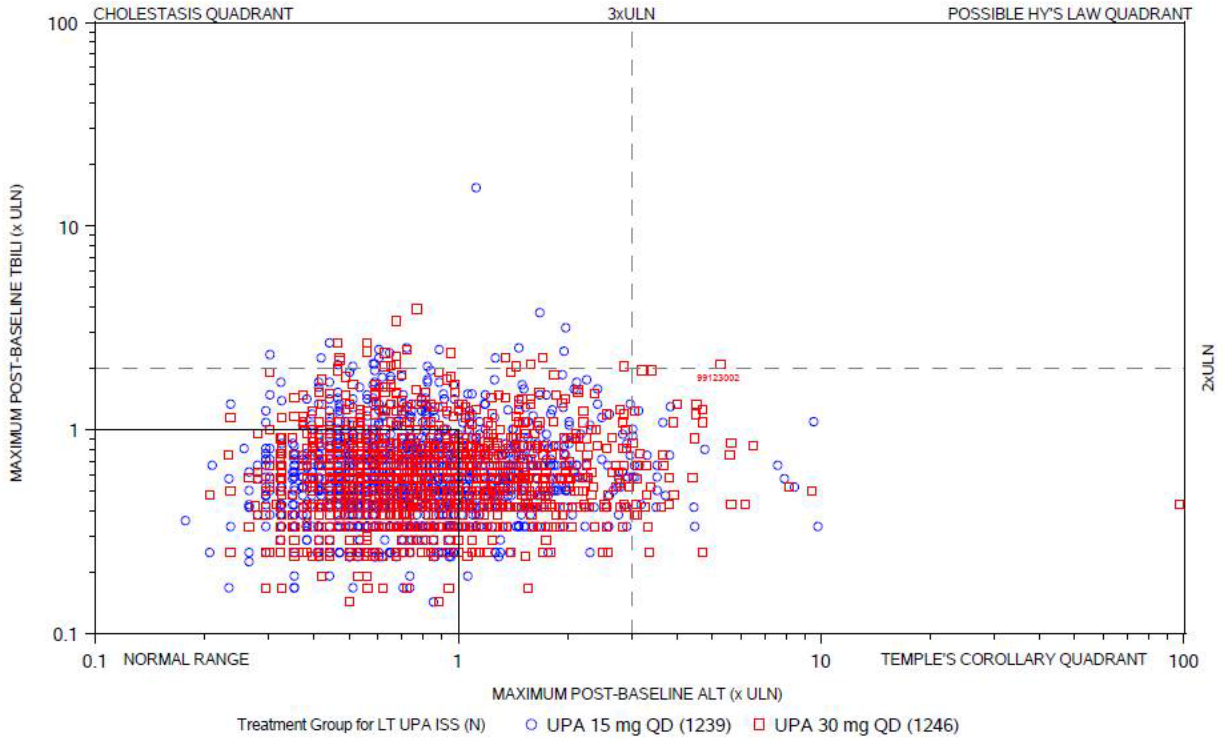
Source: SUR Table 19.

In the Long-term Upadacitinib Phase 3 AD Analysis set, one subject was identified as possibly meeting biochemical criteria for possible Hy's Law while on upadacitinib 30 mg (see Figure 14).

Subject [redacted] (b) (6) in Study M16-047, a 35 year-old male, experienced herpes zoster on Day 128 of upadacitinib treatment (UPA Day 128), and was treated with amenamevir (antiviraldrug), loxoprofen (non-steroidal anti-inflammatory drug), and teprenone (anti-gastric ulcer drug). He was later treated with loxoprofen and teprenone again for post-herpetic neuralgia on UPA Day 162-192. At baseline, he had normal AST value of 27 U/L (ULN at 36 U/L), but had elevated ALT value at 52 U/L (ULN at 43 U/L) and elevated bilirubin value at 34 U/L (ULN at 20.5 U/L). On UPA Day 249, he had elevated ALT of 227 U/L (ULN at 43 U/L), AST of 112 U/L (ULN at 36 U/L), but his bilirubin was 24 U/L which was lower that his baseline level. On UPA Day 585, his bilirubin was elevated at 43 U/L (≥ 2 × ULN), but his ALT was < 3 × ULN at 75 U/L (ULN at 43 U/L), and

AST was within the normal range at that time. According to the Applicant, no gastrointestinal AEs were reported for this subject. This reviewer agrees that this case was unlikely a true Hy's Law case. This subject had elevated baseline ALT and bilirubin levels, and the concomitant treatments with amenamevir, loxoprofen and teprenone for herpes zoster and post-herpetic neuralgia most likely have contributed to the elevated ALT and AST on UPA Day 249. In addition, the LFT's improved with continued upadacitinib treatment.

Figure 14. eDISH Plot of Maximum Postbaseline Total Bilirubin Versus Maximum Post-baseline ALT (Long-term Upadacitinib Phase 3 AD Analysis Set)



Abbreviations: AD = atopic dermatitis; ALT = alanine aminotransferase; LT = long-term; QD = once daily; TBILI = total bilirubin; ULN = upper limit of normal; UPA = upadacitinib

No consistent pattern of treatment effects among the treatment groups in adolescent population in both the PBO-controlled and the Long-term Upadacitinib Phase 3 AD Analysis set.

8.2.4.4.1.8. GI Perforation

Per the Applicant, no treatment-emergent adjudicated GI perforation was reported in the AD clinical program.

8.2.4.4.1.9. Thrombosis

Venous thromboembolic events were defined as DVT and fatal/non-fatal pulmonary embolism (PE). In the overall AD program, 3 adjudicated VTE events were reported in subjects on upadacitinib.

One case of PE was reported in the Phase 2b Study:
Subject (b) (6) in Study M16-048 (upadacitinib 30 mg), a 69-year-old female with a history of hypertension, hypercholesterolemia, ischemic heart disease, obesity, and current smoker, had PE on Study Day 463 while on 30 mg of upadacitinib. No DVT was found. The event was assessed as having no reasonable possibility of being related to study drug by the investigator and sponsor. However, this reviewer assesses that upadacitinib cannot be completely excluded as a cause of PE in this subject.

Two cases of VTE were reported in the Long-term Upadacitinib Phase 3 AD Analysis Set:

- Subject (b) (6) in Study M16-045, a 41 year old female with a history of prothrombin (Factor II) 20210G A mutation, prior history of DVT and PE, obesity, hypertension, smoking and family history of blood clot in leg, developed a DVT in the left lower extremity on Day 250 of 15mg upadacitinib treatment. Study drug was discontinued. Investigator assessed the event of DVT as having a reasonable possibility of being related to the study drug.

- Subject (b) (6) in Study M18-891, a 70 year old female with a history of PE, diabetes mellitus and prolonged immobilization, was diagnosed with pulmonary embolism in the setting of COVID-19 infection on Day 384 of 30mg upadacitinib treatment. The study drug was discontinued. The event was assessed as having no reasonable possibility of being related to study drug by the investigator.

In addition, one case each of PE and one case of arterial thrombosis was reported in subjects on placebo.

- Subject (b) (6) in Study M18-891 (placebo), a 22-year-old female with a medical history of oral contraceptive use, experienced a PE on Study Day 55. Study treatment was discontinued.

- Subject (b) (6) in Study M16-047 (placebo), a 65-year-old female with a history of peripheral arterial disease status post bilateral thrombectomy, experienced a thrombosis of right lower extremity arterial stent Study Day 58. No action was taken with study treatment.

No adolescent subjects had a treatment-emergent adjudicated VTE in the upadacitinib AD clinical program.

No adjudicated arterial thrombosis event occurred in subjects receiving upadacitinib through the data cutoff date.

8.2.4.4.1.10. MACE

In the PBO-controlled AD Analysis Set, no subject had a treatment-emergent MACE.

In the Long-term upadacitinib Phase 3 AD analysis Set, one subject on upadacitinib 30 mg and 2 subjects on upadacitinib 15 mg experienced an adjudicated MACE with incidence rates of < 0.1 n/100 PY and 0.2 n/100 PY for upadacitinib 30 mg and 15 mg, respectively.

- Subject (b) (6) in Study M16-045, a 68 year old male with a history of uncontrolled hypertension, smoking and family history of stroke, experienced non-fatal ischemic stroke (acute lunar infarcts on MRI) on Day 9 of 15mg upadacitinib treatment. Study drug was discontinued. The event was assessed as having no reasonable possibility of being related to study drug by the investigator.

- Subject (b) (6) in Study M16-047, a 60 year old male with a history of hyperlipidemia, had subarachnoid hemorrhage on Day 268 of 15mg upadacitinib treatment. Study drug was discontinued. The event was assessed as having no reasonable possibility of being related to study drug by the investigator.

- Subject (b) (6) in Study M16-047, a 69 year old male, with a history of high cholesterol, diabetes, hypertension, congestive heart failure, and angioplasty heart stents, had a left subacute ischemic stroke on Day 328 of 30mg upadacitinib treatment. Study drug was discontinued. The event was assessed as having no reasonable possibility of being related to study drug by the investigator.

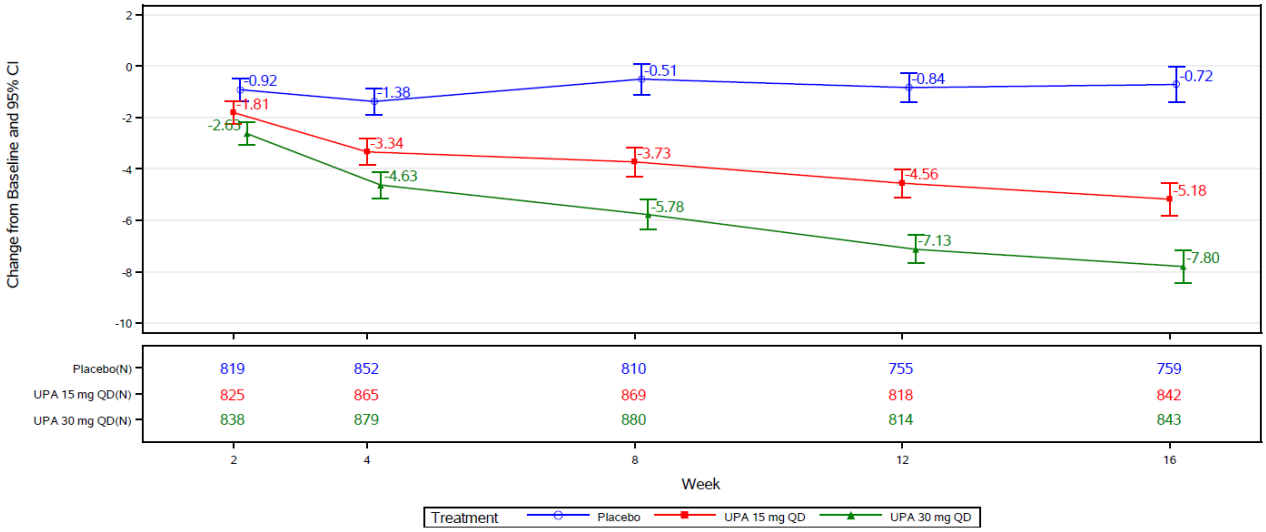
This reviewer assesses that although these subjects had significant medical co-morbidities, upadacitinib cannot be completely excluded as a cause or contributor of these MACE events.

An additional case of MACE event occurred in the Japan regional study. Subject (b) (6) in Study M17-377, a 22 year old male, had a cerebellar hemorrhage on Day 65 of 15mg upadacitinib treatment. Study drug was discontinued. The event was assessed as having a reasonable possibility of being related to study drug by the investigator.

8.2.4.4.1.11. Anemia

The Applicant reported that the mean hemoglobin values decreased in a dose-dependent pattern over the first 16 weeks of upadacitinib 30 mg and 15 mg treatment, and then improved towards baseline and stabilized with continued treatment, as shown in Figure 15 and Figure 16 below.

Figure 15. Plot of Mean Change from Baseline in Selected Laboratory Values (Placebo-Controlled AD Analysis Set)



Within group least square means and 95% CI are displayed in this figure, based on ANCOVA analysis with treatment, baseline, and study in the model.
Baseline is defined as the last non-missing value prior to the first dose of study drug or randomization if no study drug is given.
Subjects with non-missing baseline and at least one post-baseline value are included in the analyses.
Source: CSS Figure 3.

In the PBO-controlled Analysis Set, Grade 3 hemoglobin decreases (hemoglobin < 8.0 g/dL) occurred in one subject in the 30mg group (0.1%). No Grade 4 hemoglobin decrease in any of the treatment groups was reported.

As shown in Table 58, TEAEs of anemia were similar in the placebo and upadacitinib 15 mg groups, but higher in the upadacitinib 30 mg group. One event of anemia was serious and 2 led to discontinuation of study drug in subjects on upadacitinib 30 mg.

Table 58. Number and Percentage of Subjects with Treatment-Emergent Anemia (Placebo-Controlled AD Analysis Set)

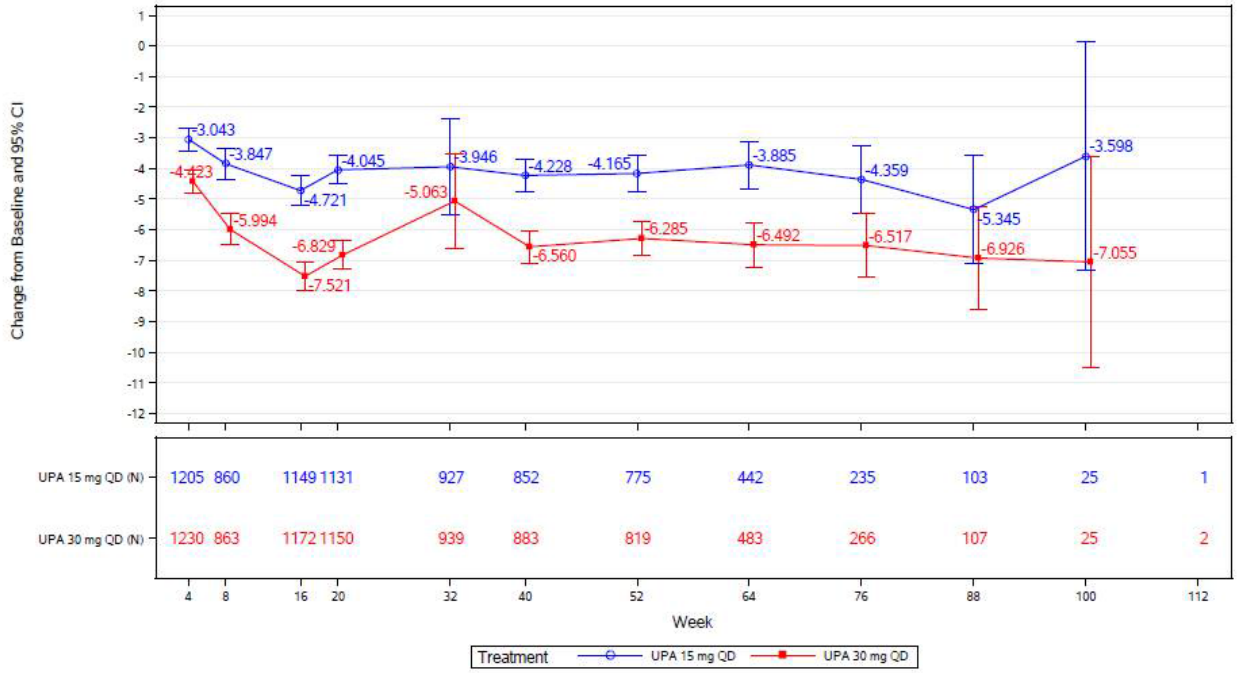
	Overall Population			Adolescent Population		
	Placebo (N=902) n (%)	UPA 15 mg (N=899) n (%)	UPA 30 mg (N=906) n (%)	Placebo (N=115) n (%)	UPA 15 mg (N=114) n (%)	UPA 30 mg (N=114) n (%)
Any adverse event	4 (0.4)	3 (0.3)	13 (1.4)	0	1 (0.9)	0
Anaemia	2 (0.2)	2 (0.2)	9 (1.0)	0	0	0
Iron deficiency anaemia	1 (0.1)	0	1 (0.1)	0	0	0
Haemoglobin decreased	1 (0.1)	1 (0.1)	3 (0.3)	0	1 (0.9)	0

Source: Modified from ISS Tables 2.4__1.3.17.11. and 2.4__1.6.7.11.

In the Long-term Upadacitinib Phase 3 AD Analysis Set, the decrease in mean hemoglobin from baseline was greater in the upadacitinib 30 mg group than the 15 mg group (Figure 16). At Week 64, the mean hemoglobin change from baseline was –6.492 g/L in the upadacitinib 30 mg

group, and –3.885 g/L in the 15 mg group. The fewer number of subjects after Week 64 precluded a meaningful interpretation of the data at time points thereafter.

Figure 16. Mean Change from Baseline in Hemoglobin Over Time (Long-term Upadacitinib Phase 3 AD Analysis Set)



AD = atopic dermatitis; CI = confidence interval; QD = once daily; UPA = upadacitinib
Note: Within group least square means and 95% CI are displayed in this figure, based on ANCOVA analysis with treatment, baseline, and study in the model. Baseline is defined as the last non-missing value prior to the first dose of study drug or randomization if no study drug is given. Subjects with non-missing baseline and at least 1 post-baseline value are included in the analyses.
M16047-45498-95083008 had an outlier for Hemoglobin Week 64 (1450 G/L), which was excluded from the table.
Source: SUR Figure 4.

8.2.4.4.1.12. Neutropenia

Upadacitinib treatment was associated with decreases in mean neutrophil count in a dose-dependent pattern in the PBO-controlled AD Analysis Set.

The proportions of subjects with ≥ Grade 3 and ≥ Grade 4 (neutrophils <1000 and <500) decreases in neutrophil count are shown in Table 59. The ≥ Grade 3 decrease was greater in the upadacitinib 30 mg group than the upadacitinib 15 mg group, and none in the placebo group. No subjects had ≥ Grade 4 decreases in neutrophils in any treatment group. Similar trend was observed in the adolescent population.

Table 59. Number and Percentage of Subjects Meeting Criteria for Potentially Clinically Significant Values for Neutrophils (PBO-controlled AD Analysis Set)

	Overall Population			Adolescent Population		
Neutrophils (10^9/L)	**PBO (N = 902) n/N_OBS (%)**	**UPA 15 mg (N = 899) n/N_OBS (%)**	**UPA 30 mg (N = 906) n/N_OBS (%)**	**PBO (N = 115) n/N_OBS (%)**	**UPA 15 mg (N = 114) n/N_OBS (%)**	**UPA 30 mg (N = 114) n/N_OBS (%)**
≥ Grade 3 (< 1.0 - 0.5)	0	4/896 (0.4)	12/904 (1.3)	0	1/114 (0.9)	3/114 (2.6)
≥ Grade 4 (< 0.5)	0	0	0	0	0	0

AD = atopic dermatitis; OBS = observed; PBO = placebo; QD = once daily; UPA = upadacitinib
Source: CSS Table 49.

As shown in Table 60, there was a dose-related increase in the percentage of subjects with neutropenia, though none of which was serious. Two events of neutropenia, both in the upadacitinib 30 mg group, led to discontinuation of study drug and were considered by the investigator to be possibly related to the study drug. The Applicant reported that neither of these subjects had any concurrent symptoms or infections associated with the episodes of neutropenia.

- Subject (b) (6) in Study M16-045 (upadacitinib 30 mg QD): a 54-year-old female developed Grade 3 decrease in neutrophil count (0.92 x 10^9/L) on Study Day 29. Study treatment was discontinued Study Day 31 due to this event. Event resolved Study Day 36.

- Subject (b) (6) in Study M16-047 (upadacitinib 30 mg QD): a 54-year-old male with a baseline neutrophil count of 1.39 x 10^9/L experienced three episodes of Grade 3 decrease in neutrophil count on Study Day 17 (0.54 x 10^9/L), Day 72 (0.99 x 10^9/L), and Day 85 (0.89 x 10^9/L). Study drug was interrupted for the first 2 episodes with resolution of the neutropenia. However, on Study Day 85 after the third episode of Grade 3 decrease in neutrophil count, the study drug was permanently discontinued. The neutropenia resolved by Study Day 94.

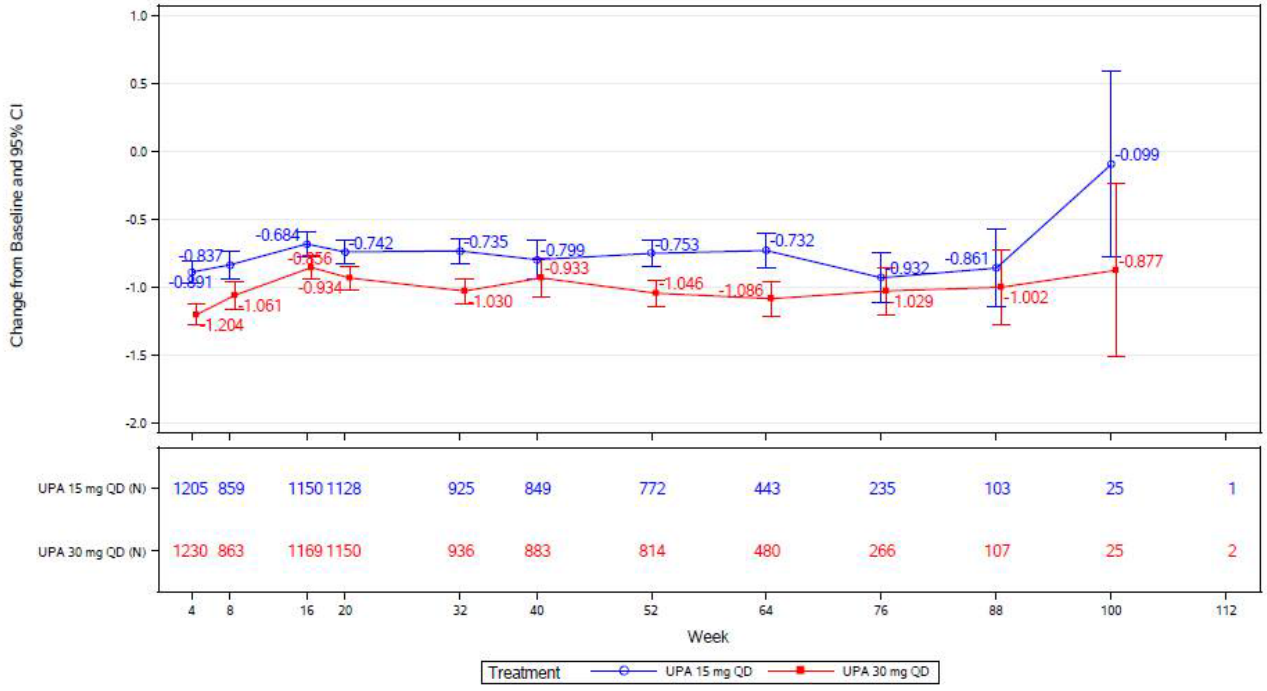
Table 60. Number and Percentage of Subjects with Treatment-Emergent Neutropenia (Placebo-Controlled AD Analysis Set)

	Overall Population			Adolescent Population		
	Placebo (N=902) n (%)	UPA 15 mg (N=899) n (%)	UPA 30 mg (N=906) n (%)	Placebo (N=115) n (%)	UPA 15 mg (N=114) n (%)	UPA 30 mg (N=114) n (%)
Any adverse event	3 (0.3)	10 (1.1)	26 (2.9)	1 (0.9)	2 (1.8)	6 (5.3)
Neutropenia	2 (0.2)	7 (0.8)	21 (2.3)	1 (0.9)	1 (0.9)	5 (4.4)
Neutrophil count decreased	1 (0.1)	3 (0.3)	5 (0.6)	0	1 (0.9)	1 (0.9)

Source: Modified from ISS Tables 2.4__1.3.17.12 and 2.4__1.6.7.12.

As shown in Figure 17, in the Long-term Upadacitinib Phase 3 AD Analysis Set, the decreases in neutrophil counts were associated with upadacitinib treatment. At Week 64, the mean change from baseline in neutrophil counts was –1.086 × 10^9/L for the upadacitinib 30 mg group, and –0.732 × 10^9/L for the 15 mg group. It is difficult to interpret the data after Week 64 due to the small population.

Figure 17. Mean Change from Baseline in Neutrophils Over Time (Long-term Upadacitinib Phase 3 AD Analysis Set)



Abbreviations: AD = atopic dermatitis; CI = confidence interval; QD = once daily; UPA = upadacitinib
Note: Within group least square means and 95% CI are displayed in this figure, based on ANCOVA analysis with treatment, baseline, and study in the model. Baseline is defined as the last non-missing value prior to the first dose of study drug or randomization if no study drug is given. Subjects with non-missing baseline and at least 1 post-baseline value are included in the analyses.
Source: SUR Figure 5

As shown in Table 61, the percentages of subjects with Grade ≥ 3 and Grade ≥ 4 decreases in neutrophils were higher in the upadacitinib 30 mg group than the upadacitinib 15 mg group. Most of these decreases in neutrophil counts continued to be transient and returned to baseline levels or within the normal range without study drug discontinuation with extended upadacitinib treatment.

Table 61. Number and Percentage of Subjects Meeting Criteria for Potentially Clinically Significant Values for Neutrophils (Long-term Upadacitinib Phase 3 AD Analysis Set)

	Overall Population		Adolescent Population	
Neutrophils (10^9/L)	**UPA 15 mg (N=1239) n/N_OBS (%)**	**UPA 30 mg (N=1246) n/N_OBS (%)**	**UPA 15 mg (N=167) n/N_OBS (%)**	**UPA 30 mg (N=166) n/N_OBS (%)**
≥ Grade 3 (< 1.0 - 0.5)	10/1232 (0.8)	18/1241 (1.5)	3/166 (1.8)	4/165 (2.4)
≥ Grade 4 (< 0.5)	0	2/1241 (0.2)	0	1/165 (0.6)

AD = atopic dermatitis; OBS = observed; PBO = placebo; QD = once daily; UPA = upadacitinib
Source: Modified from SUR Tables 2.5__1.3.1 and 2.5__1.3.2.

In the Long-term Upadacitinib Phase 3 AD Analysis Set, the SSA IR of neutropenia was higher in the upadacitinib 30 mg group (2.3/100 PY) compared with the 15 mg group (1.5 /100 PY) . No SAEs of neutropenia were reported in the AD clinical program. The treatment discontinuation due to neutropenia events occurred in 3 subjects in the upadacitinib 30 mg group (0.2/100 PY), and none in the 15 mg group.

A similar trend was observed in adolescent subjects. No adolescent subject discontinued study drug due to an event of neutropenia.

8.2.4.4.1.13. Lymphopenia

Upadacitinib treatment was associated with initial small increases in mean lymphocyte count from baseline followed by normalizing levels with continued treatment.

8.2.4.4.1.14. Creatine Phosphokinase Elevation

As shown in Table 62, in the PBO-controlled AD Analysis Set, the mean increases from baseline in CPK, the percentage of subjects with ≥ Grade 3 (> 5 x ULN - 10 x ULN) and ≥ Grade 4 (> 10 x ULN) CPK elevations, and the percentage of TEAEs of CPK elevation were higher in the upadacitinib groups compared with the placebo group.

Table 62. Number and Percentage of Subjects Meeting Criteria for Potentially Clinically Significant Values for CPK (PBO-controlled AD Analysis Set)

	Overall			Adolescents		
	PBO (N = 902) n/N_OBS (%)	UPA 15 mg (N = 899) n/N_OBS (%)	UPA 30 mg (N = 906) n/N_OBS (%)	PBO (N = 115) n/N_OBS (%)	UPA 15 mg (N = 114) n/N_OBS (%)	UPA 30 mg (N = 114) n/N_OBS (%)
≥ Grade 3 (> 5 x ULN - 10 x ULN)	15/897 (1.7)	30/896 (3.3)	40/904 (4.4)	2/114 (1.8)	5/114 (4.4)	7/114 (6.1)
≥ Grade 4 (> 10 x ULN)	7/897 (0.8)	15/896 (1.7)	15/904 (1.7)	1/114 (0.9)	4/114 (3.5)	1/114 (0.9)

Source: CSS Table 51.

In the Long-term Upadacitinib Phase 3 AD Analysis Set, Grade ≥ 3 blood CPK elevations (CPK > 5X ULN) and the TEAE rates of blood CPK elevation were higher in the upadacitinib 30 mg group compared to the 15 mg group. Study drug discontinuation due to CPK elevation occurred in one subject on upadacitinib 15mg and two subjects on upadacitinib 30mg. A similar pattern was observed in adolescents.

- Subject (b) (6) in Study M18-891 (upadacitinib 15 mg QD) was a 32 year old male who experienced an asymptomatic Grade 2 (CPK >2.5 X ULN)blood CPK elevation of 1209 U/L (normal 39 to 308) on Study Day 21. No etiology was identified. The event was considered by the investigator to have reasonable possibility of being related to study drug. Study drug was withdrawn on Day 26 of upadacitinib treatment. The AE is ongoing on the report date.

- Subject (b) (6) in Study M18-891 (upadacitinib 30 mg QD) was a 54 year old male who had 2 episodes of asymptomatic Grade 2 blood CPK elevation of 1150 U/L (normal 39 to 308) on Study Day 254, and 949 U/L (normal 39 to 308) on Study Day 365. No etiology was identified. Study drug was interrupted after the first episode, and was permanently withdrawn on Study Day 367 after the second episode with resolution of the AE. The events were considered by the investigator to be possibly related to study drug.

- Subject (b) (6) in Study M16-045 (upadacitinib 30 mg QD) was a 35 year old male who experienced an asymptomatic Grade 3 blood CPK elevation of 1070 U/L (normal 26 to 192) on Study Day 113. It was considered related to exercise or other vigorous physical activity. The event was not considered by the investigator to be related to study drug. Study drug was withdrawn on Study Day 142 with resolution of the AE.

Overall, no reported TEAEs of blood CPK elevation were serious.

One event of rhabdomyolysis was reported in a subject after a physical activity (riding a jet ski). Subject (b) (6) in Study M18-891 (upadacitinib 15 mg QD) was a 23 year old male who experienced muscle pain on all four limbs, tiredness, muscle cramping and fatigue symptoms after riding a jet ski for 15 minutes on Study Day 83 of upadacitinib treatment. The fatigue symptoms resolved in 4 days. On Study Day 85, the patient was diagnosed rhabdomyolysis per lab test results, and was subsequently admitted to the hospital for blood CPK level of 47012 U/L (normal 39 to 308). The patient had no symptoms at that time. Blood tests normalized with treatments. The final diagnosis was rhabdomyolysis due to medication reaction. The study drug was permanently discontinued.

8.2.4.4.2. Acne

The Applicant reported that in the PBO-controlled AD Analysis Set, upadacitinib treatment was associated with increased rates of acne in a dose dependent pattern, as shown in Table 63. None was serious and one event was severe in a subject on upadacitinib 30 mg. Two subjects discontinued study drug due to acne, one subject each in 30 mg and 15 mg groups, both of which were moderate in severity and considered by the investigator to have a reasonable possibility of being related to study drug. Prior medical history (32.2% – 45.0% of all subjects with acne) and/or family history of acne (24.5% – 30.0% of all subjects with acne) were the most common risk factors across the upadacitinib and placebo groups.

Similar results were found in adolescent subjects. No event of acne led to discontinuation of study drug in adolescents. Family history was the most common risk factor in adolescent subjects across the upadacitinib and placebo groups.

Table 63. Number and Percentage of Subjects with Treatment-Emergent Acne Adverse Events (PBO-controlled AD Analysis Set)

	Overall			Adolescents		
	PBO (N = 902) n (%)	UPA 15 mg (N = 899) n (%)	UPA 30 mg (N = 906) n (%)	PBO (N = 115) n (%)	UPA 15 mg (N = 114) n (%)	UPA 30 mg (N = 114) n (%)
Subjects with any acne	20 (2.2)	90 (10.0)	143 (15.8)	1 (0.9)	16 (14.0)	19 (16.7)
Areas of involvement						
Face	18 (90.0)	87 (96.7)	137 (95.8)	1 (100)	16 (100)	18 (94.7)
Trunk	7 (35.0)	27 (30.0)	43 (30.1)	1 (100)	8 (50.0)	6 (31.6)
Extremities	1 (5.0)	9 (10.0)	8 (5.6)	0	0	0
Morphology for acne						
Inflammatory papules	17 (85.0)	83 (92.2)	119 (83.2)	1 (100)	13 (81.3)	14 (73.7)
Pustules	7 (35.0)	33 (36.7)	63 (44.1)	0	6 (37.5)	5 (26.3)
Inflammatory nodules and cysts	2 (10.0)	7 (7.8)	12 (8.4)	0	0	0
Comedones	6 (30.0)	36 (40.0)	58 (40.6)	1 (100)	8 (50.0)	12 (63.2)
Scarring	3 (15.0)	4 (4.4)	13 (9.1)	0	1 (6.3)	1 (5.3)

Source: CSS Table 19.

In the Long-term Upadacitinib Phase 3 AD Analysis Set, the percentage of subjects with acne was higher in the upadacitinib 30 mg group than the 15 mg group in overall population and adolescent population, as shown in Table 64. One case of acne (mild, nonserious) reported in an adult subject on upadacitinib 30 mg led to discontinuation of the study drug.

Prior medical history of acne (29.8% – 30.3%) and family history of acne (25.1% – 31.0%) were the most common risk factors for both upadacitinib groups.

Table 64. Number and Percentage of Subjects with Treatment-Emergent Acne Adverse Events (Long-term Upadacitinib Phase 3 AD Analysis Set)

	Overall		Adolescents	
	UPA 15 mg (N = 1239) n (%)	**UPA 30 mg (N = 1246) n (%)**	**UPA 15 mg (N = 167) n (%)**	**UPA 30 mg (N = 166) n (%)**
Subjects with any acne	178 (14.4)	267 (21.4)	25 (15.0)	46 (27.7)
Areas of involvement				
Face	159 (89.3)	255 (95.5)	23 (92.0)	45 (97.8)
Trunk	66 (37.1)	86 (32.2)	10 (40.0)	13 (28.3)
Extremities	17 (9.6)	13 (4.9)	2 (8.0)	0
Morphology for acne				
Inflammatory papules	159 (89.3)	225 (84.3)	23 (92.0)	41 (89.1)
Pustules	78 (43.8)	114 (42.7)	14 (56.0)	17 (37.0)
Inflammatory nodules and cysts	17 (9.6)	30 (11.2)	2 (8.0)	3 (6.5)
Comedones	73 (41.0)	118 (44.2)	12 (48.0)	27 (58.7)
Scarring	9 (5.1)	21 (7.9)	3 (12.0)	4 (8.7)

Source: Modified from SUR Table 2.4__1.3.9 and 2.4__1.9.8.1

Reviewer's Comment:
This reviewer agrees that upadacitinib treatment was associated with increased rates of acne in a dose dependent pattern. A higher rate of acne reports on upadacitinib was observed in the AD program compared to the rheumatoid arthritis program. Of note, the placebo rates of acne also were higher in the placebo-controlled period of the AD program compared to those in the rheumatoid arthritis and psoriatic arthritis programs which may reflect a younger patient population enrolled in the AD program.

8.2.4.5. Treatment Emergent Adverse Events and Adverse Reactions

8.2.4.5.1. Severe Treatment Emergent Adverse Events

PBO-controlled AD Analysis Set
As presented in Table 65, in the PBO-controlled AD Analysis Set, the percentage of subjects with severe TEAEs were similar across upadacitinib 30 mg, upadacitinib 15 mg, and placebo groups except dermatitis atopic (higher in the PBO group) and blood CPK increased (higher in the upadacitinib groups). In the adolescent population, most of the severe TEAEs occurred in one subject each.

Table 65. Severe Adverse Events Reported in > 0.1% of Subjects in Any Treatment Group (PBO-controlled AD Analysis Set)

	Overall Population			Adolescent Population		
	Placebo (N=902) n (%)	UPA 15 mg (N=899) n (%)	UPA 30 mg (N=906) n (%)	Placebo (N=115) n (%)	UPA 15 mg (N=114) n (%)	UPA 30 mg (N=114) n (%)
Any adverse event	43 (4.8)	43 (4.8)	42 (4.6)	3 (2.6)	9 (7.8)	0
Dermatitis atopic	14 (1.6)	7 (0.8)	0	2 (1.7)	2 (1.8)	0
Blood CPK increased	0	7 (0.8)	5 (0.6)	0	2 (1.8)	0
Hypersensitivity[a]	4 (0.4)	1 (0.1)	4 (0.4)	0	0	0
Eczema	2 (0.2)	2 (0.2)	0	0	1 (0.9)	0
Cellulitis	2 (0.2)	0	0	1 (0.9)	0	0
Liver function test abnormal[b]	1 (0.1)	2 (0.2)	1 (0.1)	0	1 (0.9)	0
Depression and suicidal activity[c]	1 (0.1)	1 (0.1)	2 (0.2)	0	1 (0.9)	0
Upper respiratory tract infection[d]	0	2 (0.2)	2 (0.2)	0	0	0
Appendicitis	0	3 (0.3)	0	0	0	0
Herpes zoster	0	2 (0.2)	1 (0.1)	0	0	0
Neutropenia	0	0	3 (0.3)	0	0	0
Retinal detachment[e]	1 (0.1)	2 (0.2)	0	0	0	0
Impetigo	1 (0.1)	1 (0.1)	0	0	1 (0.9)	0
Subcutaneous abscess	1 (0.1)	0	0	1 (0.9)	0	0
Nausea	0	2 (0.2)	0	0	0	0
Dental caries	0	1 (0.1)	0	0	1 (0.9)	0
Headache	0	1 (0.1)	0	0	1 (0.9)	0

a. Includes anaphylactic reaction, anaphylactic shock, dermatitis exfoliative generalised, hypersensitivity, Type I hypersensitivity, and urticaria.
b. Includes alanine aminotransferase increased, aspartate aminotransferase increased, and hepatic function abnormal.
c. Includes depression and suicide attempt.
d. Includes oropharyngeal pain, pharyngeal abscess, and pharyngitis streptococcal.
e. Includes retinal detachment retinal tear, and rhegmatogenous retinal detachment.
Source: Tables 1_1.5.2 and 1_1.9.4 in the Applicant's IR Response on 5/3/2021.

Long-term Upadacitinib Phase 3 AD Analysis Set

As shown in Table 66, in the Long-term Upadacitinib Phase 3 AD Analysis Set, the SSA IR for severe TEAEs was lower in the upadacitinib 15 mg group compared with the 30 mg group. The most common severe TEAEs that occurred at a higher SSA IR in upadacitinib 30 mg compared with 15 mg were blood CPK increased, herpes zoster, asthma, liver function test abnormal, corona virus infection, and neutropenia.

In adolescent Long-term Upadacitinib Phase 3 AD Analysis Set, the severe TEAEs were blood CPK increased, atopic dermatitis and depression and suicidal activity which occurred more in the 15mg group.

Table 66. Severe AE in Exposure-Adjusted Rate per 100 Patient Years (Long-term Upadacitinib Phase 3 AD Analysis Set)

	Overall Population		Adolescent Population	
Study Size Adjusted Incidence Rate	**UPA 15 mg (N=1239) [total PY=1373.4] n (SSA IR/100PY)**	**UPA 30 mg (N=1246) [total PY=1414.2] n (SSA IR/100PY))**	**UPA 15 mg (N=167) [total PY=191.7] n (SSA IR/100PY)**	**UPA 30 mg (N=166) [total PY=195.9] n (SSA IR/100PY)**
Any adverse event	122 (9.4)	149 (11.2)	20 (11.1)	15 (8.1)
Blood CPK increased	14 (1.0)	28 (2.2)	5 (2.7)	2 (1.0)
Dermatitis atopic	17 (1.2)	3 (0.2)	5 (2.6)	2 (1.0)
Herpes zoster[a]	7 (0.5)	8 (0.6)	0	1 (0.5)
Hypersensitivity[b]	3 (0.2)	8 (0.6)	0	1 (0.5)
Asthma	4 (0.3)	6 (0.4)	0	0
Liver function test abnormal[c]	3 (0.2)	4 (0.3)	1 (0.5)	0
Pneumonia[d]	3 (0.2)	4 (0.3)	0	1 (0.5)
Upper respiratory tract infection[e]	3 (0.2)	4 (0.3)	0	0
Eczema herpeticum	5 (0.4)	2 (0.1)	0	0
Corona virus infection[f]	1 (<0.1)	5 (0.4)	0	0
Depression and suicidal activity[g]	4 (0.3)	2 (0.1)	3 (1.6)	0
Neutropenia	0	5 (0.4)	0	1 (0.5)
Herpes simplex[h]	1 (<0.1)	4 (0.3)	0	0
Retinal detachment[i]	3 (0.2)	1 (<0.1)	0	0
Eczema	3 (0.2)	1 (<0.1)	1 (0.5)	0
Neutrophil count decreased	3 (0.2)	1 (<0.1)	1 (0.5)	1 (0.5)
Pruritus	4 (0.3)	0	1 (0.5)	0
Appendicitis	3 (0.2)	0	0	0
Cerebrovascular accident[j]	2 (0.1)	1 (<0.1)	0	0
Acne	0	3 (0.2)	0	0
Anaemia	0	3 (0.2)	0	0
Eczema infected	1 (<0.1)	2 (0.1)	1 (0.5)	1 (0.5)
Fall	1 (<0.1)	2 (0.1)	0	0
Foot fracture	1 (<0.1)	2 (0.1)	0	0
Nephrolithiasis	1 (<0.1)	2 (0.1)	0	0
Weight increased	1 (<0.1)	2 (0.1)	0	1 (0.5)
Cataract	0	2 (0.1)	0	1 (0.5)
Hepatic steatosis	0	2 (0.1)	0	0
Influenza	0	2 (0.1)	0	0
Pyelonephritis	0	2 (0.1)	0	1 (0.5)
Sepsis[k]	0	2 (0.1)	0	1 (0.5)
Headache	1 (<0.1)	1 (<0.1)	1 (0.5)	0
Syncope	1 (<0.1)	1 (<0.1)	1 (0.5)	1 (0.5)
Nausea	2 (0.1)	0	0	0
Impetigo	2 (0.1)	0	2 (1.0)	0
Back pain	2 (0.1)	0	0	0
Osteomyelitis	0	1 (<0.1)	0	1 (0.5)
Bacterial infection	1 (<0.1)	0	1 (0.5)	0
Cat scratch disease	1 (<0.1)	0	1 (0.5)	0
Dental caries	1 (<0.1)	0	1 (0.5)	0
Ovarian cyst	1 (<0.1)	0	1 (0.5)	0
Periorbital cellulitis	1 (<0.1)	0	1 (0.5)	0

Skin infection	1 (<0.1)	0	1 (0.5)	0
Weight decreased	1 (<0.1)	0	0	1 (0.5)

Note: This table lists the AEs that occurred in more than one subject in any treatment group in the overall population, and all AEs occurred in the adolescent population.
a. Includes Herpes zoster, Herpes zoster cutaneous disseminated, and Herpes zoster disseminated.
b. Includes anaphylactic reaction, angioedema, dermatitis exfoliative generalised, drug hypersensitivity, hypersensitivity, swelling of eyelid, toxic epidermal necrolysis, type I hypersensitivity, and urticaria.
c. Includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic function abnormal, and transaminases increased.
d. Includes pneumonia, and pneumonia bacterial.
e. Includes nasopharyngitis, oropharyngeal pain, pharyngeal abscess, pharyngitis streptococcal, respiratory tract infection viral, and upper respiratory tract infection.
f. Includes corona virus infection and 1 not coded (pulmonary embolism in the setting of COVID-19 infection).
g. Includes depression, suicidal ideation, and suicide attempt.
h. Includes herpes simplex and ophthalmic herpes simplex.
i. Includes retinal detachment, rhegmatogenous retinal detachment, and retinal tear.
j. Includes cerebrovascular accident, ischaemic stroke, and subarachnoid haemorrhage.
k. Includes sepsis and Staphylococcal sepsis.
Source: Tables 1_2.5.2 and 1_2.9.4 in the Applicant's IR Response on 5/3/2021.

8.2.4.5.2. Common Treatment Emergent Adverse Events

PBO-controlled AD Analysis Set

Common Adverse Reactions are presented in Table 67 for the PBO-controlled AD Analysis Set. In the overall population, a dose-response increase in occurrence was seen in the upadacitinib treated groups (and higher than the placebo group) for upper respiratory infection, acne, headache, herpes simplex, blood CPK increased, folliculitis, pyrexia, Influenza like illness, and neutropenia. Dermatitis atopic had dose-response decrease in occurrence with the highest occurrence in the placebo group. Similar results were noted for the adolescent population.

Table 67. Frequency of TEAEs Occurring in ≥ 2% of Subjects (PBO-controlled AD Analysis Set)

	Overall Population			Adolescent Population		
	Placebo (N=902) n (%)	UPA 15 mg (N=899) n (%)	UPA 30 mg (N=906) n (%)	Placebo (N=115) n (%)	UPA 15 mg (N=114) n (%)	UPA 30 mg (N=114) n (%)
Any adverse event	528 (58.5)	574 (63.8)	630 (69.6)	53 (46.0)	74 (64.9)	83 (72.9)
Upper respiratory tract infection[a]	149 (16.5)	203 (22.6)	230 (25.4)	13 (11.3)	32 (28.1)	32 (28.1)
Acne	20 (2.2)	86 (9.6)	137 (15.1)	1 (0.9)	15 (13.2)	17 (14.9)
Headache	39 (4.3)	50 (5.6)	57 (6.3)	6 (5.2)	7 (6.1)	10 (8.8)
Herpes simplex[b]	15 (1.7)	37 (4.1)	76 (8.4)	0	3 (2.6)	7 (6.1)
Dermatitis atopic	74 (8.2)	31 (3.4)	14 (1.5)	11 (9.6)	5 (4.4)	2 (1.8)
Blood CPK increased	21 (2.3)	41 (4.6)	50 (5.5)	3 (2.6)	6 (5.3)	9 (7.9)
Diarrhoea	23 (2.5)	31 (3.4)	29 (3.2)	3 (2.6)	2 (1.8)	6 (5.3)
Cough	13 (1.4)	29 (3.2)	27 (3.0)	1 (0.9)	5 (4.4)	3 (2.6)
Folliculitis	10 (1.1)	19 (2.1)	29 (3.2)	0	0	3 (2.6)
Hypersensitivity[c]	14 (1.6)	14 (1.6)	26 (2.9)	1 (0.9)	2 (1.8)	3 (2.7)
Abdominal pain[d]	7 (0.8)	26 (2.9)	21 (2.3)	1 (0.9)	3 (2.6)	8 (7.1)
Nausea	5 (0.6)	24 (2.7)	24 (2.6)	0	2 (1.8)	3 (2.6)
Urinary tract infection	18 (2.0)	12 (1.3)	22 (2.4)	1 (0.9)	1 (0.9)	2 (1.8)
Pyrexia	9 (1.0)	15 (1.7)	19 (2.1)	0	3 (2.6)	6 (5.3)
Liver function test abnormal[e]	12 (1.3)	14(1.6)	12 (1.3)	0	5 (4.4)	0
Weight increased	5 (0.6)	16 (1.8)	17 (1.9)	1 (0.9)	1 (0.9)	5 (4.4)
Influenza like illness	8 (0.9)	13 (1.4)	17 (1.9)	0	2 (1.8)	4 (3.5)
Influenza	3 (0.3)	19 (2.1)	14 (1.5)	0	2 (1.8)	6 (5.3)
Skin infection[f]	17 (1.9)	10 (1.1)	8 (0.9)	6 (5.2)	1 (0.9)	1 (0.9)
Herpes zoster[g]	5 (0.6)	14 (1.6)	15 (1.7)	0	1 (0.9)	3 (2.6)
Neutropenia	2 (0.2)	7 (0.8)	21 (2.3)	1 (0.9)	1 (0.9)	5 (4.4)
Asthma	13 (1.4)	11 (1.2)	6 (0.7)	0	3 (2.6)	2 (1.8)
Impetigo	10 (1.1)	9 (1)	9 (1.0)	1 (0.9)	4 (3.5)	2 (1.8)
Depression and suicidal activity[h]	8 (0.9)	6 (0.7)	9 (1.0)	1 (0.9)	3 (2.6)	0
Rhinorrhoea	1 (0.1)	8 (0.9)	4 (0.4)	0	3 (2.6)	2 (1.8)
Ear infection	3 (0.3)	1 (0.1)	6 (0.7)	1 (0.9)	1 (0.9)	3 (2.6)
Catarrh	1 (0.1)	3 (0.3)	3 (0.3)	1 (0.9)	1 (0.9)	3 (2.6)

a. Includes laryngitis, laryngitis viral, nasopharyngitis, oropharyngeal pain, pharyngeal abscess, pharyngitis, pharyngitis streptococcal, pharyngotonsillitis, respiratory tract infection, respiratory tract infection viral, rhinitis, rhinolaryngitis, sinusitis, tonsillitis, tonsillitis bacterial, upper respiratory tract infection, viral pharyngitis, viral upper respiratory tract infection.
b. Includes genital herpes, genital herpes simplex, herpes dermatitis, herpes ophthalmic, herpes simplex, herpes virus infection, nasal herpes, ophthalmic herpes simplex, and oral herpes.
c. Includes anaphylactic reaction, anaphylactic shock, angioedema, dermatitis exfoliative generalised, drug hypersensitivity, eyelid oedema, face oedema, hypersensitivity, periorbital swelling, pharyngeal swelling, swelling face, toxic skin eruption, type I hypersensitivity, and urticaria.
d. Includes abdominal pain and abdominal pain upper
e. Includes alanine aminotransferase abnormal, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased, hepatic enzyme increased, hepatic function abnormal, hyperbilirubinemia, and transaminases increased.
f. Includes fungal skin infection, skin bacterial infection, skin infection, and staphylococcal skin infection.
g. Includes herpes zoster and varicella.
h. Includes depressed mood, depression, intentional self-injury, major depression, mixed anxiety and depressive disorder, and suicide attempt.
Source: Tables 1_1.7.2 and 1_1.9.6 in the Applicant's IR Response on 5/3/2021.

Long-term Upadacitinib Phase 3 AD Analysis Set

The Common TEAEs are presented in Table 68 for the Long-term Upadacitinib Phase 3 AD Analysis Set. The SSA IRs were significantly higher (>1/100PY) in the upadacitinib 30mg group for upper respiratory tract infection, acne, herpes simplex, blood CPK increased, herpes zoster, urinary tract infection, and neutropenia. Similar trend was found in the adolescent population.

Table 68. TEAEs with ≥ 2 Incidence/100PY in Exposure-Adjusted Rate per 100 Patient Years (Long-term Upadacitinib Phase 3 AD Analysis Set)

	Overall Population		Adolescent Population	
Study Size Adjusted Incidence Rate	**UPA 15 mg (N=1239) [total PY=1373.4] n (SSA IR/100PY)**	**UPA 30 mg (N=1246) [total PY=1414.2] n (SSA IR/100PY)**	**UPA 15 mg (N=167) [total PY=191.7] n (SSA IR/100PY)**	**UPA 30 mg (N=166) [total PY=195.9] n (SSA IR/100PY)**
Any adverse event	912 (179.0)	1007 (240.1)	123 (177.5)	133 (241.3)
Upper respiratory tract infection[a]	348 (33.3)	375 (36.0)	47 (33.3)	54 (38.8)
Acne	164 (13.6)	246 (20.9)	24 (14.5)	42 (27.5)
Herpes simplex[b]	82 (6.3)	145 (11.2)	7 (3.8)	12 (6.5)
Blood CPK increased	74 (5.7)	123 (9.3)	10 (5.6)	20 (11.2)
Dermatitis atopic	108 (8.2)	67 (4.9)	14 (7.6)	9 (4.8)
Headache	79 (6.1)	77 (5.8)	16 (9.1)	13 (7.2)
Herpes zoster[c]	46 (3.4)	70 (5.1)	2 (1.1)	7 (3.7)
Cough	63 (4.8)	50 (3.6)	12 (6.8)	6 (3.2)
Liver function test abnormal[d]	48 (3.6)	58 (4.2)	9 (5.0)	3 (1.6)
Hypersensitivity[e]	48 (3.6)	55 (4.0)	9 (4.9)	7 (3.7)
Folliculitis	43 (3.2)	55 (4.0)	2 (1.1)	4 (2.1)
Urinary tract infection	36 (2.7)	57 (4.2)	4 (2.1)	8 (4.2)
Diarrhoea	43 (3.2)	45 (3.3)	3 (1.6)	12 (6.6)
Pyrexia	44 (3.3)	41 (3.0)	6 (3.2)	11 (6.0)
Abdominal pain[f]	42 (3.2)	41 (3.0)	8 (4.3)	16 (8.8)
Nausea	35 (2.6)	40 (2.9)	5 (2.7)	8 (4.2)
Weight increased	28 (2.1)	40 (2.9)	2 (1.1)	7 (3.7)
Influenza like illness	23 (1.7)	33 (2.4)	2 (1.0)	6 (3.2)
Gastroenteritis	25 (1.9)	31 (2.2)	2 (1.1)	4 (2.1)
Impetigo	32 (2.4)	24(1.7)	9 (4.8)	6 (3.1)
Back pain	24 (1.8)	27 (2.0)	1 (0.5)	1 (0.5)
Influenza	25 (1.9)	25 (1.8)	2 (1.1)	6 (3.2)
Asthma	24 (1.8)	24 (1.7)	5 (2.6)	3 (1.6)
Skin infection[g]	23 (1.7)	24 (1.7)	5 (2.6)	4 (2.1)
Eczema	25 (1.8)	20 (1.4)	4 (2.1)	0
Conjunctivitis	18 (1.3)	20 (1.4)	2 (1.1)	5 (2.6)
Neutropenia	10 (0.7)	24 (1.7)	2 (1.1)	6 (3.2)
Depression and suicidal activity[h]	16 (1.2)	19 (1.4)	6 (3.2)	3 (1.6)
Skin papilloma	17 (1.3)	17 (1.2)	5 (2.7)	4 (2.1)
Vomiting	13 (1.0)	20 (1.4)	3 (1.6)	10 (5.4)
Pruritus	18 (1.3)	7 (0.5)	4 (2.1)	2 (1.0)
Dermatitis contact	8 (0.6)	17 (1.2)	2 (1.1)	4 (2.1)
Rhinorrhoea	11 (0.8)	9 (0.6)	4 (2.1)	3 (1.6)
Catarrh	6 (0.4)	5 (0.4)	4 (2.1)	5 (2.7)
Proteinuria	6 (0.4)	5 (0.4)	4 (2.1)	1 (0.5)

a. Includes acute sinusitis, laryngitis, laryngitis viral, nasopharyngitis, oropharyngeal pain, pharyngeal abscess, pharyngitis, pharyngitis streptococcal, pharyngotonsillitis, respiratory tract infection, respiratory tract infection bacterial, respiratory tract infection viral, rhinitis, rhinolaryngitis, sinusitis, tonsillitis, tonsillitis bacterial, tonsillitis streptococcal, upper respiratory tract infection, upper respiratory tract infection bacterial, viral pharyngitis, and viral upper respiratory tract infection.
b. Includes genital herpes, genital herpes simplex, herpes dermatitis, herpes ophthalmic, herpes simplex, herpes virus infection, nasal herpes, ophthalmic herpes simplex, and oral herpes.

c. Includes Herpes zoster, Herpes zoster cutaneous disseminated, and Herpes zoster disseminated, Herpes zoster oticus, ophthalmic herpes zoster, varicella, and post-herpetic neuralgia.
d. Includes alanine aminotransferase increased, alanine aminotransferase abnormal, aspartate aminotransferase abnormal, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased, hepatic enzyme increased, hepatic function abnormal, hyperbilirubinaemia, liver function test abnormal, liver function test increased, and transaminases increased.
e. Includes allergic oedema, anaphylactic reaction, angioedema, bronchospasm, dermatitis exfoliative generalised, drug eruption, drug hypersensitivity, eye oedema, eye swelling, eyelid oedema, face oedema, hypersensitivity, lip swelling, periorbital oedema, periorbital swelling, pharyngeal swelling, swelling face, swelling of eyelid, toxic epidermal necrolysis , toxic skin eruption, type I hypersensitivity, urticaria, and urticaria papular.
f. Includes abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal tenderness.
g. Includes fungal skin infection, skin bacterial infection, skin infection, and Staphylococcal skin infection.
h. Includes depressed mood, depression, depressive symptom, intentional self-injury, major depression, mixed anxiety and depressive disorder, suicidal ideation, and suicide attempt.
Source: Tables 1_2.7.2 and 1_2.9.6 in the Applicant's IR Response on 5/3/2021.

8.2.4.5.3. Adverse Drug Reactions

In this review, the Adverse Drug Reactions (ADRs) are defined as the TEAEs that are considered by the investigator to have a reasonable possibility of being study drug related.

PBO-controlled AD Analysis Set

Table 69 shows the ADRs in the PBO-controlled AD Analysis Set. In the overall population, a dose-response increase in occurrence was seen in the upadacitinib treated groups (and higher than the placebo group) for certain adverse events such as acne, blood CPK increased, herpes simplex, headache, nausea, diarrhoea, herpes zoster, folliculitis, and neutropenia. Abdominal pain and weight increased also occurred more frequently in the upadacitinib groups than the placebo group. Dermatitis atopic had dose-response decrease in occurrence with the highest occurrence in the placebo group. Similar results were noted for the adolescent population.

Table 69. Adverse Drug Reactions that occurred in ≥ 1% of Subjects (PBO-controlled AD Analysis Set)

	Overall Population			Adolescent Population		
	Placebo (N=902) n (%)	UPA 15 mg (N=899) n (%)	UPA 30 mg (N=906) n (%)	Placebo (N=115) n (%)	UPA 15 mg (N=114) n (%)	UPA 30 mg (N=114) n (%)
Any adverse event	185 (20.5)	298 (33.1)	367 (40.5)	14 (12.3)	35 (30.7)	40 (35.1)
Acne	14 (1.6)	67 (7.5)	109 (12.0)	0	12 (10.5)	14 (12.3)
Upper respiratory tract infection[a]	42 (4.7)	67 (7.5)	68 (7.5)	1 (0.9)	12 (10.5)	10 (8.9)
Blood CPK increased	13 (1.4)	29 (3.2)	32 (3.5)	2 (1.7)	6 (5.3)	4 (3.5)
Herpes simplex[b]	9 (1.0)	21 (2.3)	44 (4.9)	0	1 (0.9)	2 (1.8)
Headache	9 (1.0)	17 (1.9)	26 (2.9)	2 (1.7)	2 (1.8)	3 (2.6)
Dermatitis atopic	17 (1.9)	14 (1.6)	6 (0.7)	1 (0.9)	1 (0.9)	1 (0.9)
Nausea	3 (0.3)	14 (1.6)	16 (1.8)	0	1 (0.9)	2 (1.8)
Diarrhoea	7 (0.8)	10 (1.1)	15 (1.7)	0	1 (0.9)	3 (2.6)
Herpes zoster[c]	2 (0.2)	13 (1.4)	15 (1.7)	0	1 (0.9)	3 (2.6)
Abdominal pain[d]	3 (0.3)	14 (1.6)	10 (1.1)	1 (0.9)	1 (0.9)	3 (2.6)
Folliculitis	4 (0.4)	10 (1.1)	13 (1.4)	0	0	1 (0.9)
Neutropenia	2 (0.2)	7 (0.8)	18 (2.0)	1 (0.9)	1 (0.9)	4 (3.5)
Weight increased	3 (0.3)	12 (1.3)	12 (1.3)	0	1 (0.9)	4 (3.5)
Liver function test abnormal[e]	4 (0.4)	10 (1.1)	7 (0.8)	0	3 (2.6)	0
Myalgia	4 (0.4)	4 (0.4)	10 (1.1)	0	0	0
Fatigue	2 (0.2)	6 (0.7)	10 (1.1)	0	0	0
Impetigo	5 (0.6)	4 (0.4)	4 (0.4)	1 (0.9)	2 (1.8)	0
Influenza	1 (0.1)	2 (0.2)	6 (0.7)	0	1 (0.9)	2 (1.8)
Dyspepsia	0	4 (0.4)	5(0.6)	0	1 (0.9)	2 (1.8)
Vomiting	1 (0.1)	2 (0.2)	3 (0.3)	0	0	3 (2.6)
Ear infection	0	0	2 (0.2)	0	0	2 (1.8)

a. Includes laryngitis, nasopharyngitis, oropharyngeal pain, pharyngeal abscess, pharyngitis, pharyngitis streptococcal, pharyngotonsillitis, respiratory tract infection, respiratory tract infection viral, rhinitis, rhinolaryngitis, sinusitis, tonsillitis, tonsillitis bacterial, upper respiratory tract infection, viral pharyngitis, and viral upper respiratory tract infection.
b. Includes genital herpes, genital herpes simplex, herpes dermatitis, herpes ophthalmic, herpes simplex, herpes virus infection, ophthalmic herpes simplex, and oral herpes.
c. Includes herpes zoster and varicella.
d. Includes abdominal pain and abdominal pain upper.
e. Includes alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, hepatic enzyme increased, hyperbilirubinemia, and transaminases increased.
Source: Tables 1__1.8.2 and 1__1.9.3, Applicant's IR Response on 5/3/2021.

The ADRs of hypersensitivity are presented in Table 70 for the PBO-controlled AD Analysis Set.

Table 70. Adverse Drug Reactions of Hypersensitivity (PBO-controlled AD Analysis Set)

	Overall Population			Adolescent Population		
	Placebo (N=902) n (%)	UPA 15 mg (N=899) n (%)	UPA 30 mg (N=906) n (%)	Placebo (N=115) n (%)	UPA 15 mg (N=114) n (%)	UPA 30 mg (N=114) n (%)
Hypersensitivity	5 (0.6)	5 (0.6)	9 (1.0)	1 (0.9)	1 (0.9)	1 (0.9)
Dermatitis exfoliative generalised	1 (0.1)	0	0	0	0	0
Drug hypersensitivity	2 (0.2)	0	0	1 (0.9)	0	0
Eyelid oedema	1 (0.1)	0	0	0	0	0
Face oedema	0	0	2 (0.2)	0	0	0
Hypersensitivity	0	1 (0.1)	0	0	1 (0.9)	0
Pharyngeal swelling	0	0	1 (0.1)	0	0	0
Swelling face	1 (0.1)	2 (0.2)	0	0	0	0
Toxic skin eruption	0	0	1 (0.1)	0	0	0
Urticaria	0	2 (0.2)	5 (0.6)	0	0	1 (0.9)

Source: Tables 1__1.9.3, Applicant's IR Response on 5/3/2021.

Long-term Upadacitinib Phase 3 AD Analysis Set

The Adverse Drug Reactions are presented in Table 71 for the Long-term Upadacitinib Phase 3 AD Analysis Set.

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Table 71. Adverse Drug Reactions with ≥ 1 event/100PY in Exposure-Adjusted Rate per 100 Patient Years (Long-term Upadacitinib Phase 3 AD Analysis Set)

	Overall Population		Adolescent Population	
Study Size Adjusted Incidence Rate	**UPA 15 mg (N=1239) [total PY=1373.4] n (SSA IR/100PY)**	**UPA 30 mg (N=1246) [total PY=1414.2] n (SSA IR/100PY))**	**UPA 15 mg (N=167) [total PY=191.7] n (SSA IR/100PY)**	**UPA 30 mg (N=166) [total PY=195.9] n (SSA IR/100PY)**
Any adverse event	503 (54.4)	623 (75.1)	59 (43.5)	78 (66.2)
Acne	131 (10.6)	199 (16.3)	17 (9.8)	33 (20.4)
Upper respiratory tract infection[a]	119 (9.4)	109 (8.3)	21 (12.3)	12 (6.7)
Herpes simplex[b]	55 (4.1)	83 (6.2)	6 (3.2)	4 (2.1)
Blood CPK increased	45 (3.4)	73 (5.4)	7 (3.9)	8 (4.3)
Herpes zoster[c]	36 (2.7)	58 (4.2)	2 (1.1)	6 (3.1)
Liver function test abnormal[d]	29 (2.1)	38 (2.7)	7 (3.8)	2 (1.0)
Dermatitis atopic	31 (2.3)	19 (1.4)	3 (1.6)	5 (2.6)
Folliculitis	23 (1.7)	27 (1.9)	0	2 (1.0)
Headache	22 (1.6)	28 (2.0)	5 (2.7)	3 (1.6)
Weight increased	20 (1.5)	26 (1.9)	2 (1.1)	5 (2.6)
Nausea	16 (1.2)	19 (1.4)	2 (1.0)	3 (1.6)
Cough	17 (1.3)	13 (0.9)	3 (1.6)	0
Neutropenia	9 (0.7)	20 (1.4)	2 (1.0)	6 (3.2)
Diarrhoea	11 (0.8)	17 (1.2)	1 (0.5)	4 (2.1)
Abdominal pain[e]	17 (1.3)	11 (0.8)	2 (1.1)	4 (2.1)
Urinary tract infection	8 (0.6)	19 (1.4)	2 (1.0)	4 (2.1)
Eczema herpeticum	16 (1.2)	9 (0. 6)	1 (0.5)	1 (0.5)
Hypersensitivity[f]	9 (0.7)	15 (1.1)	1 (0.5)	2 (1.0)
Impetigo	15 (1.1)	8 (0.6)	6 (3.2)	1 (0.5)
Pyrexia	11 (0.8)	12 (0.9)	2 (1.0)	1 (0.5)
Neutrophil count decreased	12 (0.9)	7 (0.5)	3 (1.6)	2 (1.1)
Skin infection[g]	11 (0.8)	5 (0.4)	2 (1.0)	1 (0.5)
Dermatitis acneiform	7 (0.5)	9 (0.7)	0	2 (1.0)
Pneumonia[h]	8 (0.6)	7 (0.5)	0	2 (1.0)
Eczema	8 (0.6)	5 (0.4)	3 (1.6)	0
Bronchitis	6 (0.4)	7 (0.5)	0	2 (1.0)
Haemoglobin decreased	5 (0.4)	7 (0.5)	2 (1.0)	1 (0.5)
Influenza	4 (0.3)	7 (0.5)	1 (0.5)	2 (1.0)
Skin papilloma	4 (0.3)	6 (0.4)	1 (0.5)	2 (1.0)
Dyspnoea	4 (0.3)	6 (0.4)	1 (0.5)	3 (1.5)
Dyspepsia	5 (0.4)	5 (0.4)	1 (0.5)	2 (1.0)
Vomiting	3 (0.2)	6 (0.4)	0	3 (1.6)
Depression and suicidal activity[i]	3 (0.2)	6 (0.4)	1 (0.5)	2 (1.0)
Leukopenia	1 (0.1)	4 (0.3)	0	2 (1.0)
Hyperhidrosis	1 (0.1)	4 (0.3)	0	3 (1.5)
Sinus congestion	2 (0.1)	3 (0.2)	2 (1.0)	1 (0.5)
Ear infection	2 (0.1)	3 (0.2)	0	2 (1.0)
Proteinuria	3 (0.2)	2 (0.1)	3 (1.6)	0
Otitis media	3 (0.2)	2 (0.1)	2 (1.0)	0

a. Includes laryngitis, nasopharyngitis, oropharyngeal pain, pharyngeal abscess, pharyngitis, pharyngitis streptococcal, pharyngotonsillitis, respiratory tract infection, respiratory tract infection bacterial, respiratory tract infection viral, rhinitis, rhinolaryngitis, sinusitis, tonsillitis, tonsillitis bacterial, tonsillitis streptococcal, upper respiratory tract infection, viral pharyngitis, and viral upper respiratory tract infection.

b. Includes genital herpes, genital herpes simplex, herpes dermatitis, herpes ophthalmic, herpes simplex, herpes virus infection, nasal herpes, ophthalmic herpes simplex, and oral herpes.
c. Includes Herpes zoster, Herpes zoster cutaneous disseminated, and Herpes zoster disseminated, Herpes zoster oticus, ophthalmic herpes zoster, and varicella.
d. Includes alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased, hepatic enzyme increased, hepatic function abnormal, hyperbilirubinaemia, liver function test abnormal, liver function test increased, and transaminases increased.
e. Includes abdominal pain and abdominal pain upper.
f. Includes anaphylactic reaction, drug hypersensitivity, eye oedema, eyelid oedema, face oedema, hypersensitivity, lip swelling, pharyngeal swelling, swelling face, swelling of eyelid, toxic skin eruption, and urticaria.
g. Includes skin bacterial infection, skin infection, and Staphylococcal skin infection.
h. Includes pneumonia, and pneumonia mycoplasmal.
i. Includes depressed mood, depression, intentional self-injury, mixed anxiety and depressive disorder, suicidal ideation, and suicide attempt.
Source: Tables 1__2.8.2 and 1__2.9.3, Applicant's IR Response on 5/3/2021.

The ADRs of hypersensitivity are presented in Table 72 for the Long-term Upadacitinib Phase 3 AD Analysis Set.

Table 72. Adverse Drug Reactions of Hypersensitivity in Exposure-Adjusted Rate per 100 Patient Years (Long-term Upadacitinib Phase 3 AD Analysis Set)

	Overall Population		Adolescent Population	
Study Size Adjusted Incidence Rate	**UPA 15 mg (N=1239) [total PY=1373.4] n (SSA IR/100PY)**	**UPA 30 mg (N=1246) [total PY=1414.2] n (SSA IR/100PY))**	**UPA 15 mg (N=167) [total PY=191.7] n (SSA IR/100PY)**	**UPA 30 mg (N=166) [total PY=195.9] n (SSA IR/100PY)**
Hypersensitivity	9 (0.7)	15 (1.1)	1 (0.5)	2 (1.0)
Urticaria	6 (0.4)	8 (0.6)	0	1 (0.5)
Swelling face	2 (0.1)	0	0	0
Face oedema	1 (< 0.1)	1 (< 0.1)	0	0
Anaphylactic reaction	0	1 (< 0.1)	0	0
Drug hypersensitivity	0	1 (< 0.1)	0	0
Eye oedema	0	1 (< 0.1)	0	0
Eyelid oedema	0	1 (< 0.1)	0	1 (0.5)
Hypersensitivity	1 (< 0.1)	0	1 (0.5)	0
Lip swelling	0	1 (< 0.1)	0	1 (0.5)
Pharyngeal swelling	0	1 (< 0.1)	0	0
Swelling of eyelid	0	1 (< 0.1)	0	0
Toxic skin eruption	0	1 (< 0.1)	0	0

Source: Tables 1__2.9.3, Applicant's IR Response on 5/3/2021.

8.2.4.5.4. Suicidal Ideation and Behavior

Per the Applicant, events of suicidal ideation and behaviors (SIB), include events coded to the preferred terms of intentional overdose, intentional self-injury, suicidal ideation, suicidal behavior, depression suicidal, suicide attempt and completed suicide.

The events of SIB occurred in both Placebo-controlled and Long-term Upadacitinib Phase 3 AD Analysis Sets as shown in the tables below. All subjects experiencing an event of SIB had an underlying history of psychiatric disorder including depression, suicide attempt, bipolar

disorder, personality disorder, and/or social stressors. No cases of completed suicide were reported in the upadacitinib AD program. No dose relationship was observed.

The frequency of Suicide/Self-Injury in Placebo-controlled AD Analysis Set is shown in Table 73.

Table 73. Number and Percentage of Subjects with Suicide/Self-Injury (PBO-controlled AD Analysis Set)

	Overall Population			Adolescent Population		
	Placebo (N=902) n (%)	UPA 15 mg (N=899) n (%)	UPA 30 mg (N=906) n (%)	Placebo (N=115) n (%)	UPA 15 mg (N=114) n (%)	UPA 30 mg (N=114) n (%)
Any adverse event	2 (0.2)	3 (0.3)	2 (0.2)	0	2 (1.8)	0
Intentional self-injury	1 (0.1)	2 (0.2)	1 (0.1)	0	1 (0.9)	0
Suicide attempt	1 (0.1)	1 (0.1)	1 (0.1)	0	1 (0.9)	0

Source: Table 1__1.1.17.2 in the Applicant's IR Response on 4/7/2021.

The SSA IR for Suicide/Self-Injury in Long-term Upadacitinib Phase 3 AD Analysis Set is shown in Table 74.

Table 74. Suicide/Self-Injury in Exposure-Adjusted Rate per 100 Patient Years (Long-term Upadacitinib Phase 3 AD Analysis Set)

	Overall Population		Adolescent Population	
Study Size Adjusted Incidence Rate	UPA 15 mg (N=1239) [total PY=1373.4] n (SSA IR/100PY)	UPA 30 mg (N=1246) [total PY=1414.2] n (SSA IR/100PY))	UPA 15 mg (N=167) [total PY=191.7] n (SSA IR/100PY)	UPA 30 mg (N=166) [total PY=195.9] n (SSA IR/100PY)
Any adverse event	5 (0.4)	3 (0.2)	3 (1.6)	1 (0.5)
Suicidal ideation	1 (<0.1)	2 (0.1)	1 (0.5)	1 (0.5)
Suicide attempt	3 (0.2)	1 (<0.1)	2 (1.1)	0
Intentional self-injury	2 (0.1)	0	1 (0.5)	0

a. One event of "Overdose" was coded for a subject taking overdose of multiple drugs which was assessed to be an intentional overdose. After database lock, the event was corrected and presented as suicide attempt in the SUR.
b. One event of major depression reported in a subject on upadacitinib 15 mg was revised by the investigator to be an event of suicide attempt after database lock.
c. One event of intentional self-injury reported in a subject on upadacitinib 30 mg was revised by the investigator after database lock to be an event of inflammation of the eye. This case was not included.
Source: Table 1__2.1.17.2 in the Applicant's IR Reponses on 4/7/2021.

Reviewer's Comment:
This reviewer did not find any increased rates of SIB related to the upadacitinib treatments.

8.2.4.6. Laboratory Findings

Clinical Hematology

Treatment-emergent AEs of abnormal hematology laboratory values (anemia, neutropenia, lymphopenia) have been discussed in the section for the respective associated AESIs.

In the PBO-controlled AD Analysis Set, no clinically meaningful differences in platelet counts were seen between the upadacitinib groups compared with placebo group. In long-term analyses, similar results were seen in the upadacitinib 30 mg and 15 mg groups.

Clinical Chemistry
Treatment-emergent AEs of abnormal laboratory clinical chemistry values (ALT, AST, creatinine, and blood CPK) have been discussed in the section for the respective associated AESIs.

Lipids
The Applicant reported that, in the PBO-controlled AD Analysis Set, there were dose-dependent mean increases in total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) with upadacitinib 15 mg and 30 mg treatments compared to placebo. Despite increases in lipids with upadacitinib treatment, the ratios of TC/HDL-C and LDL-C/HDL-C were maintained.

In the Long-term Upadacitinib Phase 3 AD Analysis Set, the mean increases in TC, HDL-C, and LDL-C were higher in the upadacitinib 30 mg group compared to the 15 mg group. Although total lipids increased, the ratios of TC/HDL-C and LDL-C/HDL-C ratios remained relatively stable. The mean change from baseline in LDL-C increased gradually and stabilized starting at or after Week 52.

Reviewer's Comments:
This reviewer agrees that upadacitinib treatment in subjects with AD was associated with a dose dependent increase in lipid parameters (TC, HDL-C and LDL-C). While total lipids did increase, the atherogenic index did not show a significant increase as assessed by ratios of TC/HDL-C and LDL-C/HDL-C.

8.2.4.1. Vital Signs

Systolic and Diastolic Blood Pressure Increase
In the PBO-controlled AD Analysis Set, the percentages of subjects meeting criteria for potentially clinically significant (PCS) changes in blood pressure were similar between the upadacitinib 30 mg group, upadacitinib 15 mg group, and the placebo group. The Applicant reported that no subjects discontinued study drug due to abnormal blood pressure. No adolescent subjects in either upadacitinib groups had a PCS increase in systolic or diastolic blood pressure during the placebo-controlled period.

No significant changes in BP from baseline throughout the treatment period in the Long-term Upadacitinib Phase 3 AD Analysis Set. The percentage of subjects with PCS changes in blood pressure are shown in Table 75.

Table 75. Number and Percentage of Subjects Meeting Criteria For Potentially Clinically Significant Values For Blood Pressure (Long-Term Upadacitinib Phase 3 AD Analysis Set)

	Overall Population		Adolescent Population	
	UPA 15 mg (N=1239) n/N_OBS (%)	UPA 30 mg (N=1246) n/N_OBS (%)	UPA 15 mg (N=167) n/N_OBS (%)	UPA 30 mg (N=166) n/N_OBS (%)
Sitting Systolic Blood Pressure (mmHg)				
<=90 AND >=20 DECREASE	21/1233 (1.7)	24/1243 (1.9)	6/166 (3.6)	5/166 (3.0)
>=160 AND >=20 INCREASE	40/1233 (3.2)	42/1243 (3.4)	1/166 (0.6)	2/166 (1.2)
Sitting Diastolic Blood Pressure (mmHg)				
<=50 AND >=10 DECREASE	30/1233 (2.4)	30/1243 (2.4)	12/166 (7.2)	9/166 (5.4)
>=100 AND >=10 INCREASE	56/1233 (4.5)	61/1243 (4.9)	2/166 (1.2)	0

Source: SUR Table 2.6__1.2.1.

8.2.4.2. Weight

In the PBO-controlled AD Analysis Set, the percentage of subjects who experienced weight changes (> 7%) are shown in Table 76. Weight gain of 7% or more occurred more frequently in the upadacitinib groups, and it appeared to be dose-dependent. Weight increases of > 7% were only assessed in the adult population.

Table 76. Number and Percentage of Subjects with Weight Change of >7% (Placebo-Controlled AD Analysis Set)

	Overall Population			Adolescent Population		
WEIGHT (KG)	Placebo (N=902) n/N_OBS (%)	UPA 15 mg (N=899) n/N_OBS (%)	UPA 30 mg (N=906) n/N_OBS (%)	Placebo (N=115) n/N_OBS (%)	UPA 15 mg (N=114) n/N_OBS (%)	UPA 30 mg (N=114) n/N_OBS (%)
> 7% DECREASE	34/892 (3.8)	19/894 (2.1)	17/903 (1.9)	6/114 (5.3)	3/114 (2.6)	0/114
> 7% INCREASE	34/778 (4.4)	76/780 (9.7)	107/789 (13.6)	-	-	-

Source: Modified from ISS Tables 2.6__1.2.1 and 2.6__1.2.2.

In the Long-Term Upadacitinib Phase 3 AD Analysis Set, the percentage of subjects who experienced weight changes (> 7%) are shown in Table 77. Weight increases of > 7% were only assessed in the adult population.

Table 77. Number and Percentage of Subjects Meeting Criteria for Potentially Clinically Significant Values for Weight Change (Long-Term Upadacitinib Phase 3 AD Analysis Set)

	Overall Population		Adolescent Population	
WEIGHT (KG)	UPA 15 mg (N=1239) n/N_OBS (%)	UPA 30 mg (N=1246) n/N_OBS (%)	UPA 15 mg (N=167) n/N_OBS (%)	UPA 30 mg (N=166) n/N_OBS (%)
> 7% DECREASE	87/1229 (7.1)	75/1241 (6.0)	7/166 (4.2)	7/166 (4.2)
> 7% INCREASE	283/1063 (26.6)	347/1075 (32.3)	-	-

Source: Modified from SUR Tables 2.6__1.2.1 and 2.6__1.2.2.

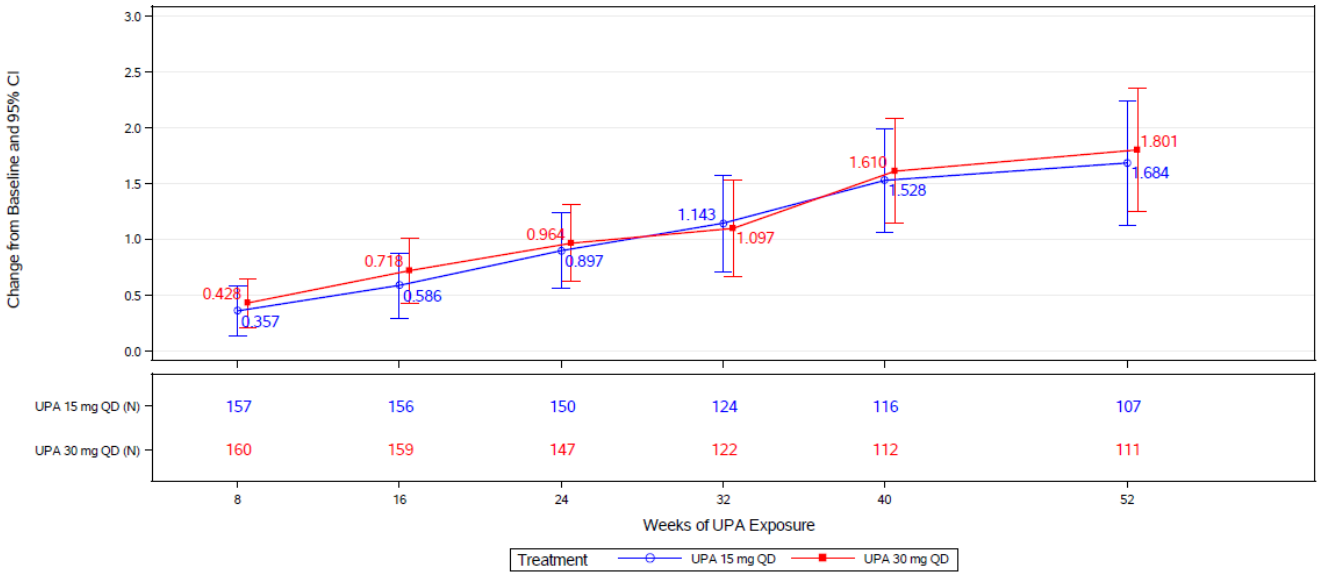
Reviewer's Comments:
This reviewer agrees that there was a dose-dependent association of weight gain with upadacitinib treatment.

8.2.4.3. Height

For adolescents in the PBO-controlled AD Analysis Set, the Applicant reported that the mean change of height (in cm) at Week 16 from baseline was 0.654, 0.627, and 0.411 for the upadacitinib 30 mg, upadacitinib 15 mg, and placebo groups, respectively. Due to the small sample size, it varied more for the younger adolescents (12 - 14 years old) compared with the older adolescents (15 – 17 years old). No apparent differences in the mean height were observed between the treatment groups at Week 16.

In the Long-Term Upadacitinib Phase 3 AD Analysis Set, the mean change from baseline in height in adolescents increased similarly in the first 52 weeks for the upadacitinib 30 mg and 15 mg groups (Figure 18).

Figure 18. Plot of Mean Change from Baseline in Height (cm) in Adolescents by Randomized Treatment Group (Long-Term Upadacitinib Phase 3 AD Analysis Set)



Source: SUR FIGURE 2.6__1.6.

Reviewer's Comments:
This reviewer agrees that no significant differences in height change were observed between the upadacitinib treatment groups at Week 52 from baseline.

8.2.4.4. Tanner Score

This review agrees that although the available data on Tanner Score are limited, upadacitinib therapy did not appear to affect the maturation of the adolescents.

8.2.4.5. Electrocardiograms (ECGs)

In the Phase 3 studies, 12 lead ECGs were performed at screening only. As discussed in the Section Dropouts and/or Discontinuations Due to Adverse Effects, one subject (Subject (b) (6) in M16-045) had abnormal ECG with QTc Prolongation, sinus arrhythmia and chest pain during the study that led to study drug discontinuation. Repeat ECGs before and after the study drug discontinuation were normal. A cardiology evaluation did not reveal any clinically significant findings that required further treatment or evaluation. The event was considered possibly related to study drug.

8.2.4.6. QT

Extensive monitoring and evaluation of ECG parameters including exposure-response analyses

during the upadacitinib Phase 1 studies showed no evidence of upadacitinib effects on cardiac conduction, including no effect on QT/QTc interval. Consequently, based on the compiled evidence from the Phase 1 studies, the Agency agreed that additional thorough QT studies for upadacitinib were not required.

8.2.5. Analysis of Submission-Specific Safety Issues

Summary of serious risks identified:

- Retinal Detachment, reviewed by Dr Wiley Chambers (Ophthalmology)

8.2.5.1. Retinal Detachment

The Division (DDD) requested the Division of Ophthalmology to review the cases of retinal detachment reported in the development program for AD and comment on the possible relationship between upadacitinib and this adverse event. This is the summary of the consult review by Dr. Wiley Chambers:

"A potential association between patients receiving upadacitinib and the development of retinal detachments is weak. While 5 patients developing retinal detachments were reported in atopic dermatitis trials, in most cases, the patients who developed the retinal detachments had other factors which may have contributed to the retinal detachment. The lack of retinal detachments in patients receiving upadacitinib for other indications decreases the likelihood that upadacitinib is the cause of the retinal detachments in patients with atopic dermatitis.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

No COA analyses were conducted to inform safety/tolerability in the AD studies.

8.2.7. Safety Analyses by Demographic Subgroups

8.2.7.1. Race

As shown in Table 78 and Table 79, across the AD Analysis Sets (PBO-controlled and Long-Term Phase 3) and treatment groups, no consistent pattern of difference was found in the rates of AEs between whites and nonwhites.

Table 78. Number and Percentage of Subjects with TEAEs by Race (Placebo-Controlled AD Analysis Set)

	White			Non-White		
	Placebo (N=629) n (%)	**UPA 15 mg (N=591) n (%)**	**UPA 30 mg (N=630) n (%)**	**Placebo (N=273) n (%)**	**UPA 15 mg (N=308) n (%)**	**UPA 30 mg (N=276) n (%)**
Adverse event	374 (59.5)	370 (62.6)	444 (70.5)	154 (56.4)	204 (66.2)	186 (67.4)
Adverse Drug Reaction	124 (19.7)	185 (31.3)	248 (39.4)	61 (22.3)	113 (36.7)	119 (43.1)
Severe AE	32 (5.1)	31 (5.2)	31 (4.9)	11 (4.0)	12 (3.9)	11 (4.0)
Serious AE	17 (2.7)	12 (2.0)	16 (2.5)	9 (3.3)	7 (2.3)	3 (1.1)
AE leading to study drug discontinuation	23 (3.7)	16 (2.7)	23 (3.7)	11 (4.0)	5 (1.6)	3 (1.1)
AE leading to death	0	0	0	0	0	0

Source: CSS Table 2.4__1.4.1.

Table 79. TEAEs in Exposure-Adjusted Rate per 100 Patient Years by Race (Long-Term Upadacitinib Phase 3 AD Analysis Set)

	Whites		Non-Whites	
	UPA 15 mg (N=836)	**UPA 30 mg (N=876)**	**UPA 15 mg (N=403)**	**UPA 30 mg (N=370)**
Exposure-Adjusted Event Rate	**(PYS=894.4) Events (E/100PY)**	**(PYS=976.3) Events (E/100PY)**	**(PYS=478.9) Events (E/100PY)**	**(PYS=437.9) Events (E/100PY)**
Adverse event	2510 (280.6)	3070 (314.4)	1261 (263.3)	1341 (306.2)
Adverse Drug Reaction	861 (96.3)	1097 (112.4)	447 (93.3)	566 (129.3)
Severe AE	123 (13.8)	155 (15.9)	47 (9.8)	60 (13.7)
Serious AE	65 (7.3)	84 (8.6)	33 (6.9)	25 (5.7)
AE leading to study drug discontinuation	44 (4.9)	63 (6.5)	16 (3.3)	18 (4.1)
AE leading to death	0	1 (0.1)	0	0

Source: SUR Table 2.4__1.5.1.

As shown in Table 80 and Table 81, for AESIs across both analysis sets, malignancies occurred mostly in the whites. The rates of herpes zoster and neutropenia were dose dependent and higher for non-whites than whites. Hepatic disorder, anemia and CPK elevation occurred more often in the nonwhites in the Long-Term Upadacitinib Phase 3 AD Analysis Set. There were no noticeable differences across races for other variables analyzed.

Table 80. Number and Percentage of Subjects with AESI by Race (Placebo-Controlled AD Analysis

	White			Non-White		
	Placebo (N=629) n (%)	UPA 15 mg (N=591) n (%)	UPA 30 mg (N=630) n (%)	Placebo (N=273) n (%)	UPA 15 mg (N=308) n (%)	UPA 30 mg (N=276) n (%)
Serious infection	5 (0.8)	5 (0.8)	3 (0.5)	0	2 (0.6)	1 (0.4)
Opportunistic infection excluding tuberculosis and herpes zoster	1 (0.2)	4 (0.7)	3 (0.5)	3 (1.1)	2 (0.6)	4 (1.4)
Herpes zoster	2 (0.3)	7 (1.2)	9 (1.4)	3 (1.1)	7 (2.3)	5 (1.8)
Active tuberculosis	0	0	0	0	0	0
Malignancy	0	3 (0.5)	6 (1.0)	0	0	0
Non-melanoma skin cancer (NMSC)	0	3 (0.5)	2 (0.3)	0	0	0
Malignancy excluding NMSC	0	0	4 (0.6)	0	0	0
Lymphoma	0	0	1 (0.2)	0	0	0
Hepatic disorder	6 (1.0)	10 (1.7)	8 (1.3)	6 (2.2)	5 (1.6)	7 (2.5)
Adjudicated gastrointestinal perforation	0	0	0	0	0	0
Anemia	0	2 (0.3)	10 (1.6)	4 (1.5)	1 (0.3)	3 (1.1)
Neutropenia	0	5 (0.8)	14 (2.2)	3 (1.1)	5 (1.6)	12 (4.3)
Lymphopenia	3 (0.5)	1 (0.2)	2 (0.3)	0	1 (0.3)	1 (0.4)
Creatine phosphokinase (CPK) elevation	9 (1.4)	24 (4.1)	36 (5.7)	12 (4.4)	17 (5.5)	14 (5.1)
Renal dysfunction	0	1 (0.2)	0	0	0	0
Adjudicated MACE*	0	0	0	0	0	0
Adjudicated VTE**	1 (0.2)	0	0	0	0	0

Source: Modified from ISS Table 2.4__1.4.15.

Table 81. AESI in Exposure-Adjusted Rate per 100 Patient Years by Race (Long-Term Upadacitinib Phase 3 AD Analysis Set)

	Whites		Non-Whites	
	UPA 15 mg (N=836)	**UPA 30 mg (N=876)**	**UPA 15 mg (N=403)**	**UPA 30 mg (N=370)**
Exposure-Adjusted Event Rate				
	(PYS=894.4) Events (E/100 PY)	**(PYS=976.3) Events (E/100 PY)**	**(PYS=478.9) Events (E/100 PY)**	**(PYS=437.9) Events (E/100 PY)**
Serious infection	24 (2.7)	27 (2.8)	8 (1.7)	12 (2.7)
Opportunistic infection excluding tuberculosis and herpes zoster	14 (1.6)	10 (1.0)	8 (1.7)	17 (3.9)
Herpes zoster	23 (2.6)	47 (4.8)	25 (5.2)	27 (6.2)
Active tuberculosis	1 (0.1)	0	0	1 (0.2)
Hepatic disorder	38 (4.2)	46 (4.7)	46 (9.6)	60 (13.7)
Adjudicated gastrointestinal perforation	0	0	0	0
Anemia	9 (1.0)	28 (2.9)	9 (1.9)	18 (4.1)
Neutropenia	15 (1.7)	19 (1.9)	10 (2.1)	26 (5.9)
Lymphopenia	5 (0.6)	7 (0.7)	1 (0.2)	2 (0.5)
Creatine phosphokinase (CPK) elevation	55 (6.1)	100 (10.2)	42 (8.8)	53 (12.1)
Renal dysfunction	1 (0.1)	0	0	2 (0.5)
Exposure-Adjusted Incidence Rate				
	n/total PY (n/100 PY)	**n/total PY (n/100 PY)**	**n/total PY (n/100 PY)**	**n/total PY (n/100 PY)**
Malignancy	5/890.4 (0.6)	12/972.4 (1.2)	1/478.9 (0.2)	0
Non-melanoma skin cancer (NMSC)	4/890.5 (0.4)	5/973.0 (0.5)	0	0
Malignancy excluding NMSC	1/894.3 (0.1)	7/975.8 (0.7)	1/478.9 (0.2)	0/437.9
Lymphoma	0	1/976.3 (0.1)	0	0
Adjudicated MACE	2/894.4 (0.2)	1/976.3 (0.1)	0	0
Adjudicated VTE	1/894.4 (0.1)	1/976.2 (0.1)	0	0

E/100 PY = Events per 100 patient-years; n/100 PY = Number of subjects with at least one event per 100 patient-years.
Subjects with missing race are excluded from the table.
Source: Modified from SUR Table 2.4__1.5.8.

Reviewer's Comments:
Because the majority of subjects were white (approximately 70%), no conclusions could be made regarding differences in the rate of AEs based on race.

8.2.7.2. Age

No consistent trend related to age was found in all categories of AEs in age groups < 65 year of age. All cases of malignancies were observed in adults ≥ 40 years old. There were no cases of malignancy in the placebo group regardless of age.

As shown in Table 82, in both Placebo-Controlled and Long-Term Upadacitinib Phase 3 AD Analysis Set, there was a higher rate of malignancy and anemia among those subjects ≥ 65 years of age, in particular with the upadacitinib 30 mg dose, compared to those < 65 years of

age. In the Long-Term Upadacitinib Phase 3 AD Analysis Set, the rate of serious infection was also higher in subjects ≥ 65 years of age, in the upadacitinib 30 mg dose group. However, the small sample size in this sub-group of subjects ≥ 65 years precludes definitive conclusions regarding the effect of age.

Table 82. Number and Percentage of Subjects with Treatment-Emergent Adverse Events by Age Group (Placebo-Controlled AD Analysis Set)

	< 65 years			≥ 65 and ≤75 years		
	Placebo (N=861) n (%)	**UPA 15 mg (N=863) n (%)**	**UPA 30 mg (N=852) n (%)**	**Placebo (N=41) n (%)**	**UPA 15 mg (N=36) n (%)**	**UPA 30 mg (N=54) n (%)**
Adverse event	503 (58.4)	550 (63.7)	588 (69.0)	25 (61.0)	24 (66.7)	42 (77.8)
Adverse drug reaction	182 (21.1)	289 (33.5)	349 (41.0)	3 (7.3)	9 (25.0)	18 (33.3)
Severe AE	39 (4.5)	41 (4.8)	38 (4.5)	4 (9.8)	2 (5.6)	4 (7.4)
Serious AE	23 (2.7)	17 (2.0)	15 (1.8)	3 (7.3)	2 (5.6)	4 (7.4)
AE leading to discontinuation of study drug	30 (3.5)	20 (2.3)	21 (2.5)	4 (9.8)	1 (2.8)	5 (9.3)
AE leading to death	0	0	0	0	0	0

Source: Modified from ISS Table 2.4__1.4.3.

The proportions of subjects with AESIs by Age group in the Placebo-Controlled AD Analysis Set are shown in Table 83.

Table 83. Number and Percentage of Subjects with AESI by Age Group (Placebo-Controlled AD Analysis Set)

	< 65 years			>= 65 and <= 75 years		
Adverse Event	**Placebo (N=861) n (%)**	**UPA 15 mg (N=863) n (%)**	**UPA 30 mg (N=852) n (%)**	**Placebo (N=41) n (%)**	**UPA 15 mg (N=36) n (%)**	**UPA 30 mg (N=54) n (%)**
Serious infection	5 (0.6)	6 (0.7)	4 (0.5)	0	1 (2.8)	0
Opportunistic infection excluding tuberculosis and herpes zoster	4 (0.5)	6 (0.7)	6 (0.7)	0	0	1 (1.9)
Herpes zoster	5 (0.6)	14 (1.6)	14 (1.6)	0	0	0
Active tuberculosis	0	0	0	0	0	0
Malignancy	0	3 (0.3)	3 (0.4)	0	0	3 (5.6)
Non-melanoma skin cancer (NMSC)	0	3 (0.3)	2 (0.2)	0	0	0
Malignancy excluding NMSC	0	0	1 (0.1)	0	0	3 (5.6)
Lymphoma	0	0	1 (0.1)	0	0	0
Hepatic disorder	12 (1.4)	15 (1.7)	15 (1.8)	0	0	0
Adjudicated gastrointestinal perforation	0	0	0	0	0	0
Anemia	3 (0.3)	1 (0.1)	6 (0.7)	1 (2.4)	2 (5.6)	7 (13.0)
Neutropenia	3 (0.3)	10 (1.2)	24 (2.8)	0	0	2 (3.7)
Lymphopenia	3 (0.3)	2 (0.2)	2 (0.2)	0	0	1 (1.9)
CPK elevation	21 (2.4)	40 (4.6)	50 (5.9)	0	1 (2.8)	0
Renal dysfunction	0	1 (0.1)	0	0	0	0
Adjudicated MACE	0	0	0	0	0	0
Adjudicated VTE	1 (0.1)	0	0	0	0	0

Source: ISS Table 2.4__1.4.17.

The rates of subjects with categories of TEAEs by age group in the Long-Term Upadacitinib Phase 3 AD Analysis Set are shown in Table 84.

Table 84. Treatment-Emergent Adverse Events in Exposure-Adjusted Rate per 100 Patient Years by Age Group (Long-Term Upadacitinib Phase 3 AD Analysis Set)

	< 65 years		>= 65 and <= 75 years	
	UPA 15 mg (N=1191)	**UPA 30 mg (N=1179)**	**UPA 15 mg (N=48)**	**UPA 30 mg (N=67)**
Exposure-Adjusted Event Rate	**(PYS=1326.3) Events (E/100 PY)**	**(PYS=1341.1) Events (E/100 PY)**	**(PYS=47.1) Events (E/100 PY)**	**(PYS=73.1) Events (E/100 PY)**
Adverse event (AE)	3637 (274.2)	4133 (308.2)	134 (284.4)	278 (380.4)
Adverse drug reaction	1275 (96.1)	1594 (118.9)	33 (70.0)	69 (94.4)
Severe AE	160 (12.1)	187 (13.9)	10 (21.2)	28 (38.3)
Serious AE	92 (6.9)	86 (6.4)	6 (12.7)	23 (31.5)
AE leading to discontinuation of study drug	55 (4.1)	65 (4.8)	5 (10.6)	16 (21.9)
AE leading to death	0	0	0	1 (1.4)

Source: Modified SUR Table 2.4__1.5.3

The rates of subjects with AESIs by age group in the Long-Term Upadacitinib Phase 3 AD Analysis Set are shown in Table 85.

Table 85. AESI in Exposure-Adjusted Rate per 100 Patient Years by Age Group (Long-Term Upadacitinib Phase 3 AD Analysis Set)

	< 65 years		>= 65 and <= 75 years	
	UPA 15 mg (N=1191)	**UPA 30 mg (N=1179)**	**UPA 15 mg (N=48)**	**UPA 30 mg (N=67)**
Exposure-Adjusted Event Rate				
	(PYS=1326.3) Events (E/100 PY)	**(PYS=1341.1) Events (E/100 PY)**	**(PYS=47.1) Events (E/100 PY)**	**(PYS=73.1) Events (E/100 PY)**
Serious infection	32 (2.4)	33 (2.5)	0	6 (8.2)
Opportunistic infection excluding tuberculosis and herpes zoster	22 (1.7)	26 (1.9)	0	1 (1.4)
Herpes zoster	47 (3.5)	72 (5.4)	1 (2.1)	2 (2.7)
Active tuberculosis	1 (<0.1)	1 (<0.1)	0	0
Hepatic disorder	83 (6.3)	104 (7.8)	1 (2.1)	2 (2.7)
Adjudicated gastrointestinal perforation	0	0	0	0
Anemia	15 (1.1)	31 (2.3)	3 (6.4)	15 (20.5)
Neutropenia	25 (1.9)	42 (3.1)	0	3 (4.1)
Lymphopenia	6 (0.5)	8 (0.6)	0	1 (1.4)
CPK elevation	95 (7.2)	148 (11.0)	2 (4.2)	5 (6.8)
Exposure-Adjusted Incidence Rate				
	n/total PY (n/100 PY)	**n/total PY (n/100 PY)**	**n/total PY (n/100 PY)**	**n/total PY (n/100 PY)**
Malignancy	6/1322.2 (0.5)	8/1338.7 (0.6)	0	4/71.6 (5.6)
Non-melanoma skin cancer (NMSC)	4/1322.4 (0.3)	4/1339.1 (0.3)	0	1/71.8 (1.4)
Malignancy excluding NMSC	2/1326.1 (0.2)	4/1340.8 (0.3)	0	3/72.9 (4.1)
Lymphoma	0	1/1341.1 (<0.1)	0	0
Adjudicated MACE	1/1326.3 (<0.1)	0	1/47.1 (2.1)	1/73.1 (1.4)
Adjudicated VTE	1/1326.2 (<0.1)	0	0	1/72.9 (1.4)

Source: SUR Table 2.4__1.5.10.

8.2.7.3. Sex

In both PBO-controlled and Long-term Upadacitinib Phase 3 AD Analysis Sets, the rates of subjects with TEAEs, ADRs, SAEs, severe TEAEs, and AEs leading to discontinuation of study drug were generally comparable in females and males in both upadacitinib doses, except the rate of AEs leading to discontinuation of study drug was higher in females only in the upadacitinib 15 mg group. The rates of most AESIs were similar between males and females, no obvious trend was noted in either of the analysis sets, except CPK elevation and hepatic disorders occurred

more often in males in both doses. Nausea, acne, and herpes simplex occurred more often in females in both upadacitinib doses.

Reviewer's Comments:
Overall, no significant difference in AEs between the males and females.

8.2.7.4. BMI and Weight

There was no consistent pattern or trend for the types of TEAEs and AESIs by BMI or weight groups across both PBO-controlled and Long-term Upadacitinib Phase 3 AD Analysis Sets.

8.2.7.5. Screening eGFR

According to the Applicant, due to the markedly smaller number of subjects with screening eGFR 40-60mL/min/1.73 m^2, comparison with other subgroups were not done to avoid misleading interpretation. Only results from subjects with screening eGFR 60-90 mL/min/1.73 m^2 (mild renal impairment) and those with eGFR $\geq$ 90 mL/min/1.73 m^2 (normal renal function) were analyzed.

In both PBO-controlled and Long-term Upadacitinib Phase 3 AD Analysis Sets, there was no consistent pattern for overall AEs, SAEs, and AEs leading to discontinuation of study drug, between these 2 subgroups of subjects (mild renal impairment and normal renal function). Most of the AESIs were reported in small numbers, but the rates of serious infection, opportunistic infection (excluding TB and herpes zoster) and herpes zoster appeared to be slightly lower in subjects with mild renal impairment compared to those with normal renal function in both the upadacitinib treatment groups. Most of the malignancies were reported in subjects with mild renal impairment, but the overall numbers of malignancies were very small. In the Long-term Upadacitinib Phase 3 AD Analysis Sets, anemia occurred more often in the 30 mg group in subjects with mild renal impairment than those with normal renal function. Overall, the small numbers of most AESIs made it difficult to make any meaningful comparison between the subjects with mild renal impairment and those with normal renal function.

Reviewer's Comments:
No consistent pattern was found for overall AEs, SAEs, and AEs leading to discontinuation of study drug between these 2 subgroups of subjects (mild renal impairment and normal renal function) in both Upadacitinib Phase 3 AD Analysis Sets. Most of the AESIs were reported in a small number, which made it difficult to make any meaningful comparison between the two subgroups.

8.2.7.6. Upadacitinib Monotherapy vs. Upadacitinib Combination Therapy

The rates of subjects with TEAEs, SAEs, severe TEAEs, and TEAEs leading to discontinuation were generally similar between the upadacitinib monotherapy and upadacitinib combination therapy subgroups across the PBO-controlled and the Long-term Upadacitinib Phase 3 AD Analysis Sets and across the upadacitinib treatment groups.

8.2.8. Specific Safety Studies/Clinical Trials

No specific safety studies were conducted.

8.2.9. Additional Safety Explorations

8.2.9.1. Human Carcinogenicity or Tumor Development

No clinical studies were completed specifically for human carcinogenicity or tumor development.

8.2.9.2. Human Reproduction and Pregnancy

The Division (DDD) requested assistance from Division of Pediatric and Maternal Health (DPMH) to determine whether postmarketing requirement (PMR) studies on pregnancy and lactation would be appropriate for this product. This is the summary of the consult review.

Review of Clinical Data

Review of Clinical Data Review of Literature
Neither the Applicant nor this reviewer identified any relevant publications. ReproTox did not identify any human data with use of Rinvoq during pregnancy. Briggs GG and Freeman RK in Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk do not have any entries on Rinvoq or upadacitinib.

Review of Pharmacovigilance Database (PV) and Drug Utilization
The Applicant performed a cumulative search of all case reports for Rinvoq (upadacitinib), NDA 211675, and provided a review and summary of all pregnancy cases reported during clinical trials from all indications for upadacitinib; rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), atopic dermatitis (AD), ulcerative colitis (UC), Crohn's disease (CD), hidradenitis suppurativa (HS), juvenile idiopathic arthritis (JIA), and giant cell arthritis (GCA), as well as from the postmarketing setting through February 15, 2021.

The Applicant identified a total of 106 maternal exposure pregnancies, 87 from clinical trials and 19 postmarketing reports. Table 86 references the 87 pregnancies and outcomes from clinical trials (maternal age 18-45, exposure range 3-9 weeks from LMP to last dose)

Table 86. Reported Pregnancies in Upadacitinib Clinical Trials with Drug Exposure starting 1 Month prior to Conception and during the First Trimester

N of pregnancies (patients)	**Treatment Exposed**	**Blinded/Unblinded to treatment allocation**	**Outcomes**
11(11)	N/A	Remain blinded	a. 2 live births without congenital anomalies b. 5 elective terminations without fetal defects or unknown c.4 ongoing pregnancies
22(19)	No	unblinded	NA
54(53)	Yes	Unblinded	One patient with 2 pregnancies: a spontaneous abortion and later a live birth without congenital anomaly Disposition of the 54 pregnancies in Table Table 87.

Table 87. Outcome of the 54 Pregnancies with Exposure to the Drug

Pregnancy Outcomes for Maternal Exposure Reports	**Patients on Upadacitinib and Background Methotrxate at Time of Pregnancy (n = 27)**	**Patients on Upadacitinib Monotherapy at Time of Pregnancy (n = 27)**	**N = 54**
Total live births:			17
Live birth without congenital	8	9	17[a]
Live birth with congenital	-	-	0
Total fetal deaths:			24
Spontaneous abortion	10	4	14
Stillbirth without fetal defects	-	-	0
Stillbirth with fetal defects	-	-	0
Ectopic pregnancy	1	0	1
Elective termination (no fetal defects or unknown)	3	6	9
Elective termination (with fetal defects)	-	-	0
Ongoing pregnancy	5	7	12
Lost to follow up	-	1	1
Other (molar and blighted ovum)	-	-	0

From Applicant's submission, Table 1, P-5. Response to IR, March 18, 2021

Table 88. Outcome of the 19 Pregnancies with Exposure to the Drug Post-Marketing

16 pregnancies: ongoing (11) or unknown (5)
1 live birth without congenital anomaly in an RA patient
1 spontaneous abortion in a 40-year-old female patient with RA who was taking upadacitinib alone during the first trimester of pregnancy
1 ectopic pregnancy in an RA patient with limited information reported

Reviewer Comment
The review of literature and Applicant's PV on Rinvoq use in pregnant women has not identified a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. The findings are not sufficient to draw any conclusions about the safe use of Rinvoq during pregnancy. We cannot determine from the small number of reported outcomes and limited information the impact of upadacitinib on pregnancy outcomes.

The Applicant evaluated drug utilization rate among females of reproductive potential using the Optum Clinformatics Data Mart, an administrative claims database from a large U.S. insurance provider. Patients who received upadacitinib were identified from the time of Rinvoq approval (August 16, 2019) through September 30, 2020, the latest date available in the dataset. A total of 1,656 patients were identified within the database who received at least one prescription for upadacitinib. Among these, 1,341 (81%) patients were women, and 196 (11.8%) were women aged 15-44 years old, the age range chosen to identify reproductive age. Of these, there was one female patient (0.5%) who had a single prescription provided after her estimated LMP but prior to confirmation of the pregnancy. The pregnancy resulted in a live birth, and the baby had no identified major or minor congenital anomalies. There was no evidence of delivery complications.

Reviewer Comment
From the information provided by the Applicant, PV and drug utilization, it appears the use of Rinvoq during pregnancy is occurring. As half of all pregnancies in the U.S. are unplanned, a PMR for a single-arm pregnancy safety study will be helpful to collect better quality information on duration of exposures, complications, and outcomes following inadvertent exposure of Rinvoq during pregnancy. Inadvertent exposure includes unintentional pregnancies that occur outside of mitigation recommendations as described in Warnings and Precautions of the labeling.

There is neither disease-based registry nor pregnancy registry for upadacitinib for any indication; therefore, no interim of final reports exist.

DISCUSSION AND CONCLUSIONS

Pregnancy

AD is a common disease that affects up to 10% of adults and of those affected, it is likely more than half of these adults have moderate-severe disease for which systemic immunomodulators may be needed, including in females of reproductive potential.

The review of literature and Applicant's PV on Rinvoq use in pregnant women are insufficient to identify a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In the approximately 100 women exposed in clinical trials and post- marketing, there have been no signals of embryofetal toxicity. However, this is not enough to dismiss the animal findings. Animal reproduction studies have demonstrated that upadacitinib may adversely affect a developing fetus.

Upadacitinib is considered teratogenic; therefore, DPMH recommends pregnancy testing prior to initiating treatment with Rinvoq and use of effective contraception in pregnant women during the duration of the treatment. DPMH usually recommends for nongenotoxic drugs contraception to continue for 5 ½ half-lives of the drug (5.5*14=77 ~4 days for Upadacitinib) after the last dose of the drug. In discussions with the review team, it was decided, in the absence of any additional information, to allow the labeling to remain unchanged in reference to the previous recommendations for the duration of contraception after the last dose.

Given the anticipated use of Rinvoq in females of reproductive potential (who may encounter inadvertent exposure with an unplanned pregnancy), and the limited information to date, post-marketing studies should be considered to capture any reported pregnancy and infant outcomes. DPMH recommends a single-arm pregnancy safety study as a PMR. For more information, see the May 2019 FDA draft Guidance for Industry Post-approval Pregnancy Safety Studies.

A single-arm pregnancy safety study would assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to upadacitinib during pregnancy. The Applicant should use a structured approach to data collection and targeted questionnaires throughout pregnancy and postpartum to obtain follow-up information on all exposed pregnancies of which they become aware.

Lactation
There are no data on the presence of upadacitinib in human milk, the effects on the breastfed infant, or the effects on milk production. Upadacitinib is present in animal milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk, however, due to differences in species-to-species lactation physiology, the amount of drug transferred into milk will vary. Because of the potential for serious adverse reactions in the breastfed infant based on adverse reactions seen in adult patients taking Rinvoq (e.g., serious infections, malignancy, and thrombosis etc.), breastfeeding is not recommended during treatment with Rinvoq. Given that upadacitinib will be used in females of reproductive potential with atopic dermatitis and based on the lack of available data in lactating women, DPMH recommends a PMR for a clinical lactation (milk only) study to better understand whether the amount of drug present in human milk is clinically significant.

The Applicant should conduct a lactation study (milk only) in healthy lactating women who volunteer for clinical research and/or women prescribed upadacitinib who are planning to discontinue breastfeeding their infants. A milk-only study is recommended because of the risk of serious adverse events seen in adult patients who have taken upadacitinib. In this type of study, the infant is not exposed to upadacitinib. For more information, see the May 2019 FDA draft Guidance for Industry Clinical Lactation Studies: Considerations for Study Design.

DPMH RECOMMENDATIONS FOR POSTMARKETING REQUIREMENTS
Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Rinvoq (upadacitinib), for any indication, during pregnancy and /or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.

DPMH LABELING RECOMMENDATIONS
For labeling recommendations, please refer to the review from Christos Mastroyannis, M.D., Division of Pediatric and Maternal Health.

8.2.9.3. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

8.2.9.3.1. Overdose

One accidental overdose of upadacitinib was reported in Subject (b) (6) (Study M16-045, upadacitinib 30 mg group), a 49-year-old female with previously reported short term memory loss, accidentally took two 30 mg tablets on Day 163 of study. The AE of overdose was nonserious and the subject did not experience any other AEs as a result of the overdose event. The subject subsequently withdrew consent from the study.

Another event of overdose reported in Subject (b) (6) (Study M16-047, upadacitinib 15 mg group) was reassessed by the Applicant as an event of intentional overdose. This event has been included in the assessment of Suicidal Ideation and Behavior Section 8.2.4.5.4.

In case of an overdose, the Applicant recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate treatment.

8.2.9.3.2. Drug Abuse

Based on the mode of action, there is no reason to assume that there is a potential for abuse or dependency of upadacitinib.

8.2.9.3.3. Withdrawal and Rebound

The Applicant reported no evidence of rebound effects upon discontinuation of treatment in any of the studies in the upadacitinib AD program.

8.2.9.4. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

The Applicant reported no evidence for and no anticipation of upadacitinib to affect the ability to drive or operate machinery, or to otherwise impair mental ability.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Upadacitinib 15 mg daily was first approved for the treatment of RA on August 15, 2019 in the US. Through 31 July 2020, upadacitinib has been approved in 50 countries with estimated cumulative postmarketing exposure of (b) (4) patient treatment years.

The Applicant reported that the overall safety of upadacitinib 15 mg QD therapy was evaluated through review of postmarketing reports (spontaneous, solicited, literature) received from August 16, 2019 through 15 August 2020. Review of the postmarketing safety data reported for upadacitinib up to date demonstrated a similar safety profile as observed in the clinical studies for RA. Pneumonia was the most commonly reported serious infection. However, recent reviews of the safety information from the postmarketing experience by Office of Pharmacovigilance and Epidemiology have identified cardiovascular disorders and hypersensitivity as new safety signals for upadacitinib.

Expectations on Safety in the Postmarket Setting

Recent postmarketing, long-term clinical safety studies on tofacitinib for RA treatment showed that:

1. In RA patients who were 50 years of age and older with at least one additional cardiovascular risk factor treated with tofacitinib, a higher rate of all-cause mortality, including sudden cardiovascular (CV) death, was observed in patients treated with tofacitinib compared with TNF blockers (etanercept and adalimumab).
2. In RA patients treated with tofacitinib, a higher rate of malignancies (excluding non-melanoma skin cancer (NMSC) was observed in patients treated with tofacitinib compared with TNF blockers.
3. In RA patients who were 50 years of age and older treated with tofacitinib, a higher rate of major adverse cardiovascular events (MACE), including cardiovascular death, myocardial infarction, and stroke, was observed with tofacitinib compared with TNF blockers.

4. In RA patients who were 50 years of age and older treated with tofacitinib, a higher rate of thrombosis was observed compared to those treated with TNF blockers.

The overall safety concerns in the JAK inhibitor class led to Agency's decision to include a Safety Labeling Change (SLC), restricted indicated populations (restriction to patients who have failed or unable to tolerate approved topical and systemic therapies), and stepwise dosing such that initially the 15 mg dose would be prescribed and increased to 30 mg only if adequate response is not achieved.

The Applicant reported the following planned or ongoing Post-Marketing Safety Studies for upadacitinib.

- For RA indication: 2 ongoing long term safety studies (prospective observational cohort) aimed at comparing the incidence of malignancies, VTEs, MACE, and serious infection events in patients treated with upadacitinib relative to patients treated with biologic medications approved for the treatment of moderately to severely active RA.
  - In the US:
    (b) (4)
  - (b) (4)
- For AD indication: 3 studies are planned.
  - (b) (4)

(b) (4)

Office of Surveillance and Epidemiology (OSE)/Division of Epidemiology (DEPI) recommended PMR for long term safety evaluation:

Conduct a prospective observational study (analyses conducted in patient cohorts enrolled prospectively and followed actively in accordance with a written protocol) to assess the long-term safety of upadacitinib treatment in U.S. patients with moderate-to-severe atopic dermatitis. Fully ascertain and centrally verify serious adverse events, Major Adverse Cardiovascular Events (myocardial infarction, stroke, cardiovascular death, and sudden death), malignancies (including lymphoma, lung cancer, and other malignancies), serious infections, opportunistic infections (including herpes zoster), retinal detachment, thrombosis (including deep venous thrombosis, pulmonary embolism, and arterial thrombosis), hepatoxicity (including drug induced liver injury), and possibly other adverse events of special interest. For each adverse-event outcome separately, compare incidence in upadacitinib-treated patients against reference rates internally derived from analyses conducted in patients treated with dupilumab or other chronic systemic treatments for moderate to-severe atopic dermatitis. Regardless of treatment discontinuation or switch to a different treatment for atopic dermatitis, continue following patients for malignancy outcomes and possibly other adverse events with delayed onset. Enroll a sufficient number of patients to describe the frequency of the adverse events of special interest in representative U.S. patients who start treatment with upadacitinib for atopic dermatitis in the setting of routine clinical practice. Implement a plan that uses rigorous, transparent, and verifiable methods to ascertain and characterize safety events that occur during and after treatment with upadacitinib. Enroll patients over a 4-year period and follow each patient for at least 8 years from time of enrollment.

DPMH recommended PMRs for pregnancy study (Section 8.2.9.2).

This reviewer considers the post-marketing studies planned by the Applicant, the long term safety PMR recommended by OSE/DEPI, and the pregnancy PMR study recommended by DPMH sufficient for long term safety evaluation.

8.2.11. Integrated Assessment of Safety

The intended use of upadacitinib is for the (b) (4) The clinical studies showed that upadacitinib was effective. The efficacy of upadacitinib is similar and potentially higher than that of the currently marketed systemic therapeutic product for the same indication.

Review of the upadacitinib safety database demonstrate that upadacitinib treatment was associated with increased frequencies of TEAEs, ADRs, infections, opportunistic infections, herpes zoster, anemia, neutropenia, lymphopenia, lipid elevations and blood CPK elevations. These findings are consistent with what has been observed with other JAK inhibitors. Acne was also found to occur more frequently in the upadacitinib groups in a dose-dependent pattern.

There was a slight increase the rate of malignancies excluding NMSC in the upadacitinib groups and higher in the 30 mg group, compared with the 15 mg group. However, because 4 out of the 7 malignancies excluding NMSC occurred in the first 64 days of upadacitinib treatment, it is unlikely that they were caused by upadacitinib treatment.

In addition, increased rates of serious infections and malignancies were reported in the adult subjects ≥ 65 years of age in the upadacitinib 30mg group. The Applicant recommended 15 mg QD only for adults ≥ 65 years of age.

In light of the recent safety risks identified in the postmarketing long-term clinical studies of tofacitinib for RA treatment, the benefit/risk analyses of upadacitinib for AD studies were presented to the Medical Policy and Program Review Committee (MPPRC). The overall safety concerns in upadacitinib and the JAK inhibitor class led to Agency's decision to include a SLC, restricted indicated populations (restriction to patients who have failed or unable to tolerate approved topical and systemic therapies), and stepwise dosing such that initially the 15 mg dose would be prescribed and increased to 30 mg only if adequate response is not achieved. The Agency also recommended that adult patients ≥ 65 years of age be treated with 15 mg QD only.

8.3. Summary and Conclusions

8.3.1. Statistical Issues

There were no major statistical issues affecting overall conclusions. The treatment effects were generally large and consistent across trials and endpoints (see Sections 8.1.6 and 8.1.7). There were no substantial differences in efficacy among subgroups. The amount of missing data was relatively small (4-8%) at Week 16 (i.e., the primary efficacy timepoint) across the three Phase 3 trials. Under the worst-case scenario (i.e., missing data for upadacitinib was imputed as non-responders and missing data for placebo was imputed as responders), both doses of upadacitinib remained significantly superior to placebo (p-values < 0.001) for both coprimary efficacy endpoints in all three trials (see Table 27, Table 28, and Table 29).

8.3.2. Conclusions and Recommendations

To establish the efficacy and safety of upadacitinib, the Applicant submitted data from 3 randomized, double-blinded, placebo-controlled Phase 3 studies that evaluated upadacitinib for the treatment of moderate to severe atopic dermatitis (AD) in patients 12 years of age and older who are candidates for systemic therapy. These include 2 monotherapy studies (M16-045 and M18-891) and one combination study (M16-047), that enrolled a total of 2584 subjects (including 344 adolescent subjects) with moderate to severe AD. Subjects were treated with upadacitinib for 16 weeks at doses of 15 mg QD, 30 mg QD or with a placebo. The co-primary endpoints were the proportion of subjects achieving both Investigators Global Assessments Scale (IGA) of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥ 2 points at Week 16; and proportion of subjects achieving EASI75 (≥ 75% improvement from baseline) at Week 16. In these studies, upadacitinib (both 15 mg QD and 30 mg QD) was statistically superior to the placebo for the primary endpoints at Week 16.

In addition to the 3 Phase 3 studies, data from the placebo-controlled period of the Phase 2b study M16-048 (placebo, upadacitinib 15 mg, and upadacitinib 30 mg doses only) were also included for safety analysis. The safety profile of upadacitinib was similar to that for the rheumatoid arthritis indication. The most frequently reported adverse reactions in upadacitinib treatment groups were upper respiratory tract infection, acne, herpes simplex, headache, increased blood creatine phosphokinase, cough, nausea, hypersensitivity, folliculitis, abdominal pain, pyrexia, increased weight, herpes zoster, influenza, fatigue, neutropenia, and dermatitis acneiform. A dose dependent increase of adverse reaction rates was apparent. In the AD clinical program, higher proportion of subjects treated with upadacitinib experienced retinal detachment. However, the causal relationship to the drug treatment could not be established due to presence of confounding factors. In addition, during the clinical trials, subjects had dose-dependent increase in blood lipid parameters, reduction in absolute neutrophil counts, and anemia.

In light of the recent safety results identified in the postmarketing long-term clinical studies of

tofacitinib for RA, the benefit/risk analyses of upadacitinib for AD studies were presented to the MPPRC. The overall safety concerns in upadacitinib and the JAK inhibitor class as a whole led to Agency's decision to include a Safety Labeling Change, restricted indicated populations (restriction to patients who have failed or unable to tolerate approved topical and systemic therapies), and stepwise dosing such that initially the 15 mg dose would be prescribed and increased to 30 mg only if adequate response is not achieved. The Agency also recommended that adult patients ≥ 65 years of age be treated with 15 mg QD only.

In the opinion of this reviewer, the Applicant has provided adequate evidence of safety and efficacy for the use of upadacitinib in patients 12 years of age and older with moderate to severe AD who have failed or unable to tolerate approved topical and systemic therapies, at following doses: 15 mg QD and 30 mg QD in adolescents 12 years and older with moderate-to-severe atopic dermatitis, and for adults 18-64 years of age. Due to the increased rates of serious infections and malignancies reported in adults ≥ 65 years of age in the upadacitinib 30 mg group, this reviewer recommends 15 mg QD only for adults ≥ 65 years of age.

This reviewer recommends to Division and Office leadership that upadacitinib be approved for the treatment of moderate-to-severe atopic dermatitis as follows:

- For the treatment of adults and pediatric patients 12 years of age and older with refractory, moderate to severe atopic dermatitis whose disease is not adequately controlled with other systemic drugs, including biologics, or when use of those therapies are inadvisable.

- Pediatric Patients 12 Years of Age and Older Weighing at Least 40 kg and Adults Less than 65 years of Age:
  Initiate treatment with 15 mg once daily. If an adequate response is not achieved, consider increasing the dosage to 30 mg once daily. Discontinue RINVOQ if an adequate response is not achieved with the 30 mg dose. Use the lowest effective dose needed to maintain response.

- Adults 65 Years of Age and Older:
  The recommended dosage is 15 mg once daily.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting was not conducted for this application.

Upadacitinib safety and efficacy data was presented to MPPRC on April 14, 2021.

During the review of this efficacy supplement, the FDA received the results from a post-marketing required (PMR) study A392113 of tofacitinib conducted in rheumatoid arthritis (RA) patients that showed increased risk for major adverse cardiovascular events (MACEs), opportunistic infections, and malignancies. Tofacitinib is an orally administered, small-molecule inhibitor of JAK approved for the treatment of rheumatoid arthritis (RA), psoriatic arthritis, and ulcerative colitis. FDA first approved tofacitinib, dosed at 5 mg twice daily (BID), in November 2012 for the treatment of patients with RA. Upon approval, FDA required Pfizer to conduct "a controlled clinical trial to evaluate the long-term safety of tofacitinib in patients with RA. The trial should include two doses of tofacitinib and an active comparator. The trial should be of sufficient size and duration to evaluate safety events of interest, including cardiovascular adverse events, opportunistic infections, and malignancy."

Study A3921133 enrolled RA patients 50 years of age and older with at least one cardiovascular risk factor and evaluated the long-term safety of two doses of tofacitinib (5 and 10 mg BID) compared to tumor necrosis factor inhibitors (etanercept and adalimumab). The evaluated safety events of interest included major adverse cardiovascular events (MACEs), opportunistic infections, and malignancies. In 2019, interim results from the study showed an increased risk of thrombosis and death with the 10 mg BID dose, and FDA required updates to the tofacitinib labeling as a result. Following review of the final data from the study, on January 19, 2021, the Applicant informed the Agency about an Emerging Safety Issue for tofacitinib, including an increased incidence of adjudicated MACE and adjudicated malignancies. Based on the information, the Agency issued a Drug Safety Communication on February 04, 2021.

The information from postmarketing tofacitinib trial was presented to the Medical Policy and Program Review Council (MPPRC) on April 14, 2021. MPPRC considered, based on data available from the tofacitinib program, whether the magnitude of risks associated with tofacitinib can be reasonably expected to apply across the entire JAK inhibitor drug class.

The MPPRC considered that JAK inhibitors exhibit a spectrum of pharmacodynamic profiles, and it is not known which JAK (or related enzyme) is responsible for the adverse drug reactions seen with tofacitinib. Also, although the selectivity profiles of the various JAK inhibitors differ, it is not known whether these differences are relevant to risk of the adverse events seen with tofacitinib. There is no animal model showing that inhibition of particular JAKs leads to an outcome that is comparable to those seen in the tofacitinib outcome study. The pharmacokinetic, pharmacodynamic, toxicity, and animal model data would be needed to enhance the understanding of JAK inhibitors and to see if there is evidence that differences in profile of enzyme inhibition may lead to differences in safety profile.

MPPRC concluded that because there is insufficient information to determine the specific profile of JAK inhibition that is associated with the tofacitinib findings, a class-wide W&P, referencing another member of the JAK inhibitor class, would be appropriate, but making it clear that the particular JAK has not been studied and found to have these safety findings.

The Division considered the relevance of the findings from the tofacitinib safety PMR study to the safety and benefit-risk assessment of other JAK inhibitor programs, including upadacitinib. The Division requested that the Applicant provide an updated assessment of the benefit-risk profile for upadacitinib for the proposed indication of treatment of adults and adolescents 12 years and older with moderate to severe atopic dermatitis who are candidates for systemic therapy, and to consider whether additional changes would be appropriate to the proposed indication to support a favorable benefit-risk for their application. The Applicant responded with the following proposed changes:

- For adults with moderate to severe AD, based on the demonstrated dose response for efficacy and available safety data for both doses, there is a favorable benefit-risk profile for both the 15 mg and 30 mg QD upadacitinib doses.
- In patients aged 65 and older, although upadacitinib demonstrated efficacy benefits in treatment of moderate to severe AD, the limited data in this subgroup precludes a definitive conclusion regarding the added benefit of the 30 mg dose relative to the 15 mg dose. Safety data suggest a higher risk for serious infections and malignancies with the 30 mg dose versus the 15 mg dose. Based on the need for treatment options, and the favorable benefit risk profile of the 15 mg dose, the 15 mg dose is recommended for patients > 65 years of age.
- In adolescents, available data indicate a favorable benefit risk profile for both the 15 and 30 mg doses, however, AbbVie recommended the 15 mg dose for adolescents based on rationale that there is a need for further characterization of the upadacitinib 30 mg dose in this population.

The data on efficacy and safety for upadacitinib, (b) (4) was presented to MPPRC on April 14, 2021. The MPPRC considered the need to change the proposed indication as well as whether 15mg and 30mg doses should be approved in the context of safety findings in subpopulations of adolescents and patients ≥65 years of age. The MPPRC agreed that in light of tofacitinib trial results, upadacitinib should be approved for the treatment of moderate to severe AD in patients who have failed other systemic therapies. The Council recommended approving both the 15 and 30 mg doses for both adult and adolescent patients. They also recommended stepwise dosing labeling such that initially the 15 mg dose would be prescribed and increased to 30 mg only if response is not achieved. Due to MACE events, higher risk of malignancy, and serious infections in adults >65 years of age (b) (4) the Division recommended the approval of 15mg dose in this subpopulation.

10 Pediatrics

The Applicant submitted an initial pediatric study plan (iPSP) on April 20, 2018, requesting a partial waiver for upadacitinib for the treatment of AD in children younger (b) (4) of age based on the rationale that trials are "impossible or highly impractical", and a deferral of pediatric studies in patient (b) (4) to 11- years of age.

On June 27, 2018, the Division presented the initial Pediatric Study Plan (iPSP) to the Pediatric Review Committee (PeRC). The Division agreed with Partial Waiver of Pediatric Studies for pediatric patients, although decreased the age to less than 6 months of age, because studies are impossible or highly impractical in this population due to the small numbers of patients under the age of 6 months receiving medium- to long-term systemic treatment secondary to the greater efficacy of topical therapies in infants; and a deferral of pediatric studies in patients 6 months to 11-years of age. The Division agreed with the Agreed iPSP on November 14, 2018.

The Applicant reported that the Phase 1 PK, safety, and tolerability study in pediatric subjects with AD (Study M16-049) is ongoing. This study consists of 2 sequential multiple ascending dose groups (Group 1 and Group 2). The study duration will be 9 days for each dose group, including 7 days of dosing and 2 days of follow-up during washout. Male and female pediatric patients (6 months to 11 years of age) with AD will be selected to participate. The study will initially enroll approximately 16 subjects aged 6 to 11 years, followed by approximately 16 subjects aged 2 to 5 years. Once the PK and initial safety and tolerability data from subjects 2 to 11 years of age is available, approximately 10 subjects aged 6 months to < 2 years will be allowed to participate.

The Applicant proposed two phase 3 pediatric AD studies in younger children (6 months to 11 years inclusive): Study A and Study B.

- Study A is a Phase 3 multicenter, randomized, placebo-controlled, double-blind, dose-ranging study. Approximately 180 subjects aged 6 months to 11 years, satisfying all inclusion and exclusion criteria, will be randomized in a 1:1:1 ratio to receive one of the following 3 treatments for 16 weeks combined with topical corticosteroid treatment:
  - Upadacitinib Dose A (equivalent to adult 15 mg QD; n = 60)
  - Upadacitinib Dose B (equivalent to adult 30 mg QD; n = 60)
  - Matching Placebo (n = 60)

  The doses will be determined based on population PK analyses of data available from adult subjects with RA and AD, adolescent subjects with AD as well as from pediatric subjects with polyarticular juvenile idiopathic arthritis (pJIA) and AD. Based on the current data available, the aim is to select doses to achieve exposures comparable to those achieved by the 15 mg and 30 mg doses in adult and adolescent AD (aged 12 years and older) subjects.

The study will be enrolled in 2 cohorts. Cohort 1, consisting of approximately 90 subjects 6 to 11 years old, will complete enrollment (approximately 30 subjects per treatment group) and be evaluated by a data monitoring committee before Cohort 2 begins enrollment. Cohort 2 will consist of approximately 90 subjects 6 months to 5 years old (approximately 30 subjects per treatment group).

- Study B is a Phase 3, multicenter, extension study. The primary objective is to evaluate the long-term safety and efficacy of upadacitinib monotherapy in the treatment of pediatric subjects (6 months to 11 years of age) with severe AD. This study will enroll up to approximately 180 subjects who successfully complete Study A. Subjects who received active treatment with upadacitinib Dose A or Dose B in Study A will continue to receive the same dose throughout the 120-week treatment period. Those receiving placebo in Study A will be re-randomized in a 1:1 ratio to receive either Dose A or Dose B of upadacitinib. Treatment assignments will be blinded until all subjects have completed Study A.

This product was presented to MPPRC on April 14, 2021. The Council recommended approving both the 15 and 30 mg doses for adolescent patients, although the Applicant only recommended 15 mg dose.

PeRC convened on October 6, 2021. Due to concerns of possible retinal detachment related to upadacitinib treatment and because younger patients may not be able to report symptoms of retinal detachment, PeRC recommended that PREA PMR studies in pediatric subjects 6 months to 5 years of age be deferred until data from studies in older children (6 to 11 years of age) are available. PeRC also recommended that patients 3 years of age and younger and those with cognitive impairment not be enrolled in the ongoing pediatric PK study. The following Pediatric Research Equity Act (PREA) PMR study will be issued:

PMR #2:
Conduct an active controlled efficacy and safety study (with sparse PK assessment) in patients 6 years to 11 years of age with refractory, moderate to severe atopic dermatitis whose disease is not adequately controlled with other systemic therapies, or when use of these therapies is not advisable. Subjects should initiate treatment with low dose upadacitinib or active control. The study should evaluate the treatment benefit of higher upadacitinib dosage in subjects who had inadequate response to the initial upadacitinib low dosage. The study should include at least 300 subjects treated with the upadacitinib and exposed for at least 52 weeks.

Provide the results of PK study (Study M16-049) with the protocol for study A.

Final Protocol Submission:	September 2022
Study Completion:	December 2025
Final Report Submission:	June 2026

Results from PMR #2 for pediatric subjects 6-11 years of age will inform FDA decision on whether to require a pediatric trial to support the use of upadacitinib for refractory, moderate to severe atopic dermatitis in the pediatric population age 6 months to 5 years and on the type of data that should be required.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

Other Prescription Drug Labeling

The medical officer has reviewed all labeling. Labeling negotiations were pending at the time of closure of this review. Refer to discussions in the sessions of the corresponding safety review.

APPEARS THIS WAY ON ORIGINAL

12 Risk Evaluation and Mitigation Strategies (REMS)

REMS will not be required for this application.

APPEARS THIS WAY ON ORIGINAL

13 Postmarketing Requirements and Commitment

The Applicant reported that there are 2 ongoing long term safety studies in US and Europe for rheumatoid arthritis indication to compare the incidence of malignancies, venous thromboembolism, major adverse cardiovascular events, and serious infection events in patients treated with upadacitinib relative to patients treated with biologic medications approved for the treatment of moderately to severely active RA. (b) (4)

OSE/DEPI recommended the following long-term safety PMR:

PMR#1:
Conduct a prospective observational study (analyses conducted in patient cohorts enrolled prospectively and followed actively in accordance with a written protocol) to assess the long-term safety of upadacitinib treatment in U.S. patients with moderate-to-severe atopic dermatitis. Fully ascertain and centrally verify serious adverse events, Major Adverse Cardiovascular Events (myocardial infarction, stroke, cardiovascular death, and sudden death), malignancies (including lymphoma, lung cancer, and other malignancies), serious infections, opportunistic infections (including herpes zoster), retinal detachment, thrombosis (including deep venous thrombosis, pulmonary embolism, and arterial thrombosis), hepatoxicity (including drug induced liver injury), and possibly other adverse events of special interest. For each adverse-event outcome separately, compare incidence in upadacitinib-treated patients against reference rates internally derived from analyses conducted in patients treated with dupilumab or other chronic systemic treatments for moderate-to-severe atopic dermatitis. Regardless of treatment discontinuation or switch to a different treatment for atopic dermatitis, continue following patients for malignancy outcomes and possibly other adverse events with delayed onset. Enroll a sufficient number of patients to describe the frequency of the adverse events of special interest in representative U.S. patients who start treatment with upadacitinib for atopic dermatitis in the setting of routine clinical practice. Implement a plan that uses rigorous, transparent, and verifiable methods to ascertain and characterize safety events that occur during and after treatment with upadacitinib. Enroll patients over a 4-year period and follow each patient for at least 8 years from time of enrollment.

Draft Protocol Submission:	June 2022
Final Protocol Submission:	June 2023
Study/Trial Completion:	December 2035
Final Report Submission:	December 2036

The Agency will issue the following PREA PMRs:

PMR #2:
Conduct an active controlled efficacy and safety study (with sparse PK assessment) in patients 6 years to 11 years of age with refractory, moderate to severe atopic dermatitis whose disease is not adequately controlled with other systemic therapies, or when use of these therapies is not advisable. Subjects should initiate treatment with low dose upadacitinib or active control. The study should evaluate the treatment benefit of higher upadacitinib dosage in subjects who had inadequate response to the initial upadacitinib low dosage. The study should include at least 300 subjects treated with the upadacitinib and exposed for at least 52 weeks.

Provide the results of PK study (Study M16-049) with the protocol for study A.

Final Protocol Submission:	September 2022
Study Completion:	December 2025
Final Report Submission:	June 2026

Results from PMR #2 for pediatric subjects 6-11 years of age will inform FDA decision on whether to require a pediatric trial to support the use of upadacitinib for refractory, moderate to severe atopic dermatitis in the pediatric population age 6 months to 5 years and on the type of data that should be required.

DPMH recommended the following pregnancy PMR:

PMR #3:
Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Rinvoq (upadacitinib), for any indication, during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.

Draft Protocol Submission:	June 2022
Final Protocol Submission:	December 2022
Interim/Other:	December 2025
Study/Trial Completion:	December 2027
Final Report Submission:	June 2028

Risk management strategies beyond the above postmarketing studies and product labeling are not needed for this product, if approved.

DPMH also recommended a lactation study (see Section 8.2.9.2). Following an internal discussion, it was decided that a negative lactation study would not change labeling recommendation not to breastfeed because the animal studies predict that the drug will be present in human milk, and a study would likely not provide enough evidence to remove this

recommendation.

APPEARS THIS WAY ON ORIGINAL

14 Division Director (DHOT) Comments

Not applicable.

APPEARS THIS WAY ON ORIGINAL

15 Division Director (OCP) Comments

Not applicable.

APPEARS THIS WAY ON ORIGINAL

16 Division Director (OB) Comments

Not applicable.

APPEARS THIS WAY ON ORIGINAL

17 Division Director (Clinical) Comments

APPEARS THIS WAY ON ORIGINAL

18 Appendices

18.1. References

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18.2. Financial Disclosure

Covered Clinical Study (M16-045, M18-891, M16-047, M16-048 and M17-377): Five Covered Clinical Studies

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from Applicant)
Total number of investigators identified: 2150		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 68		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

18.3. Nonclinical Pharmacology/Toxicology

Not applicable.

18.4. OCP Appendices (Technical documents supporting OCP recommendations)

18.4.1. Population PK

Population PK models were developed by the Applicant to describe the PK profile of upadacitinib and to identify clinically relevant patient covariates that may contribute to the variability in its PK profile, especially for the dose justification for upadacitinib in adult and adolescent subjects with moderate to severe AD in this application.

The population pharmacokinetic analysis included data from one Phase 1 study (Study M14-680), one Phase 2 study (Study M16-048) and four Phase 3 studies (Studies M16-045, M16-047, M17-377 and M18-891). The population, doses, dosing regimens and PK sampling time points were summarized in Table 89.

Table 89. Overview of Studies Included in the Population PK Analysis.

Study (N[a])	Phase/ Population	Upadacitinib Regimen(s), Formulation	Pharmacokinetic Sampling Times[b]
M14-680 Parts 1, 2, 5, 6 (sequence 2 each), Part 3 (N = 81)	Phase 1 / Healthy Volunteers	15 and 30 mg, Extended-Release	12 samples up to 24 h post Day 1 dose and 15 samples up to 72 h post Day 7 dose Single pre-dose sample on Days 3, 4, 5, and 6
M16-048 (N = 167)	Phase 2b/ Adult subjects with moderate to severe AD	7.5, 15, 30 mg QD, Extended-Release	Weeks 2, 4, 8, 12,16, 20, 24, 32, 40 and every 12 Weeks until Week 88 or premature discontinuation (PD)
M16-045 (N = 847)	Phase 3/ Adult and adolescent subjects with moderate to severe AD	15 and 30 mg QD, Extended-Release	Weeks 2, 8, 12, 16, or PD
M16-047 (N = 901)	Phase 3/ Adult and adolescent subjects with moderate to severe AD receiving concomitant topical corticosteroids	15 and 30 mg QD, Extended-Release	Weeks 2, 8, 12, 16, or PD
M17-377 (N = 272)	Phase 3/ Adult and adolescent Japanese subjects with moderate to severe AD receiving concomitant topical corticosteroids	15 and 30 mg QD, Extended-Release	Weeks 2, 8, 12, 16, or PD
M18-891 (N = 836)	Phase 3/ Adult and adolescent subjects with moderate to severe AD	15 and 30 mg QD, Extended-Release	Weeks 2, 8, 12, 16, or PD

a. N is the total number of subjects enrolled in the study.
b. PK samples were collected in only select number of sites and subjects.

Source: Population PK Report R&D/20/0641, Page 16, Table 1.

A total of 911 subjects who received upadacitinib with at least one PK sample collected and measurable upadacitinib concentration were included in the population PK analysis. 4161 upadacitinib plasma concentrations were collected following administration of upadacitinib doses of 7.5, 15 and 30 mg QD in the population PK model. As there were only 195 records below the LLOQ, M5 method was used by imputing BLQ concentrations with LLOQ/2. The second and all subsequent concentrations below the LLOQ after the last dose were ignored.

Demographic and baseline characteristics data for subjects included in the population PK analysis compared to all subjects enrolled in the studies are shown in Table 90. The demographics and baseline characteristics for subjects included in the population PK analysis were similar to all the subjects in these studies, indicating generalizability of the analysis results to the overall patient population. The majority of the subjects within the population PK analysis were white (72%). 89% of subjects were adults and 11% were adolescents with age ≥12 to <18 years. The median age of subjects was 32 years old (range: 12-75), 59.6% were males, and median body weight was 74 kg (range: 33-169). Median ALT, AST, total bilirubin and creatinine clearance (CrCL) were 19 IU/L (range: 5-148), 21 IU/L (range: 10-134), 0.41 mg/dL (range: 0.18-2.5) and 114.77 mL/min (range: 42.44-328.83) accordingly. The median baseline EASI score of patients was 25.8 (range: 16-72).

Table 90. Summary of Demographic Characteristics for Subjects Included in Studies M14-680, M16-048, M16-045, M16-047, M17-377 and M18-891.

Characteristics		Subjects with PK sampling (N = 911)	Subjects without PK sampling (N = 2169)	All Subjects (N = 3080)
Sex	Male	543 (59.60%)	1295 (59.70%)	1838 (59.68%)
	Female	368 (40.40%)	874 (40.30%)	1242 (40.32%)
Weight (kg)	Mean (SD)	76.10 (18.98)	73.91 (18.83)	74.56 (18.90)
	Median	74.00	71.20	72.00
	Min, Max	33.00, 169.00	36.10, 175.00	33.00, 175.00
Age (years)	Mean (SD)	35.53 (16.01)	34.01 (14.79)	34.46 (15.17)
	Median	32	30	31
	Min, Max	12, 75	12, 75	12, 75
Age Group	Adolescent	103 (11.31%)	226 (10.42%)	329 (10.68%)
	Adult	808 (88.69%)	1943 (89.58%)	2751 (89.32%)
Race	White	656 (72.01%)	1250 (57.63%)	1906 (61.88%)
	Black	92 (10.10%)	114 (5.26%)	206 (6.69%)
	Asian	133 (14.60%)	748 (34.49%)	881 (28.60%)
	Others / Multiple	30 (3.29%)	57 (2.63%)	87 (2.82%)
Hispanic Ethnicity	Non-Hispanic	812 (89.13%)	1996 (92.02%)	2808 (91.17%)
	Hispanic	99 (10.87%)	173 (7.98%)	272 (8.83%)
Geographic Region	USA/PR/Canada	487 (53.46%)	718 (33.10%)	1205 (39.12%)
	Japan	53 (5.82%)	325 (14.98%)	378 (12.27%)
	China/Hong Kong	9 (0.99%)	99 (4.56%)	108 (3.51%)
	Others	362 (39.74%)	1027 (47.35%)	1389 (45.10%)

Characteristics		Subjects with PK sampling (N = 911)	Subjects without PK sampling (N = 2169)	All Subjects (N = 3080)
Alanine Amino Transferase (ALT) (IU/L)	Mean (SD)	22.22 (14.17)	22.49 (13.35)	22.41 (13.60)
	Median	19.00	19.00	19.00
	Min, Max	5.00, 148.00	4.00, 145.00	4.00, 148.00
Aspartate Amino Transferase (AST) (IU/L)	Mean (SD)	22.24 (8.37)	22.95 (8.46)	22.74 (8.44)
	Median	21.00	21.00	21.00
	Min, Max	10.00, 134.00	6.00, 120.00	6.00, 134.00
Total Bilirubin (mg/dL)	Mean (SD)	0.50 (0.29)	0.52 (0.32)	0.52 (0.31)
	Median	0.41	0.41	0.41
	Min, Max	0.18, 2.50	0.18, 3.90	0.18, 3.90
Baseline EASI Score[a]	Mean (SD)	29.39 (12.23)	30.26 (12.57)	30.01 (12.48)
	Median	25.80	26.40	26.30
	Min, Max	16.00, 72.00	16.00, 72.00	16.00, 72.00
Creatinine Clearance (ml/min)	Mean (SD)	120.32 (37.85)	121.85 (36.74)	121.40 (37.07)
	Median	114.77	116.17	115.66
	Min, Max	42.44, 328.83	38.43, 343.38	38.43, 343.38

SD = standard deviation

a. HV subjects (N = 48 from Study M14-680) were excluded from EASI score statistics.

Source: Population PK Report R&D/20/0641, Page 37-38, Table 3.

A previous population PK model was developed for the upadacitinib across indications [healthy volunteer (VH), atopic dermatitis (AD), rheumatoid arthritis (RA), crohn's disease (CD) and ulcerative colitis (UC)] and the model was re-fit to data with VH (Study M14-680) and subjects with AD. Two-compartment model with combined first- and zero-order absorption for the extended-release formulation were used to characterize the upadacitinib concentration-time profiles. Inter-subject variability (IIV) was modeled using a full variance-covariance matrix on CL/F, V_c/F and the first order absorption rate constants. Separate proportional error terms for Phase 1 versus Phase 2/3 studies were estimated. In the previous population PK model, CrCL, sex and indication (AD versus HV) were included as covariates on CL/F; and body weight and sex were covariates on V_c/F. These covariates effects were re-estimated with the current dataset. Sex and body weight on V_c/F were no longer statistically significant and removed for the base model.

Several covariates, including age, weight, age group (adult versus adolescent) and Japan region (Japanese versus non-Japanese) were tested as covariates on clearance and volume of distribution were evaluated using the stepwise forward inclusion backward elimination approach. None of these covariates were statistically significant and the final model was identical as the base model. PK parameters of the final model and the results of bootstrap analysis are shown in Table 91 and Table 92. The estimated PK parameter values based on the

final model were in good agreement with the medians of the parameter values estimated from the bootstrap analysis.

Table 91. Parameter Estimates for Upadacitinib Population Pharmacokinetic Final Model

Parameter	Population Estimate	95% Confidence Interval
CL/F (L/h)*	53.0	47.3 - 59.3
Vc/F (L)	145	122 - 174
KA (1/h)	0.0545	0.0490 - 0.0606
Absorption Lag time (h)	0.232	0.228 - 0.237
Fraction of Dose Absorbed through Zero-Order Process (%)	66.5	64.9 - 68.1
Zero-Order Infusion Duration (h)	4.90	4.66 - 5.16
Q/F (L/h)	26.8	19.2 - 37.5
Vp/F (L)	56.3	48.6 - 65.1
Creatinine Clearance on CL/F	0.249	0.140 - 0.358
Sex on CL/F	-0.181	-0.252 - -0.110
AD on CL/F**	-0.160	-0.282 - -0.0379
ISV on CL/F (%)***	35.8	32.1 - 39.1
ISV on Vc/F (%)	131	111 - 148
ISV on KA (%)	45.1	36.2 - 52.5
Proportional Error (Phase 1) SD	0.305	0.294 - 0.316
Proportional Error (Phase 2/3) SD	0.542	0.522 - 0.562
Additive Error SD (ng/mL)	0.0366	0.0216 - 0.0470

* Clearance estimate for healthy subjects as a reference.
** Results in a population estimate for CL/F of 44.059 in subjects with AD.
*** %ISV was calculated as SQRT(ω^2) × 100.

Source: Population PK Report R&D/20/0641, Page 42, Table 4.

Table 92. Comparison of Model Results with Bootstrap Results for Final Population Pharmacokinetic Model.

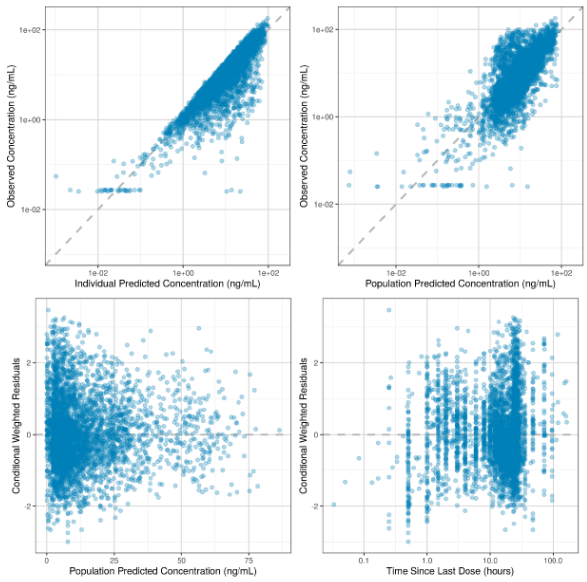
	Model Results		Bootstrap Results N = 430
Parameter	Population Estimate	Median	95% Confidence Interval
CL/F (L/h)	53.0	53.0	47.9 - 57.4
Vc/F (L)	145	148	111 - 192
KA (1/h)	0.0545	0.0545	0.0469 - 0.0699
Absorption Lag time (h)	0.232	0.232	0.219 - 0.242
Fraction of Dose Absorbed through Zero-Order Process (%)	66.5	66.8	61.8 - 72.2
Zero-Order Infusion Duration (h)	4.90	4.90	4.66 - 5.16
Q/F (L/h)	26.8	26.6	18.2 - 37.7
Vp/F (L)	56.3	56.3	36.2 - 83.1
Creatinine Clearance on CL/F	0.249	0.250	0.112 - 0.387
Sex on CL/F	-0.181	-0.178	-0.249 - -0.114
AD on CL/F	-0.160	-0.159	-0.271 - -0.0403
ISV on CL/F (%)*	35.8	35.9	31.8 - 40.7
ISV on Vc/F (%)	131	132	109 - 163
ISV on KA (%)	45.1	47.0	37.0 - 65.4
Proportional Error (Phase 1) SD	0.305	0.303	0.277 - 0.327
Proportional Error (Phase 2/3) SD	0.542	0.541	0.520 - 0.563
Additive Error SD (ng/mL)	0.0366	0.0370	0.0102 - 0.0550

* %ISV was calculated as SQRT(ω^2) × 100.

Source: Population PK Report R&D/20/0641, Page 44, Table 5.

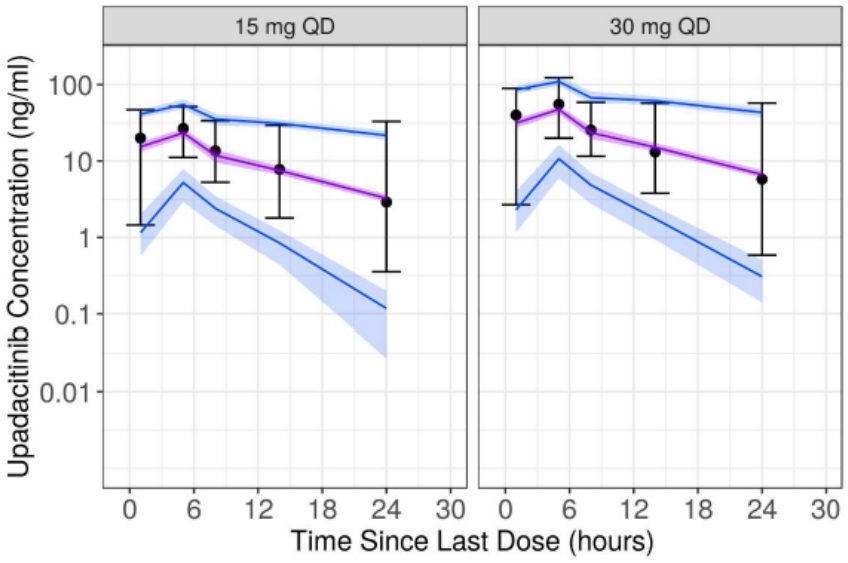
Goodness-of-fit plots for the final population PK model are shown in Figure 19. VPC (visual predictive check) stratified by dose and age groups (adolescents and adults) are shown in Figure 20 and Figure 21. The model described the observed data well and the model predictions were generally within the 90% prediction intervals. No apparent bias was observed in the overall model fit for the data.

Figure 19. Goodness-of-Fit Plots for the Upadacitinib Final Population Pharmacokinetic Model (All Subjects)



Source: Population PK Report R&D/20/0641, Page 46, Figure 8.

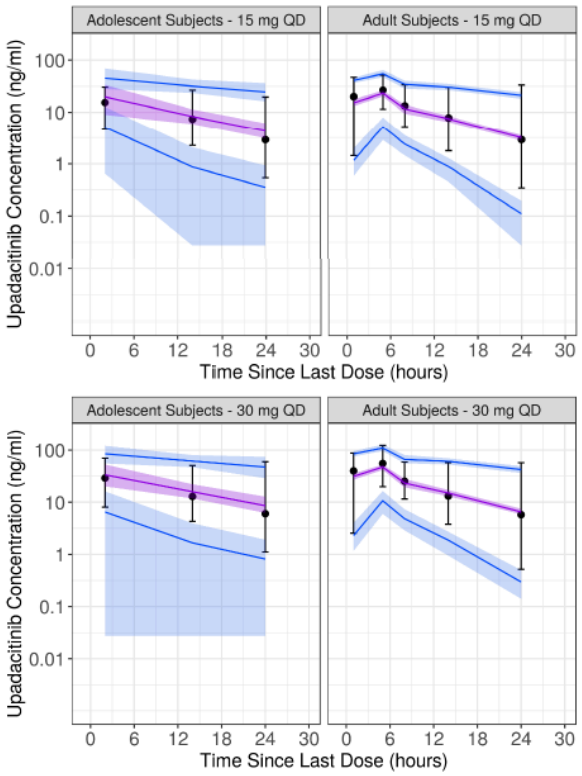
Figure 20. VPC for Subjects Receiving 15 mg QD and 30 mg QD.



The shaded blue areas represent the 90% confidence interval of the 5th and 95th percentiles of simulated concentrations, the blue line represents median of the 5th and 95th percentiles of simulated concentrations; the shaded purple areas represent the 90% confidence interval of the 50th percentile of simulated concentrations, the purple line represents median of the 50th percentiles of simulated concentrations, the black point represent the median of the binned observed concentrations, and the black error bars represent the 2.5th and 97.5th percentile of the binned observed concentrations.

Source: Population PK Report R&D/20/0641, Page 47, Figure 9.

Figure 21. VPC for Adolescent and Adult Subjects Receiving 15 mg QD and 30 mg QD.

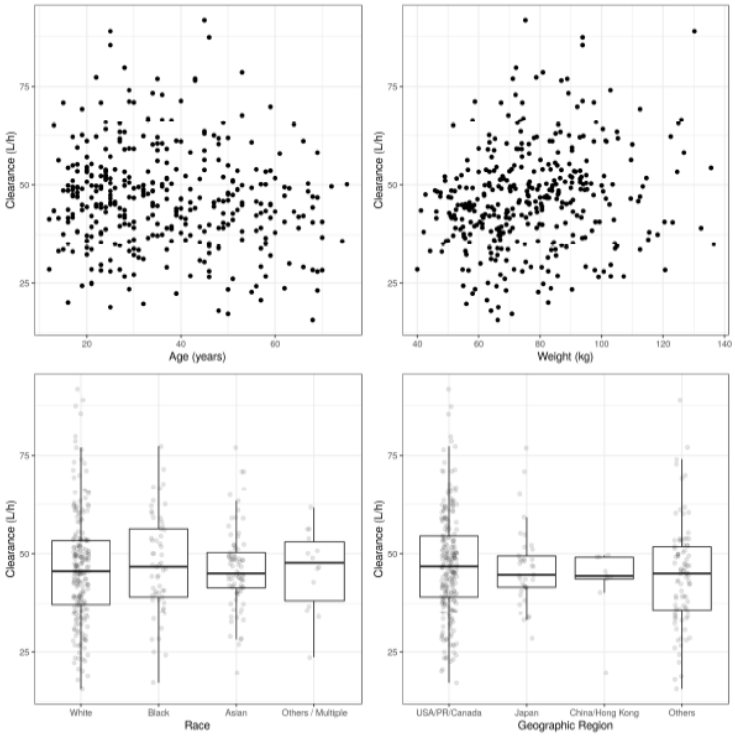


The shaded blue areas represent the 90% confidence interval of the 5th and 95th percentiles of simulated concentrations, the blue line represents median of the 5th and 95th percentiles of simulated concentrations; the shaded purple areas represent the 90% confidence interval of the 50th percentile of simulated concentrations, the purple line represents median of the 50th percentiles of simulated concentrations, the black point represent the median of the binned observed concentrations, and the black error bars represent the 2.5th and 97.5th percentile of the binned observed concentrations.

Source: Population PK Report R&D/20/0641, Page 48, Figure 10.

Empirical Bayes estimates of the PK parameters were generated with the final population PK model for individual subject. Graphical exploration of the relationships between upadacitinib CL/F and relevant covariates (including age, body weight, race, and geographic region) in subjects with AD are shown in Figure 22. No strong trends were observed for upadacitinib CL/F with these covariates.

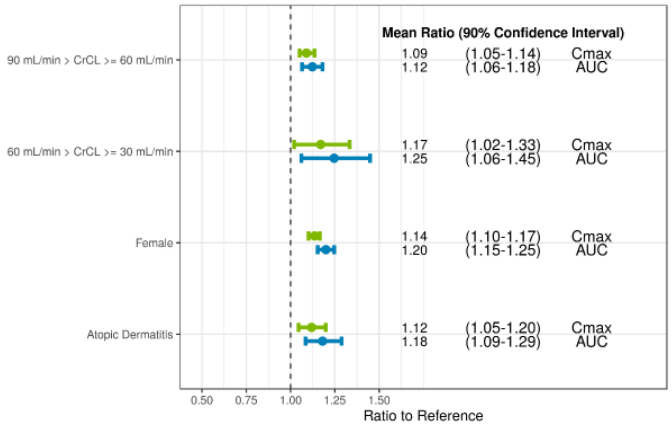
Figure 22. Effect of Intrinsic Factors on Upadacitinib CL/F.



Source: Population PK Report R&D/20/0641, Page 50, Figure 11.

Simulations were performed to explore the relationships of upadacitinib exposure paramenters and relevant covariants based on the final population PK model . Figure 23 provides the predicted covariate effect on upadacitinib exposures (C_{max} and AUC_{24h}) for different subgroup patients relative to the reference subjects. Subjects with mild and moderate renal impairment were predicted to have approximately 12% and 25% higher AUC_{24} and 9% and 17% higher C_{max}, respectively, compared to subjects with normal renal function. Female subjects were predicted to have 20% higher AUC_{24} and 14% higher C_{max}, respectively, compared to male subjects. Subjects with AD were predicted to have 18% higher AUC_{24} and 12% higher C_{max} compared to HV.

Figure 23. Model-Predicted Covariate Effect on Upadacitinib C_{max} and AUC_{24} for Different Subpopulations Relative to the Reference Population



Dots and error bars represent median and 90% prediction interval of median model-predicted exposure ratios relative to reference covariate value. The vertical dashed line shows the exposure ratio of 1 relative to the reference group. Normal creatinine clearance (≥ 90mL/min), male subjects and healthy subjects were chosen as reference covariate categories. AUC denotes AUC_{24}.

Source: Population PK Report R&D/20/0641, Page 52, Figure 12.

Comparison of summary statistics for upadacitinib C_{max}, C_{avg} and C_{min} at steady state in Japanese with non-Japanese subjects and adolescent with adult subjects with AD were shown in Table 93 and Table 94. Upadacitinib exposures were comparable between Japanese and non-Japanese subjects with AD and comparable between adult and adolescent subjects with AD for both the 15 mg and 30 mg QD regimens.

Table 93. Summary of model-estimated upadacitinib plasma exposures (C_{max}, C_{avg} and C_{min}) for 15 mg and 30 mg QD dosing regimens at steady state in Japanese and non-Japanese subjects with AD

Treatment	Population	C_{avg} (ng/mL) Median (90% CI)	C_{max} (ng/mL) Median (90% CI)	C_{min} (ng/mL) Median (90% CI)
15 mg QD	Non-Japanese	14.6 (9.54 - 29.2)	35.5 (25.6 - 44.0)	3.73 (1.56 - 23.8)
15 mg QD	Japanese	15.4 (9.63 - 22.3)	34.8 (24.9 - 43.4)	4.32 (1.57 - 14.4)
30 mg QD	Non-Japanese	29.5 (19.7 - 53.4)	71.5 (54.4 - 87.8)	7.69 (3.21 - 43.5)
30 mg QD	Japanese	26.8 (17.6 - 47.2)	72.6 (57.6 - 85.2)	6.06 (2.55 - 35.4)

Source: Population PK Report R&D/20/0641, Page 53, Table 7.

Table 94. Comparison of summary statistics of model-estimated upadacitinib plasma exposures (C_{max}, C_{avg} and C_{min}) in adolescent compared to adult subjects with AD

Treatment	Population	C_{avg} (ng/mL) Median (90% CI)	C_{max} (ng/mL) Median (90% CI)	C_{min} (ng/mL) Median (90% CI)
15 mg QD	Adolescent	14.7 (9.63 - 22.3)	37.7 (27.3 - 43.6)	3.52 (1.62 - 13.7)
15 mg QD	Adult	14.6 (9.54 - 29.2)	35.3 (25.5 - 44.0)	3.90 (1.56 - 23.9)
30 mg QD	Adolescent	29.2 (20.1 - 53.5)	73.4 (56.0 - 81.9)	7.85 (3.61 - 40.4)
30 mg QD	Adult	29.0 (19.6 - 52.8)	70.8 (54.4 - 88.7)	7.38 (3.09 - 43.5)

Source: Population PK Report R&D/20/0641, Page 54, Table 8.

Reviewer's comments:

There were 1838 subjects involved in the studies and only 911 subjects with PK samples and sampling time were included in the population PK analysis. As the demographic characteristics for subjects with PK samples were comparable with the overall study population, the population PK analyses based on the current subgroup might represent the entire population. The population PK models developed by the Applicant were checked by the reviewer. Although rounding error occurred while replicating the Applicant's analyses, the model development appears to be acceptable because of the good agreement between observations and predictions. Based on the final population PK model, the exposures of upadacitinib (C_{max}, C_{avg} and C_{min}) were comparable for adults and adolescents with AD. The effect of renal impairment on upadacitinib exposures were similar as previous study and mild or moderate renal impairment has no clinically relevant effect on upadacitinib exposure for the 15 or 30 mg QD dosing regimens.

18.4.2. Exposure-response analysis for efficacy

As mentioned in the population PK analysis, PK samples were only collected from a select number of subjects in Phase 3 studies (Studies M16-045, M16-047, M18-891). Only those subjects were included in the exposure-response analyses from the active treatment arms of these Phase 3 studies (in addition to all subjects in the Phase 2b Study M16-048). All subjects from the global Phase 2b and Phase 3 studies receiving placebo were also included in the analyses with C_{avg} and C_{max} set to 0. The demographics and other baseline characteristics for subjects included in the exposure-response analysis are shown in Table 95.

Table 95. Summary of demographic and other intrinsic factors for subjects included in the exposure-response analysis.

Characteristic		Monotherapy N = 1094	Combination N = 652
Age (years)	Mean (SD)	35.4 (16.0)	34.5 (15.3)
	Median	31.0	31.0
	Min – Max	12.0 – 75.0	12.0 – 75.0
Body Weight (kg)	Mean (SD)	76.4 (19.4)	75.9 (20.0)
	Median	74.0	74.0
	Min – Max	37.0 – 175	33.0 – 169
Sex	Male	598 (55%)	391 (60%)
	Female	496 (45%)	261 (40%)
Race	White	755 (69%)	505 (77%)
	Black	97 (9%)	38 (6%)
	Asian	209 (19%)	96 (15%)
	Other/Multiple	33 (3%)	13 (2%)
Age Group	Adolescents	113 (10%)	78 (12%)
	Adults	981 (90%)	574 (88%)
EASI Score at Baseline	Mean (SD)	29.2 (12.4)	29.7 (12.4)
	Median	25.5	25.9
	Min – Max	16.0 – 72.0	16.0 – 69.6
Disease Duration at Baseline (years)[a]	Mean (SD)	21.7 (15.2)	24.1 (15.0)
	Median	20.0	22.0
	Min – Max	0.0 – 74.0	0.0 – 73.0
Baseline Hemoglobin (g/dL)	Mean (SD)	14.3 (1.41)	14.5 (1.33)
	Median	14.3	14.5
	Min – Max	9.30 – 17.9	10.2 – 17.6
Baseline Neutrophils (10^9 cells/L)	Mean (SD)	4.70 (1.73)	4.74 (1.72)
	Median	4.49	4.47
	Min – Max	1.15 – 15.5	1.39 – 12.2
Baseline Lymphocytes (10^9 cells/L)	Mean (SD)	1.79 (0.60)	1.76 (0.57)
	Median	1.70	1.65
	Min – Max	0.47 – 4.52	0.57 – 4.37
Baseline vIGA-AD Score	3	574 (53%)	301 (46%)
	4	519 (47%)	351 (54%)
	Missing	1 (0.09%)	--

SD = Standard deviation

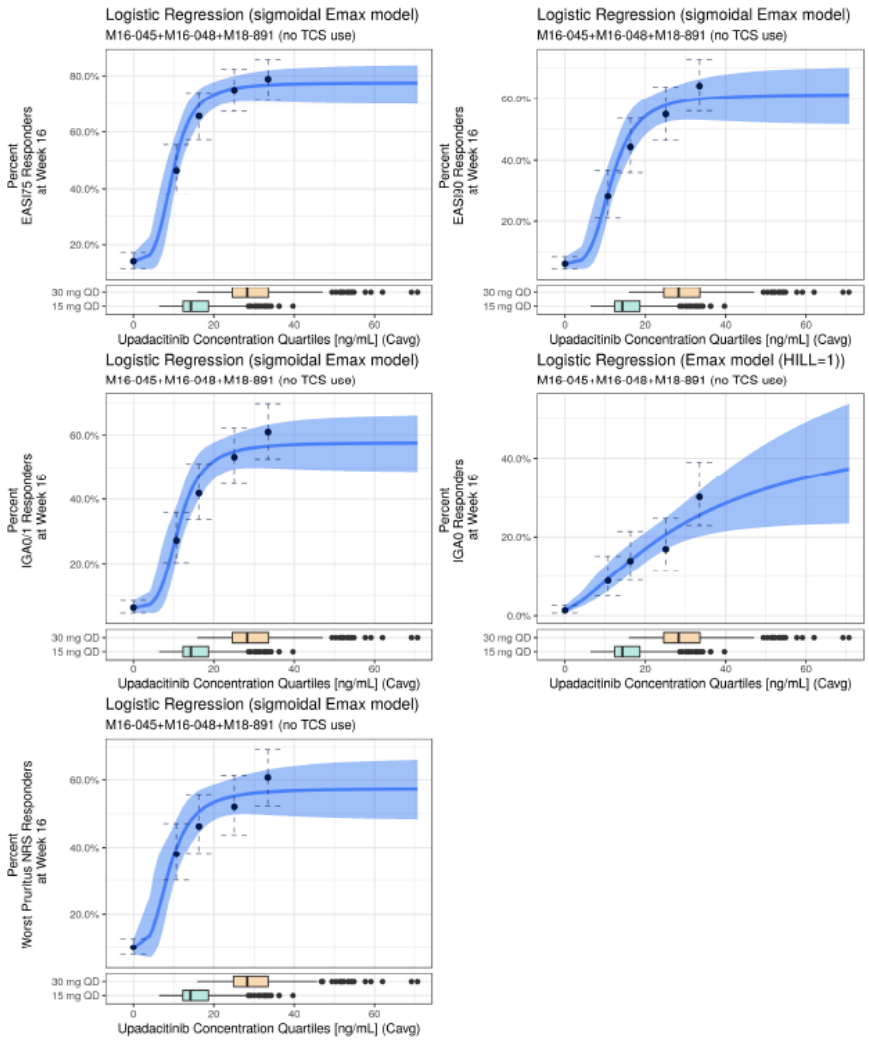
a. Disease duration was rounded to whole years.

Source: Exposure-Response Report R&D/20/0642, Page 29-30, Table 2.

The relationship of efficacy endpoints (EASI 75, EASI 90, IGA 0/1, IGA 0 and improvement in Worst Pruritus NRS ≥ 4 at Week 16) and upadacitinib exposure (average plasma concentrations over a dosing interval at steady state, C_{avg} calculated based on the empirical Bayesian PK parameters from the final population PK model) were studied by logistic regression models and logistic regression models with E_{max} function. For subjects who received upadacitinib monotherapy, logistic regression analysis demonstrated that all the five endpoints exhibited a statistically significant exposure-response relationship ($p<0.05$) for upadacitinib treatment. For

EASI 75, EASI 90, IGA 0/1 and improvement in Worst Pruritus NRS $\geq$ 4, sigmoidal Emax models with estimated Hill factor and intercept parameters were selected as the best model. For IGA 0, Emax model with intercept was selected as the best model. Base model plots for all efficacy endpoints were shown in Figure 24. Then disease duration on EC_{50} and age on intercept were identified as statistically significant covariate for IGA 0/1 and improvement in Worst Pruritus NRS ≥ 4 in the final model. The final model parameters are shown in Table 96 and the VPCs of the final models are shown in Figure 25.

Figure 24. Observed and Model-Predicted Efficacy Responses at Week 16 Versus Upadacitinib C_{avg} For Upadacitinib Monotherapy [Base Models]



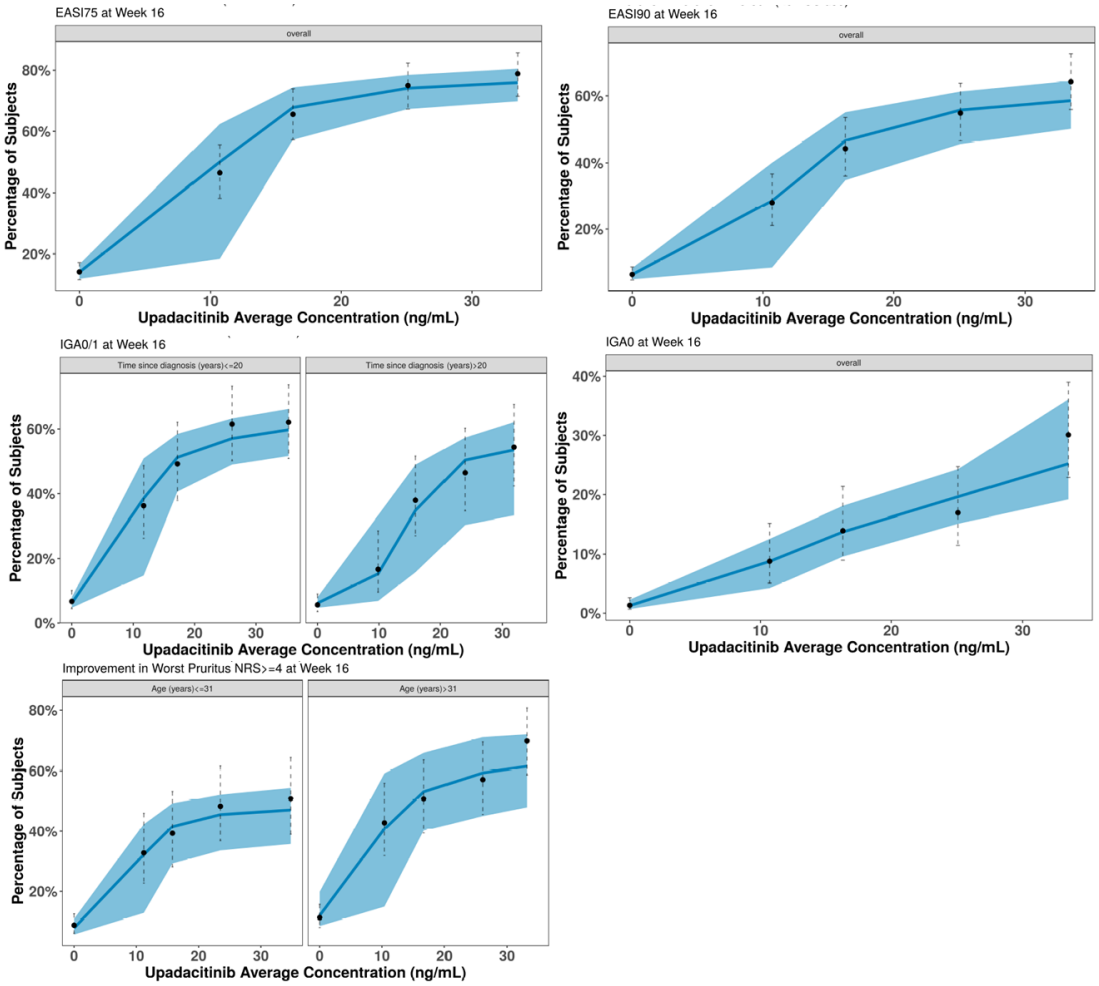
Source Exposure-Response Report R&D/20/0642, Page 33, Figure 6.

Table 96. Final Model Parameter Estimates for the Logistic Regression Exposure-Response Efficacy Models for Upadacitinib Monotherapy.

Endpoint (Week 16)	Parameter	Estimate	95% CI
EASI 75	Intercept	–1.81	–2.04 to –1.58
	E_{max}[a]	1.12	0.959 to 1.27
	EC_{50} (ng/mL)	9.38	7.68 to 11.5
	Hill Factor	3.30	0.904 to 5.70
EASI 90	Intercept	–2.70	–3.03 to –2.37
	E_{max}[a]	1.15	0.98 to 1.32
	EC_{50} (ng/mL)	9.72	7.85 to 12.0
	Hill Factor	3.15	0.69 to 5.61
IGA 0/1	Intercept	–2.73	–3.06 to –2.40
	E_{max}[a]	1.18	0.992 to 1.36
	EC_{50} (ng/mL)	9.56	7.30 to 12.5
	Hill Factor	2.61	0.713 to 4.51
	Disease Duration on EC_{50}	0.0195	0.00955 to 0.0295
IGA 0	Intercept	–4.35	–5.05 to –3.64
	E_{max}[a]	1.51	1.19 to 1.82
	EC_{50} (ng/mL)	12.70	4.83 to 33.3
Improvement in Worst Pruritus NRS ≥ 4	Intercept	–2.30	–2.58 to –2.02
	E_{max}[a]	0.890	0.712 to 1.07
	EC_{50} (ng/mL)	7.62	5.45 to 10.7
	Hill Factor	3.21	0.0168 to 6.40
	Age on intercept	0.0192	0.00993 to 0.0286

Source: Exposure-Response Report R&D/20/0642, Page 35, Table 3.

Figure 25. VPC plots for upadacitinib monotherapy efficacy regression final models.



Source Exposure-Response Report R&D/20/0642, Page 95-99, Figure 13.3_4.

Simulations were performed based on final exposure-response models to predict the efficacy responses following treatments with placebo, upadacitinib 15 mg QD and upadacitinib 30 mg QD. The results were summarized in Table 97. Simulation results showed that the clinical efficacy responses rates with upadacitinib 30 mg QD regimen were about 8-14% higher compared to 15 mg QD.

Table 97. Model-Simulated Clinical Efficacy Responses (Median and 90% Confidence Interval) Following Placebo and Upadacitinib 15 mg and 30 mg QD Monotherapy Regimens at Week 16.

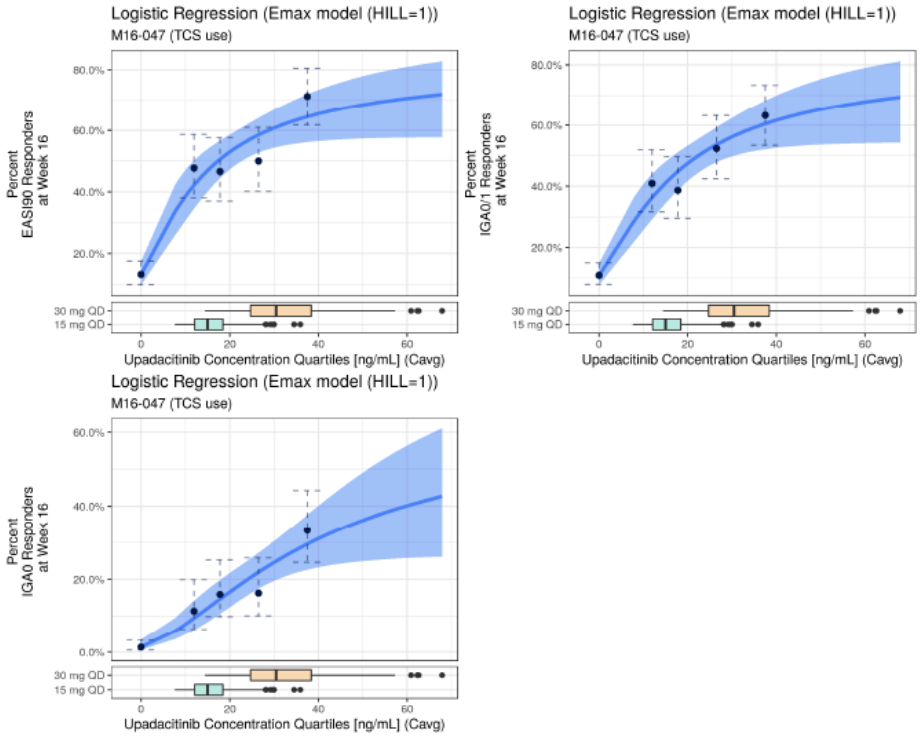
Clinical Efficacy Response Variable	Placebo	15 mg QD	30 mg QD
EASI 75	14% (11% – 18%)	63% (56% – 69%)	75% (67% – 81%)
EASI 90	6% (4% – 10%)	43% (34% – 50%)	57% (50% – 63%)
IGA 0/1	6% (4% – 9%)	41% (34% – 47%)	55% (46% – 62%)
IGA 0	1% (0% – 3%)	14% (10% – 18%)	23% (17% – 29%)
Improvement in Worst Pruritus NRS ≥ 4	10% (7% – 13%)	46% (35% – 53%)	54% (40% – 60%)

Note: Results presented as median percentage of subjects achieving response (and the 5th and 95th percentile) from 300 replicates with 300 subjects/dose group in each replicate.

Source Exposure-Response Report R&D/20/0642, Page 37, Table 4.

The relationships of efficacy endpoints and upadacitinib exposure (C_{avg}) for subjects with combination therapy were also studied and EASI 90, IGA 0/1, and IGA 0 exhibited a statistically significant exposure-response relationship ($p < 0.05$), after accounting for upadacitinib treatment effect by logistic regression analysis. For EASI 90, IGA 0/1 and IGA 0, Emax model with intercept was chosen as the best model based and plots for these efficacy endpoints are shown in Figure 26. Baseline vIGA-AD score was identified as a significant covariate on the intercept parameter in the IGA 0/1 response model. The final model parameters are shown in Table 98 and the VPCs of the final models are shown in Figure 27.

Figure 26. Observed (NRI) and Model-Predicted Efficacy Responses at Week 16 Versus Upadacitinib C_{avg} For Upadacitinib [Base Models]



Note: The blue solid line represents median predicted response and the blue shaded area represent 95% confidence intervals of the predicted response. The dots and error bars represent median and 95% binomial CIs of binned observed rates. For the horizontal box plots, the band inside the box is the median of the upadacitinib average concentration C_{avg} per 15 mg QD and 30 mg QD dosing. The lower and upper hinges correspond to the 25th and 75th percentiles. Whiskers represent 1.5 IQR. The data beyond the end of the whiskers are plotted individually.

Source Exposure-Response Report R&D/20/0642, Page 41, Figure 9.

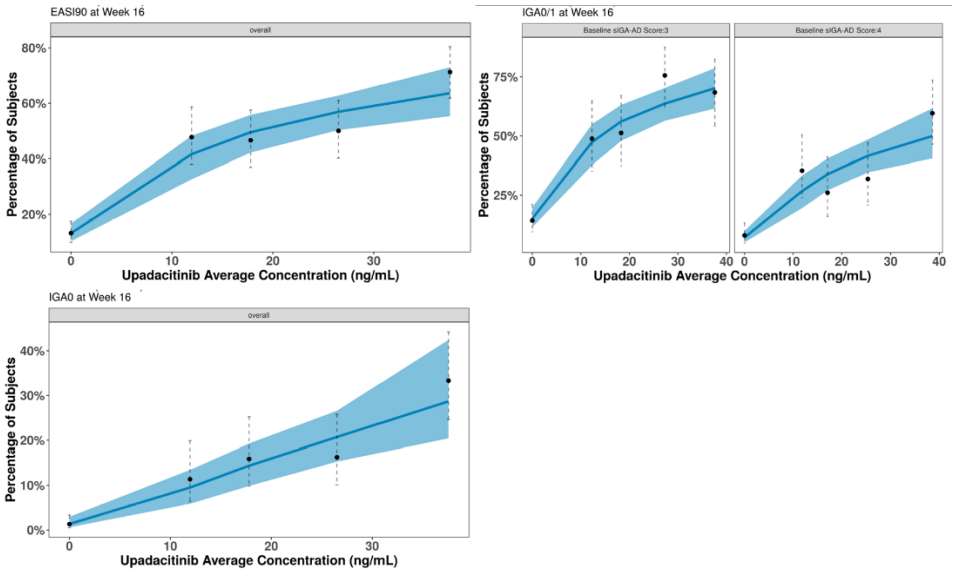
Table 98. Final Model Parameter Estimates for the Logistic Regression Exposure-Response Efficacy Models for Upadacitinib with TCS.

Endpoint (Week 16)	Parameter	Estimate	95% CI
EASI 90	Intercept	–1.89	–2.22 to –1.55
	E_{max}[a]	1.23	0.837 to 1.62
	EC_{50} (ng/mL)	14.0	4.89 to 40.1
IGA 0/1	Intercept	–1.72	–2.21 to –1.33
	E_{max}[a]	1.30	0.908 to 1.69
	EC_{50} (ng/mL)	15.3	5.47 to 42.6
	Baseline vIGA-AD score of 4 on intercept[b]	–0.847	–1.23 to –0.467
IGA 0	Intercept	–4.29	–5.25 to –3.32
	E_{max}[a]	1.62	1.24 to 1.99
	EC_{50} (ng/mL)	17.7	5.87 to 53.4

a. Values for E_{max} are on a logarithmic scale.
b. Baseline vIGA-AD score of 3 as reference.

Source Exposure-Response Report R&D/20/0642, Page 42, Table 5.

Figure 27. VPC plots for upadacitinib combination with TCS efficacy regression final models.



Source Exposure-Response Report R&D/20/0642, Page 100-102, Figure 13.3_4.

Simulations were performed based on final exposure-response models of EASI 90, IGA 0/1 and IGA 0 to predict the efficacy responses following the combination treatments with placebo, upadacitinib 15 mg QD and upadacitinib 30 mg QD. The results were summarized in Table 99. Clinical efficacy responses rates for all endpoints with upadacitinib 30 mg QD regimen were predicted to be about 12-14% higher compared to 15 mg QD.

Table 99. Model-Simulated Clinical Efficacy Responses Following Placebo and Upadacitinib 15 mg and 30 mg QD with TCS Regimens at Week 16.

Clinical Efficacy Response Variable	Placebo	15 mg QD	30 mg QD
EASI 90	13% (9% – 18%)	47% (40% – 53%)	59% (50% – 66%)
IGA 0/1	11% (7% – 16%)	41% (33% – 47%)	55% (47% – 62%)
IGA 0	1% (0% – 4%)	13% (9% – 18%)	25% (18% – 32%)

Note: Results represents median percentage of subjects (5^{th} and 95^{th} percentile) from 300 replicates with 300 subjects/dose group in each replicate.

Source Exposure-Response Report R&D/20/0642, Page 44, Table 6.

Reviewer's comments:

*The Demographic characteristics for subjects in exposure-response analysis were comparable with the overall study population. (*Table 100*) The efficacy response rates in subgroup of subjects included in the exposure-response efficacy analysis were also consistent with the overall Phase 3 study populations (*Table 101*), which indicates generalizability of the analysis results to the overall patient population. The Applicant's exposure response analyses for efficacy were checked by the reviewer. The results were generally consistent with the observed efficacy data. Positive relationships were observed for these efficacy endpoints with the exposure of upadacitinib at the evaluated doses. Simulation results also showed slightly better responses at dose of 30 mg QD comparing with 15 mg QD.*

Table 100. Summary of demographic and intrinsic factor characteristics for upadacitinib by population.

Characteristics		All Subjects in ER (N=1746)	All Subjects (N=2750)
Sex	Male	989 (56.64%)	1578 (57.38%)
	Female	757 (43.36%)	1172 (42.62%)
Weight (kg)	Mean (SD)	76.23 (19.61)	75.29 (19.26)
	Median	74.00	72.60
	Min, Max	33.00, 175.00	33.00, 175.00
BMI (kg/m2)	Mean (SD)	26.29 (6.00)	26.02 (5.88)
	Median	25.10	24.92
	Min, Max	15.27, 58.59	15.27, 58.59
Age (years)	Mean (SD)	35.08 (15.75)	34.28 (15.47)
	Median	31.00	30.00
	Min, Max	12.00, 75.00	12.00, 75.00
Age Group	Adolescent	191 (10.94%)	304 (11.05%)
	Adult	1555 (89.06%)	2446 (88.95%)
Race	White	1260 (72.16%)	1874 (68.15%)
	Black	135 (7.73%)	185 (6.73%)
	Asian	305 (17.47%)	609 (22.15%)
	Others / Multiple	46 (2.63%)	82 (2.98%)
Hispanic Ethnicity	No	1561 (89.40%)	2481 (90.22%)
	Yes	185 (10.60%)	269 (9.78%)
Geographic Region	USA/PR/Canada	811 (46.45%)	1147 (41.71%)
	Japan	67 (3.84%)	106 (3.85%)
	China/Hong Kong	43 (2.46%)	108 (3.93%)
	Others	825 (47.25%)	1389 (50.51%)
Topical Corticosteroid Coadministration	No	1094 (62.66%)	1850 (67.27%)
	Yes	652 (37.34%)	900 (32.73%)
Baseline sIGA-AD Score	Missing	1 (0.06%)	1 (0.04%)
	3	875 (50.11%)	1361 (49.49%)
	4	870 (49.83%)	1388 (50.47%)
Prior Systemic Therapy	No	929 (53.21%)	1401 (50.95%)
	Yes	817 (46.79%)	1349 (49.05%)
Baseline EASI Score	Mean (SD)	29.40 (12.43)	29.52 (12.23)
	Median	25.60	25.85
	Min, Max	16.00, 72.00	16.00, 72.00
High-sensitivity C-reactive Protein (mg/L)	Mean (SD)	3.76 (7.30)	3.74 (7.25)
	Median	1.54	1.50
	Min, Max	0.20, 138.00	0.20, 138.00
Time Since AD Diagnosis (years)	Mean (SD)	22.61 (15.16)	21.82 (14.91)
	Median	20.00	20.00
	Min, Max	0.00, 74.00	0.00, 74.00
Baseline Neutrophils (10^9/L)	Mean (SD)	4.72 (1.72)	4.71 (1.75)
	Median	4.49	4.46
	Min, Max	1.15, 15.46	1.15, 26.48
Baseline Lymphocytes (10^9/L)	Mean (SD)	1.77 (0.59)	1.77 (0.58)
	Median	1.68	1.68
	Min, Max	0.47, 4.52	0.47, 7.53
Baseline Hemoglobin (g/dL)	Mean (SD)	14.33 (1.38)	14.35 (1.37)
	Median	14.40	14.40
	Min, Max	9.30, 17.90	9.30, 17.90

Source: Exposure-Response Report R&D/20/0642, Page 52-55, Table 13.1_1.

Table 101. Comparison of clinical efficacy response rates in Phase 3 studies by treatment group.

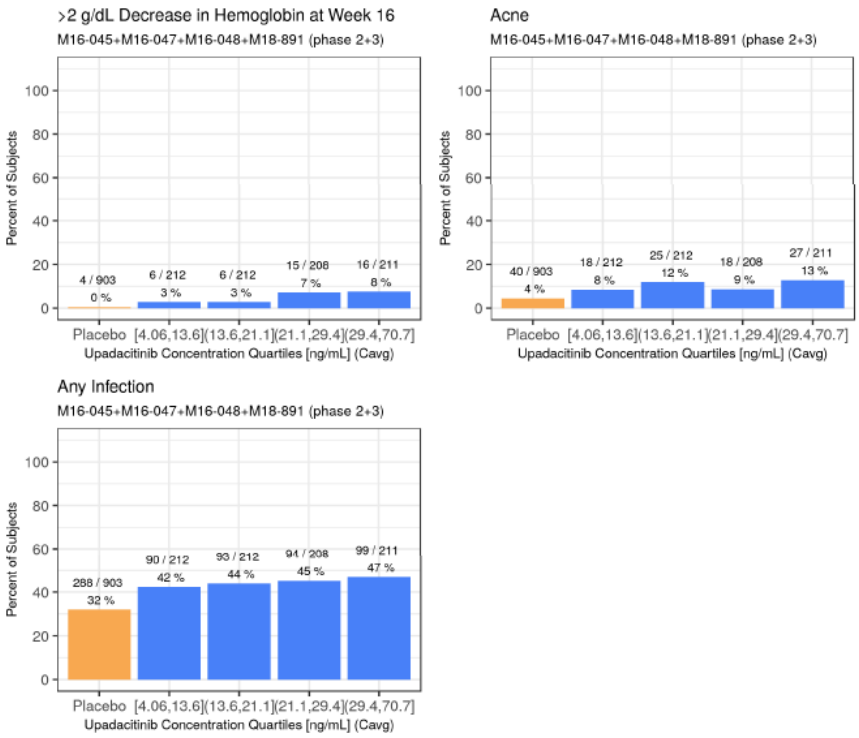
Study	Endpoint	Regimen	Clinical Response (%) per Overall Phase 3 Population	Clinical Response (%) per ER Analysis in Phase 3
M16-045	EASI75 at Week 16	Placebo	16.3	15.7
		15 mg QD	69.6	73.4
		30 mg QD	79.7	81.5
	EASI90 at Week 16	Placebo	8.1	7.8
		15 mg QD	53.1	58.5
		30 mg QD	65.8	61.7
	IGA0/1 at Week 16	Placebo	8.4	8.2
		15 mg QD	48.1	46.8
		30 mg QD	62	63
	Worst Pruritus NRS Improvement >=4 at Week 16	Placebo	11.8	11.4
		15 mg QD	52.2	50
		30 mg QD	60	61.7
M16-047	EASI75 at Week 16	Placebo	26.4	26.4
		15 mg QD	64.6	67.2
		30 mg QD	77.1	74.1
	EASI90 at Week 16	Placebo	13.2	13.2
		15 mg QD	42.7	44.8
		30 mg QD	63	63.9
	IGA0/1 at Week 16	Placebo	10.9	10.9
		15 mg QD	39.6	39.3
		30 mg QD	58.6	59
	Worst Pruritus NRS Improvement >=4 at Week 16	Placebo	15	14.5
		15 mg QD	51.7	51.4
		30 mg QD	63.9	59
M18-891	EASI75 at Week 16	Placebo	13.3	13.3
		15 mg QD	60.1	57.9
		30 mg QD	72.9	76.5
	EASI90 at Week 16	Placebo	5.4	5.4
		15 mg QD	42.4	35.8
		30 mg QD	58.5	60.2
	IGA0/1 at Week 16	Placebo	4.7	4.7
		15 mg QD	38.8	41.1
		30 mg QD	52	54.1
	Worst Pruritus NRS Improvement >=4 at Week 16	Placebo	9.1	9
		15 mg QD	41.9	42.1
		30 mg QD	59.6	55.1

Source: Exposure-Response Report R&D/20/0642, Page 60, Table 13.1_3.

18.4.3. Exposure-Response analysis for safety

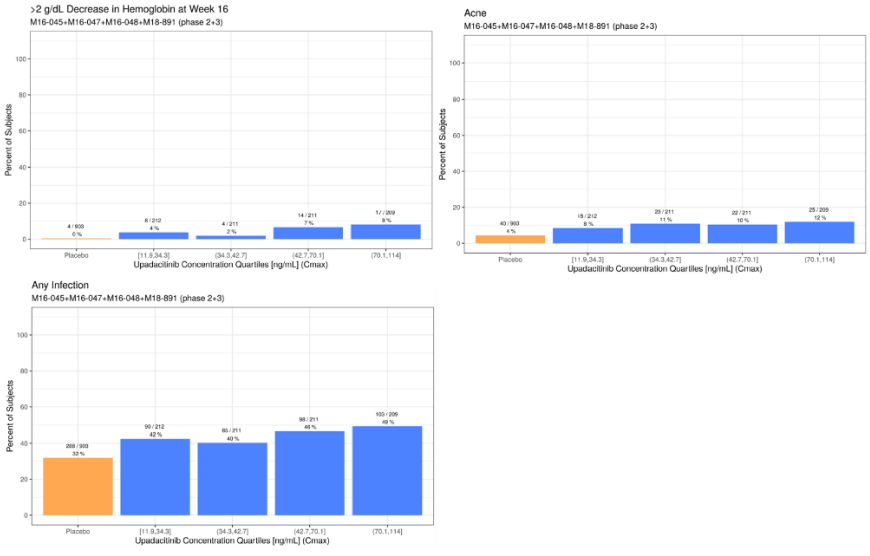
The relationship of selected safety endpoints (decrease in Hemoglobin > 2 g/dL from Baseline, any infection, and acne) and upadacitinib C_{avg} and C_{max} were shown in Figure 28 and Figure 29. No clear or marked trends for exposure-dependent relationships were observed between upadacitinib exposures and probability of occurrence of any infection or acne at Week 16. Percentage of subjects experiencing a decrease in hemoglobin > 2 g/dL from baseline at Week 16 showed a shallow increasing trend with higher upadacitinib exposures.

Figure 28. Observed Safety Response Rates Versus Upadacitinib C_{avg} Quartiles at Week 16



Source: Exposure-Response Report R&D/20/0642, Page 46, Figure 11.

Figure 29. Observed Safety Response Rates Versus Upadacitinib C_{max} Quartiles at Week 16

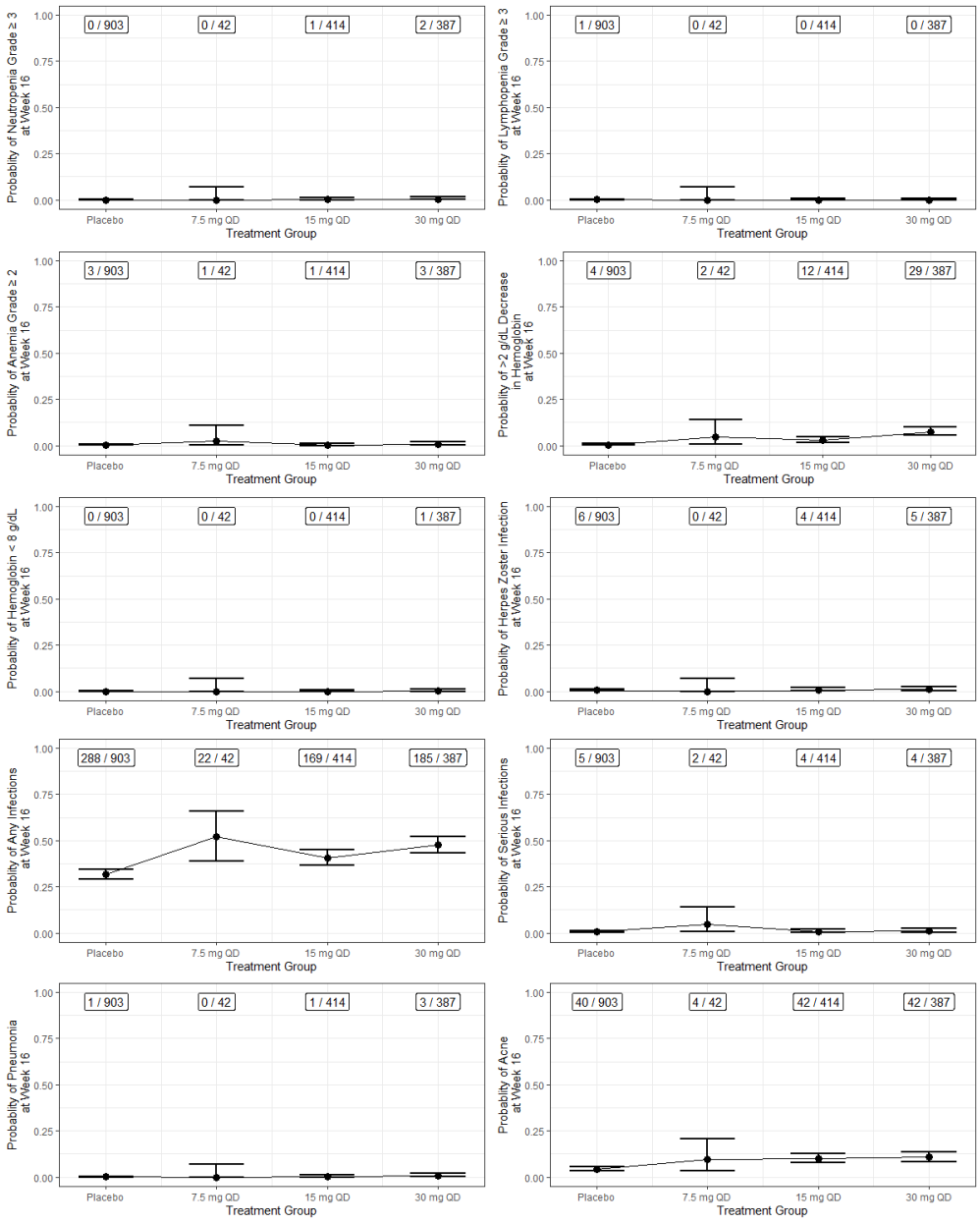


Source: Exposure-Response Report R&D/20/0642, Page 115-125, Figure 13.5_2.

Reviewer's comments:

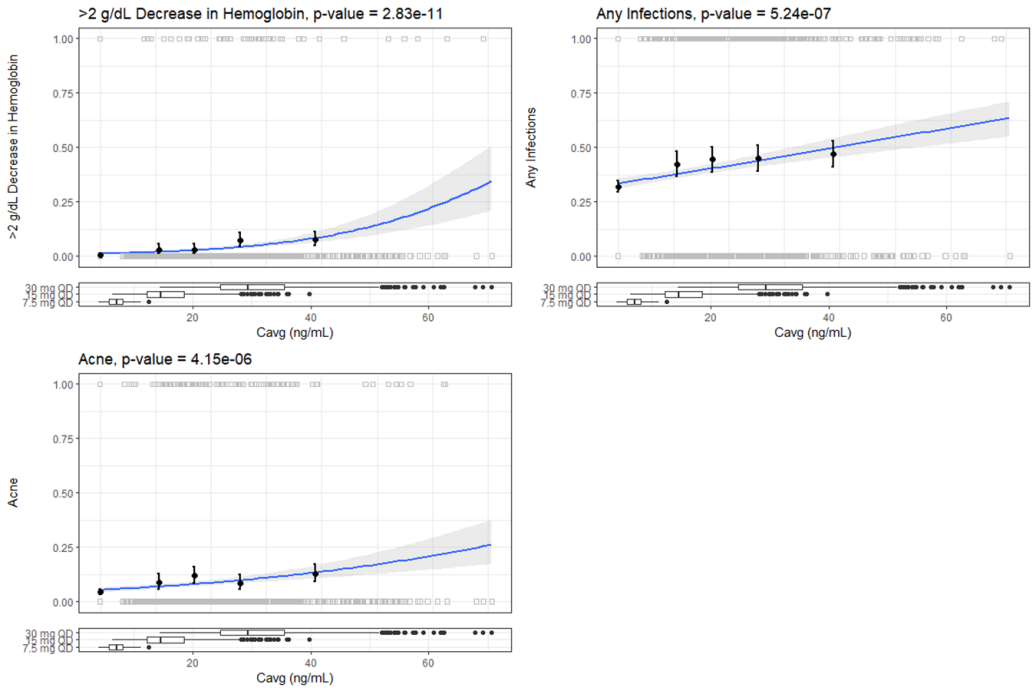
*As discussed in the exposure-responses efficacy analysis, the Demographic characteristics for subjects in exposure-response analysis were comparable with the overall study population. (*Table 100*) The results of Exposure-Response safety analysis for the selected safety endpoints were checked by the reviewer. (*Figure 30*) Logistic regression applied for the safety endpoints with upadacitinib exposures (C_{avg} and C_{max}) were shown in* Figure 31 *and* Figure 32*. Positive relationships exposure-relationship with upadacitinib exposures were identified for decreasing in Hemoglobin > 2 g/dL from baseline, infection, and acne. Higher incidences rates were observed for patients at 30 mg QD comparing with patients at 15 mg QD for these endpoints.*

Figure 30. Observed safety response rates at Week 16 in different dose groups.



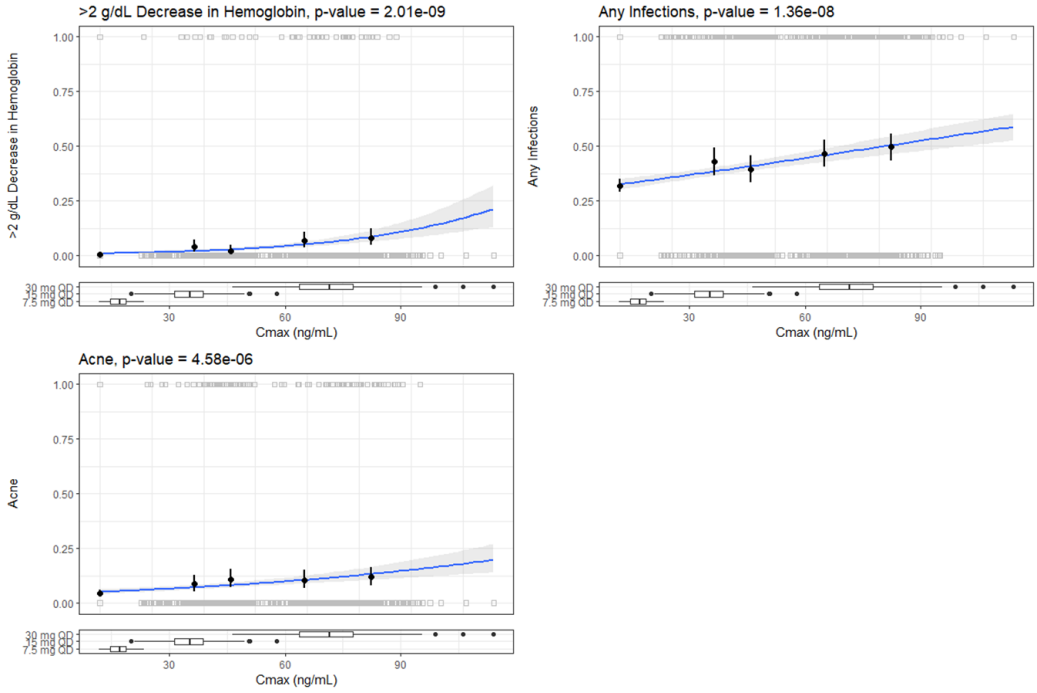
Source: Reviewer's analysis.

Figure 31. Logistic regression for selected safety endpoints vs upadacitinib C_{avg} at Week 16.



Source: Reviewer's analysis.

Figure 32. Logistic regression for selected safety endpoints vs upadacitinib C_{max} at Week 16.



Source: Reviewer's analysis.

18.4.4. Bioanalytical Methods for PK Data

The concentrations of upadacitinib in human plasma from samples obtained in clinical studies (M16-045, M16-047, M16-048, M18-891 and M20-017) were quantified using two validated LC-Ms/MS methods. The validation results of these two methods are summarized in Table 102 and Table 103. These two methods were cross-validated, which suggested that these two methods produce sufficiently similar results. The bioanalysis performance results are summarized in Table 104 to Table 109.

The bioanalytical method was adequately validated and met the acceptance criteria suggested in the FDA Bioanalytical Method Validation Guidance. Incurred sample reanalysis (ISR) for plasma samples were conducted from Studies M16-045, M16-048 and M20-017. The ISR was acceptable in terms of both sample size (at least 10% of the first 1000 samples and 5% of the remaining samples) and the results (>67% of the study samples evaluated within ±20% of the original sample concentrations). All samples were analyzed within the established long-term stability window.

Reviewer's comments: Although ISR was not conducted in two studies (M16-047 and M18-891), these two studies used the same bioanalytical method that was used for other studies without any issues identified. Therefore, the absence of ISR in these two studies does not pose a

significant concern that would affect the review decision of this supplement in this reviewer's opinion.

Table 102. Summary of LC-MS/MS Method Validation (R&D/12/654) Results

Validation Reports	R&D/12/654 R&D/16/0683 (update 1)[a] R&D/18/1039 (update 2)[b]
Matrix	Human plasma with K_2EDTA
Anticoagulant	Tripotassium Ethylene Diamine Tetra Acetic Acid (K_3EDTA)
Analytes	Upadacitinib (A-1293543)
Internal standard (ISTD)	A-1293543-d_4
Linearity (calibration curve range)	0.0503 ng/mL to 102 ng/mL
Extraction Type	Salt-Assisted Liquid/Liquid Extraction
Automation	96-Deep Well Format, Pipetting Robot (e.g., Starlet, Nimbus), Automation Station
Precision (% CV)	
LLOQ	7.4
ULOQ	4.0
QCs	≤ 5.0%
Accuracy (% Mean Bias)	
LLOQ	4.5
ULOQ	-7.4
QCs	-2.5 to 11.3
Short-term room temperature stability[c]	25 hours; mean %bias was 0.7% for the low QC and -7.2% for the high QC
Frozen storage stability at -20°C[c]	1615 days; mean %bias was 4.8% for the low QC and -2.0% for the high QC
Freeze-thaw stability[c]	at least 7 cycles
Autosampler Stability	260 hours in a cold autosampler (set point of 4°C) in a polypropylene plate
Run Storage Stability	167 hours in a cold autosampler (set point of 4°C) in a polypropylene plate
Frozen Matrix Stability	244 days stored at ~ -70°C in polypropylene cryogenic vials 1209 days stored at ~ -20°C in polypropylene cryogenic vials

Abbreviations: LLOQ = lower limit of quantification, ULOQ =upper limit of quantification, QC = quality control

[a]The update was to qualify the changes (mass spectrometer models, injection volume, procedure update, addition of working internal standard and addition of acetonitrile, and addition of water and transfer of the supernatant) to the analytical method; the validation was found to be adequate to support the changes.

[b]The update was for freeze-thaw stability and long-term storage stability.

[c]The updated data from Report R&D/18/1039.

Table 103. Summary of LC-MS/MS Method Validation (17BAS0220) Results

Validation Report	17BAS0220
Matrix	Human plasma with K_2EDTA
Anticoagulant	Tripotassium Ethylene Diamine Tetra Acetic Acid (K_3EDTA)
Analytes	Upadacitinib (ABT-494)
Internal standard (ISTD)	ABT-494-d_4
Linearity (calibration curve range)	0.0500 ng/mL to 100 ng/mL
Extraction Type	Protein precipitation
Precision (% CV)	
Intra-assay for QCs Inter-assay for QCs	≤ 8.9% ≤ 7.3%
Accuracy (% Mean Bias)	
Intra-assay for QCs Inter-assay for QCs	-4.4% to 8.7% 1.2% to 6.0%
Short-term room temperature stability	28.5 hours
Frozen matrix storage stability	35 days at -20°C and -80 °C
Freeze-thaw stability	five cycles thawed at -20°C and -80 °C

Table 104. Summary of Bioanalysis Performance Results from Study M16-045 (A)

Relevant Validation Reports	R&D/12/654 R&D/16/0683 R&D/18/1039
Matrix	Human plasma
Linearity (calibration curve range)	0.0503 ng/mL to 102 ng/mL
Performance of the assay during sample analysis	
Calibration standards	Mean Bias -2.0% to 1.2% at LLOQ Mean Bias between -4.9 and 6.9% at higher standard levels
QCs	Mean Bias between -1.8 and 2.8% CV ≤ 6.4%
Maximum sample storage period	570 days at -20°C (within the validated storage stability of 1615 days)

Table 105. Summary of Bioanalysis Performance Results from Study M16-045 (B)

Relevant Validation Report	17BAS0220
Matrix	Human plasma
Linearity (calibration curve range)	0.0500 ng/mL to 100 ng/mL

Performance of the assay during sample analysis	
Calibration standards	Mean Bias 1.0% at LLOQ Mean Bias between -1.6 to 1.0% at higher standard levels CV ≤ 8.4% at LLOQ CV ≤ 3.5% at higher standard levels
QCs	Mean Bias between -0.7 and 3.7% CV ≤ 3.9%
Incurred Sample Reanalysis	
Total no. of incurred sample reanalysis	30 (61% of samples)
Total no. of sample whose % differences are within 20%	30
% of total no. of samples whose % differences are within 20 %	100
Maximum sample storage period	358 days at -20°C (within the validated storage stability of 1615 days)

Table 106. Summary of Bioanalysis Performance Results from Study M16-047

Relevant Validation Reports	R&D/12/654 R&D/16/0683 R&D/18/1039
Matrix	Human plasma
Linearity (calibration curve range)	0.0503 ng/mL to 102 ng/mL
Performance of the assay during sample analysis	
Calibration standards	Mean Bias 0.6 to 1.4% at LLOQ Mean Bias between -3.3 to 7.9% at higher standard levels
QCs	Mean Bias between -2.8 and 1.6% CV ≤ 7.4%
Maximum sample storage period	868 days at -20°C (within the validated storage stability of 1615 days)

Table 107. Summary of Bioanalysis Performance Results from Study M16-048

Relevant Validation Reports	R&D/12/654 R&D/16/0683 R&D/18/1039
Matrix	Human plasma
Linearity (calibration curve range)	0.0505 ng/mL to 102 ng/mL 0.0506 ng/mL to 102 ng/mL

	0.0543 ng/mL to 102 ng/mL
Performance of the assay during sample analysis	
Calibration standards	Mean Bias -2.6 to 2.0% at LLOQ Mean Bias between -7.2 to 8.8% at higher standard levels
QCs	Mean Bias between -3.7 and 5.7% CV ≤ 14.2%
Incurred Sample Reanalysis	
Total no. of incurred sample reanalysis	140 (8.7% of samples)
Total no. of sample whose % differences are within 20%	138
% of total no. of samples whose % differences are within 20 %	98.6
Maximum sample storage period	813 days at -20°C (within the validated storage stability of 1615 days)

Table 108. Summary of Bioanalysis Performance Results from Study M18-891

Relevant Validation Reports	R&D/12/654 R&D/16/0683 R&D/18/1039
Matrix	Human plasma
Linearity (calibration curve range)	0.0505 ng/mL to 102 ng/mL
Performance of the assay during sample analysis	
Calibration standards	Mean Bias -0.6% at LLOQ Mean Bias between -4.3 to 2.7% at higher standard levels
QCs	Mean Bias between 0.4 and 1.5% CV ≤ 6.5%
Maximum sample storage period	620 days at -20°C (within the validated storage stability of 1615 days)

Table 109. Summary of Bioanalysis Performance Results from Study M20-017

Relevant Validation Reports	R&D/12/654 R&D/16/0683 R&D/18/1039
Matrix	Human plasma
Linearity (calibration curve range)	0.0505 ng/mL to 102 ng/mL
Performance of the assay during sample analysis	
Calibration standards	Mean Bias 1.0% at LLOQ

	Mean Bias between -1.7 to 2.3% at higher standard levels
QCs	Mean Bias between -0.6 and 3.2% CV ≤ 6.9%
Incurred Sample Reanalysis	
Total no. of incurred sample reanalysis	637 (12.5% of samples)
Total no. of sample whose % differences are within 20%	635
% of total no. of samples whose % differences are within 20 %	99.7
Maximum sample storage period	97 days at -20°C (within the validated storage stability of 1615 days)

18.5. Efficacy: Additional Information and Assessment

18.5.1. Atopic Dermatitis Impact Scale (Aderm-IS) and Atopic Dermatitis Symptom Scale (ADerm-SS)

Figure 33. Atopic Dermatitis Impact Scale (ADerm-IS)

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

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

Source: page 124 of the protocol for Trial M16-045.

Figure 34. Atopic Dermatitis Symptom Scale (ADerm-SS)

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

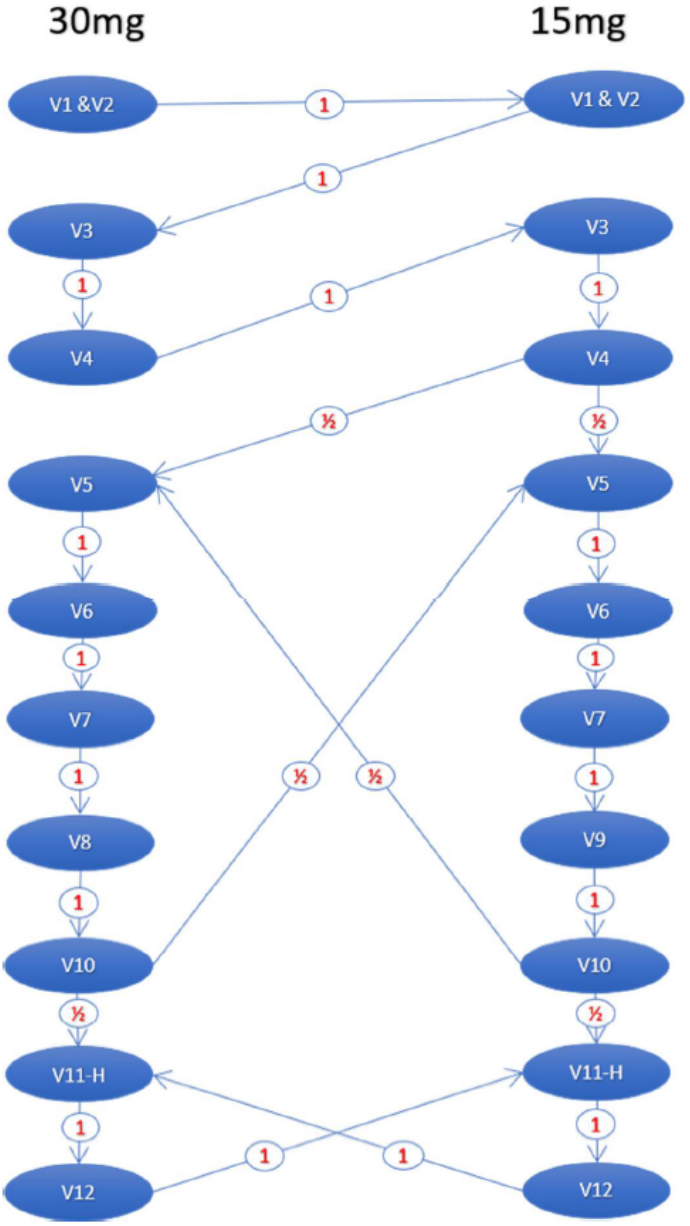
8. During the past 24 hours, how bad was your **worst rash (redness, blisters, bumpy skin)** due to AD?	No rash 0 1 2 3 4 5 6 7 8 9 10 Worst imaginable rash ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
9. During the past 24 hours, how bad was your **worst skin thickening** due to AD?	No skin thickening 0 1 2 3 4 5 6 7 8 9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

Source: page 121 of the protocol for Trial M16-045.

18.5.2. Multiplicity Testing Procedures

Figure 35 in presents the graphical approach for the monotherapy Phase 3 trials (i.e., M16-045 and M18-891). Figure 36 in presents the graphical approach for the combination Phase 3 trial (i.e., M16-047). In each graph, the arrows specify the α transfer path. Once an endpoint (or family of endpoints) is rejected at its assigned significance level, its significance level will be transferred to the subsequent endpoint(s). For the endpoint families (i.e., V11-H in Figure 35 and V12-H in Figure 36), the SAPs specified using the Hochberg approach to control the Type I error within the family. The SAPs specified that all endpoints in the family need to be significant in order to transfer α.

Figure 35. Graphical Approach for Multiplicity Adjustment – Trials M16-045 and M18-891



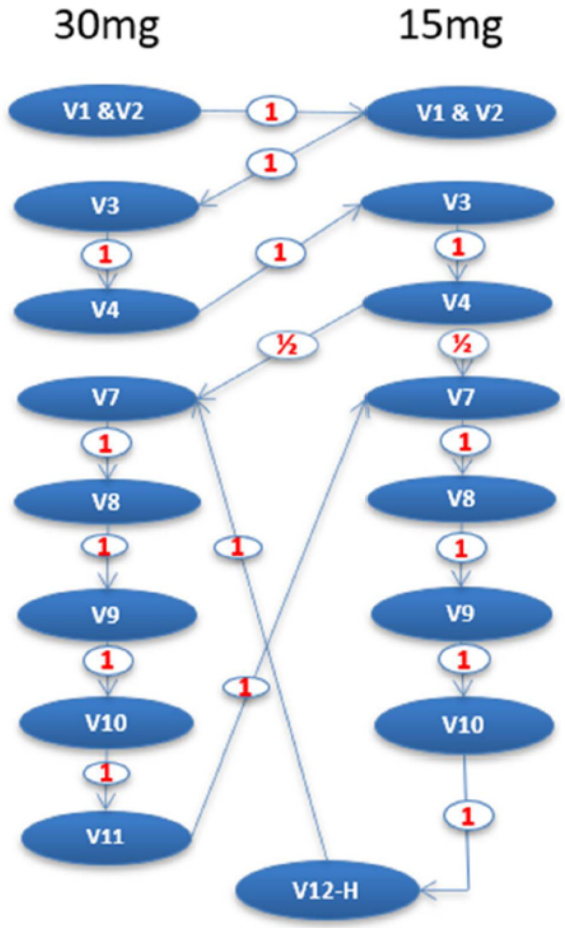
Source: page 19 of the SAP for Trial M16-045.

Below is the key to Figure 35:

- V1: Proportion of subjects achieving EASI-75 at Week 16
- V2: Proportion of subjects achieving vIGA-AD of 0 or 1 with at least two grades of reduction from baseline at Week 16
- V3: Proportion of subjects achieving an improvement (reduction) in WI-NRS ≥ 4 from baseline at Week 16 for subjects with WI-NRS ≥ 4 at baseline
- V4: Proportion of subjects achieving EASI-90 at Week 16
- V5: Proportion of subjects achieving an improvement (reduction) in WI-NRS ≥ 4 from baseline at Week 4 for subjects with WI-NRS ≥ 4 at baseline

- V6: Proportion of subjects achieving EASI-75 at Week 2
- V7: Proportion of subjects achieving an improvement (reduction) in WI-NRS ≥ 4 from baseline at Week 1 for subjects with WI-NRS ≥ 4 at baseline
- V8: Proportion of subjects achieving an improvement (reduction) in WI-NRS ≥ 4 from baseline at Day 2 for subjects with WI-NRS ≥ 4 at baseline (only 30 mg vs. placebo)
- V9: Proportion of subjects achieving an improvement (reduction) in WI-NRS ≥ 4 from baseline at Day 3 for subjects with WI-NRS ≥ 4 at baseline (only 15 mg vs. placebo)
- V10: Proportion of subjects experiencing a flare, defined as an increase of EASI by ≥ 6.6 from baseline for subjects with EASI ≤ 65.4 at baseline, during double-blind period
- V11-H:
    - Proportion of subjects achieving an improvement (reduction) in ADerm-IS sleep domain score ≥ 12 from baseline at Week 16 for subjects with ADerm-IS sleep domain score ≥ 12 at baseline
    - Proportion of subjects achieving an improvement (reduction) in ADerm-SS skin pain score ≥ 4 from baseline at Week 16 for subjects with ADerm-SS skin pain score ≥ 4 at baseline
    - Proportion of subjects achieving an improvement (reduction) in ADerm-SS TSS-7 ≥ 28 from baseline at Week 16 for subjects with ADerm-SS TSS-7 ≥ 28 at baseline
    - Proportion of subjects achieving an improvement (reduction) in ADerm-IS emotional state domain score ≥ 11 from baseline at Week 16 for subjects with ADerm-IS emotional state domain score ≥ 11 at baseline
    - Proportion of subjects achieving an improvement (reduction) in ADerm-IS daily activities domain score ≥ 14 from baseline at Week 16 for subjects with ADerm-IS daily activities domain score ≥ 14 at baseline
- V12: Proportion of subjects achieving EASI-100 at Week 16

Figure 36. Graphical Approach for Multiplicity Adjustment – Trial M16-047



Source: page 18 of the SAP for Trial M16-047.

Below is the key to Figure 36:

- V1: Proportion of subjects achieving EASI-75 at Week 16
- V2: Proportion of subjects achieving vIGA-AD of 0 or 1 with at least two grades of reduction at Week 16
- V3: Proportion of subjects achieving an improvement (reduction) in WI-NRS ≥ 4 from baseline at Week 16
- V4: Proportion of subject achieving EASI-90 at Week 16
- V7: Proportion of subjects achieving an improvement (reduction) in WI-NRS ≥ 4 from baseline at Week 4
- V8: Proportion of subjects achieving EASI-75 at Week 4
- V9: Proportion of subjects achieving EASI-75 at Week 2
- V10: Proportion of subjects achieving EASI-90 at Week 4
- V11: Proportion of subjects achieving EASI-100 at Week 16 (only 30 mg vs. placebo)
- H1: Proportion of subjects achieving an improvement (reduction) in WI-NRS ≥ 4 from baseline at Week 1

18.5.3. Baseline ADerm-IS and ADerm-SS Information

Table 110. Baseline ADerm-IS and ADerm-SS – Trials M16-045 and M18-891 (ITT[1])

	Trial M16-045			Trial M18-891		
		Upadacitinib			Upadacitinib	
	Placebo (N=281)	15 mg (N=281)	30 mg (N=285)	Placebo (N=278)	15 mg (N=276)	30 mg (N=282)
Pain NRS						
n	276	279	281	277	275	281
Mean (SD)	6.5 (2.4)	6.2 (2.3)	6.5 (2.1)	6.5 (2.2)	6.4 (2.1)	6.4 (2.3)
Median	6.7	6.3	6.9	6.8	6.8	6.6
Min, Max	0.0, 10.0	0.0, 10.0	0.0, 10.0	0.0, 10.0	0.0, 10.0	0.0, 10.0
Categories, n (%)						
< 4	43 (15)	42 (15)	32 (11)	30 (11)	38 (14)	43 (15)
≥ 4	233 (83)	237 (84)	249 (87)	247 (89)	237 (86)	238 (84)
Missing	5 (2)	2 (1)	4 (1)	1 (0)	1 (0)	1 (0)
ADerm-IS Sleep						
n	276	279	281	277	275	281
Mean (SD)	18.7 (7.5)	18.0 (7.5)	18.1 (7.6)	19.5 (7.5)	18.3 (7.3)	18.8 (7.7)
Median	19.7	19	19.7	21	19.7	19.9
Min, Max	0.0, 30.0	0.0, 30.0	0.0, 30.0	0.0, 30.0	0.0, 30.0	0.7, 30.0
Categories, n (%)						
< 12	56 (20)	61 (22)	63 (22)	44 (16)	56 (20)	53 (19)
≥ 12	220 (78)	218 (78)	218 (76)	233 (84)	219 (79)	228 (81)
Missing	5 (2)	2 (1)	4 (1)	1 (0)	1 (0)	1 (0)
ADerm-IS Emotion						
n	255	261	268	266	253	265
Mean (SD)	20.0 (8.3)	20.2 (8.0)	20.1 (8.4)	20.6 (8.0)	20.6 (7.8)	20.1 (8.2)
Median	22	22	22	22	22	22
Min, Max	0.0, 30.0	0.0, 30.0	0.0, 30.0	0.0, 30.0	0.0, 30.0	0.0, 30.0
Categories, n (%)						
< 11	43 (15)	34 (12)	42 (15)	32 (12)	25 (9)	37 (13)
≥ 11	212 (75)	227 (81)	226 (79)	234 (84)	228 (83)	228 (81)
Missing	26 (9)	20 (7)	17 (6)	12 (4)	23 (8)	17 (6)
ADerm-IS Daily Activity						
n	255	261	268	266	253	265
Mean (SD)	22.6 (10.6)	22.7 (11.0)	22.5 (11.1)	24.2 (10.6)	23.5 (9.9)	23.0 (10.0)
Median	24	24	24	25	25	23
Min, Max	0.0, 40.0	0.0, 40.0	0.0, 40.0	0.0, 40.0	0.0, 40.0	0.0, 40.0
Categories, n (%)						
< 14	58 (21)	58 (21)	63 (22)	39 (14)	46 (17)	42 (15)
≥ 14	197 (70)	203 (72)	205 (72)	227 (82)	207 (75)	223 (79)
Missing	26 (9)	20 (7)	17 (6)	12 (4)	23 (8)	17 (6)
ADerm-SS TSS-7						
n	255	261	268	266	253	265
Mean (SD)	46.1 (14.5)	45.7 (14.0)	46.3 (13.4)	47.2 (13.6)	46.8 (13.2)	46.3 (13.8)
Median	46	47	47	48.5	49	48
Min, Max	0.0, 70.0	3.0, 70.0	11.0, 70.0	9.0, 70.0	9.0, 70.0	14.0, 70.0
Categories, n (%)						
< 28	29 (10)	28 (10)	22 (8)	22 (8)	23 (8)	31 (11)
≥ 28	226 (80)	233 (83)	246 (86)	244 (88)	230 (83)	234 (83)
Missing	26 (9)	20 (7)	17 (6)	12 (4)	23 (8)	17 (6)

[1] Intent-to-Treat (ITT) population: all randomized subjects.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADSL.xpt, ADEFNRS.xpt, ADEFADR.xpt

Table 111. Baseline ADerm-IS and ADerm-SS – Trial M16-047 (ITT[1])

	Trial M16-047		
		Upadacitinib	
	Placebo + TCS (N=304)	15 mg + TCS (N=300)	30 mg + TCS (N=297)
Pain NRS			
n	301	299	295
Mean (SD)	6.3 (2.2)	6.3 (2.3)	6.5 (2.4)
Median	6.6	6.7	6.9
Min, Max	0.0, 10.0	0.0, 10.0	0.0, 10.0
Categories, n (%)			
< 4	46 (15)	47 (16)	48 (16)
≥ 4	255 (84)	252 (84)	247 (83)
Missing	3 (1)	1 (0)	2 (1)
ADerm-IS Sleep			
n	301	299	295
Mean (SD)	17.8 (7.6)	18.2 (7.8)	19.2 (7.4)
Median	18.5	19.6	20.6
Min, Max	0.0, 30.0	0.0, 30.0	0.0, 30.0
Categories, n (%)			
< 12	68 (22)	68 (23)	53 (18)
≥ 12	233 (77)	231 (77)	242 (81)
Missing	3 (1)	1 (0)	2 (1)
ADerm-IS Emotion			
n	287	286	287
Mean (SD)	20.1 (7.8)	19.6 (8.2)	19.9 (8.2)
Median	21	22	22
Min, Max	0.0, 30.0	0.0, 30.0	0.0, 30.0
Categories, n (%)			
< 11	34 (11)	47 (16)	44 (15)
≥ 11	253 (83)	239 (80)	243 (82)
Missing	17 (6)	14 (5)	10 (3)
ADerm-IS Daily Activity			
n	287	286	287
Mean (SD)	22.9 (10.5)	23.2 (10.8)	23.9 (10.5)
Median	24	25	26
Min, Max	0.0, 40.0	0.0, 40.0	0.0, 40.0
Categories, n (%)			
< 14	59 (19)	63 (21)	55 (19)
≥ 14	228 (75)	223 (74)	232 (78)
Missing	17 (6)	14 (5)	10 (3)
ADerm-SS TSS-7			
n	287	286	287
Mean (SD)	45.9 (13.5)	46.0 (14.6)	47.4 (13.9)
Median	46	48	49
Min, Max	7.0, 70.0	0.0, 70.0	6.0, 70.0
Categories, n (%)			
< 28	25 (8)	36 (12)	33 (11)
≥ 28	262 (86)	250 (83)	254 (86)
Missing	17 (6)	14 (5)	10 (3)

[1] Intent-to-Treat (ITT) population: all randomized subjects.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADSL.xpt, ADEFNRS.xpt, ADEFADR.xpt

18.5.4. Results for the Additional Subgroup Populations

Table 112. Results for IGA Response[1] at Week 16 by Sex, Race, Baseline Body Weight, Country, and Baseline IGA score for Trial M16-045 (ITT[2])

		Upadacitinib		Difference	
	Placebo (N=281)	15 mg (N=281)	30 mg (N=285)	15 mg vs. Placebo (95% CI)	30 mg vs. Placebo (95% CI)
Sex					
Male (144, 157, 155)	10%	42%	54%	32% (23%, 41%)	44% (35%, 54%)
Female (137, 124, 130)	7%	56%	71%	49% (39%, 59%)	64% (55%, 73%)
Race					
White (182, 182, 191)	10%	51%	63%	41% (32%, 49%)	53% (45%, 62%)
Asian (69, 63, 71)	3%	46%	55%	43% (30%, 56%)	52% (40%, 64%)
Black or African American (21, 26, 8)	19%	35%	50%	16% (-9%, 40%)	31% (-8%, 69%)
Other (9, 10, 15)	0%	50%	87%	50% (19%, 81%)	87% (70%, 100%)
Baseline Body Weight					
< 70 kg (119, 136, 138)	8%	52%	66%	44% (34%, 53%)	58% (48%, 67%)
70 – 100 kg (129, 115, 126)	10%	46%	59%	36% (25%, 46%)	49% (39%, 59%)
> 100 kg (33, 30, 21)	3%	40%	57%	37% (18%, 55%)	54% (32%, 76%)
Country					
United States (76, 84, 71)	9%	48%	70%	38% (26%, 51%)	61% (49%, 74%)
Outside United States (205, 197, 214)	8%	48%	59%	40% (32%, 48%)	51% (43%, 59%)
Baseline IGA Score					
3 – Moderate (154, 120, 129)	10%	56%	70%	46% (37%, 56%)	60% (51%, 69%)
4 – Severe (127, 129, 129)	7%	39%	53%	32% (22%, 41%)	46% (36%, 55%)
Overall	8%	48%	62%	40% (33%, 46%)	54% (47%, 60%)

[1] Response was defined as a vIGA-AD score of 0 ("clear") or 1 ("almost clear") with at least a 2-grade reduction from baseline.
[2] Intent-to-Treat (ITT) population: all randomized subjects. Missing data was imputed using NRI-C.
Source: Statistical Reviewer's analysis; ADEFF.xpt, ADSL.xpt

Table 113. Results for IGA Response[1] at Week 16 by Sex, Race, Baseline Body Weight, Country, and Baseline IGA score for Trial M18-891 (ITT[2])

		Upadacitinib		Difference	
	Placebo (N=278)	15 mg (N=276)	30 mg (N=282)	15 mg vs. Placebo (95% CI)	30 mg vs. Placebo (95% CI)
Sex					
Male (154, 155, 162)	4%	39%	49%	35% (27%, 43%)	45% (37%, 54%)
Female (124, 121, 120)	6%	39%	56%	33% (24%, 43%)	50% (40%, 60%)
Race					

		Upadacitinib		Difference	
	Placebo (N=278)	15 mg (N=276)	30 mg (N=282)	15 mg vs. Placebo (95% CI)	30 mg vs. Placebo (95% CI)
White (195, 184, 198)	5%	43%	53%	38% (31%, 46%)	48% (41%, 56%)
Asian (56, 65, 62)	4%	28%	48%	24% (12%, 36%)	44% (31%, 58%)
Black or African American (16, 17, 18)	6%	29%	56%	23% (-2%, 49%)	49% (23%, 75%)
Other (11, 10, 4)	9%	50%	47%	41% (6%, 76%)	38% (-16%, 92%)
Baseline Body Weight					
< 70 kg (116, 130, 124)	4%	42%	54%	37% (28%, 46%)	50% (40%, 59%)
70 – 100 kg (132, 122, 134)	5%	34%	52%	29% (20%, 38%)	47% (37%, 56%)
> 100 kg (30, 24, 24)	3%	46%	42%	43% (22%, 63%)	38% (18%, 59%)
Country					
United States (76, 78, 82)	5%	41%	47%	36% (24%, 48%)	42% (30%, 54%)
Outside United States (202, 198, 200)	4%	38%	54%	33% (26%, 41%)	49% (42%, 57%)
Baseline IGA Score					
3 – Moderate (125, 125, 125)	6%	43%	54%	38% (28%, 47%)	48% (39%, 58%)
4 – Severe (153, 151, 157)	4%	35%	50%	31% (23%, 39%)	47% (38%, 55%)
Overall	5%	39%	52%	34% (28%, 40%)	47% (41%, 54%)

[1] Response was defined as a vIGA-AD score of 0 ("clear") or 1 ("almost clear") with at least a 2-grade reduction from baseline.
[2] Intent-to-Treat (ITT) population: all randomized subjects. Missing data was imputed using NRI-C.
Source: Statistical Reviewer's analysis; ADEFF.xpt, ADSL.xpt

Table 114. Results for IGA Response[1] at Week 16 by Sex, Race, Baseline Body Weight, Country, and Baseline IGA score for Trial M16-047 (ITT[2])

		Upadacitinib		Difference	
	Placebo (N=304)	15 mg (N=300)	30 mg (N=297)	15 mg vs. Placebo (95% CI)	30 mg vs. Placebo (95% CI)
Sex					
Male (178, 179, 190)	9%	35%	54%	26% (17%, 34%)	45% (37%, 53%)
Female (126, 121, 107)	14%	47%	67%	33% (23%, 44%)	53% (42%, 64%)
Race					
White (225, 204, 218)	13%	43%	62%	30% (22%, 38%)	49% (41%, 57%)
Asian (60, 64, 61)	4%	34%	50%	31% (18%, 43%)	46% (32%, 60%)
Black or African American (18, 19, 13)	11%	30%	38%	19% (-7%, 45%)	27% (-3%, 58%)
Other (1, 13, 5)	0%	31%	80%	31% (6%, 56%)	80% (45%, 100%)
Baseline Body Weight					
< 70 kg (120, 133, 127)	13%	38%	67%	25% (15%, 35%)	54% (44%, 65%)
70 – 100 kg (154, 140, 139)	10%	41%	52%	31% (22%, 41%)	42% (33%, 52%)
> 100 kg (30, 27, 31)	10%	41%	52%	31% (9%, 52%)	42% (22%, 63%)
Country					
United States (56, 57, 53)	16%	39%	48%	23% (7%, 38%)	32% (15%, 48%)

	Placebo (N=304)	Upadacitinib 15 mg (N=300)	Upadacitinib 30 mg (N=297)	Difference 15 mg vs. Placebo (95% CI)	Difference 30 mg vs. Placebo (95% CI)
Outside United States (248, 243, 244)	10%	40%	61%	30% (23%, 37%)	51% (44%, 58%)
Baseline IGA Score					
3 – Moderate (143, 141, 140)	14%	52%	72%	38% (28%, 48%)	58% (49%, 67%)
4 – Severe (161, 159, 157)	8%	29%	46%	21% (13%, 29%)	38% (30%, 47%)
Overall	11%	40%	59%	29% (22%, 35%)	48% (41%, 54%)

[1] Response was defined as a vIGA-AD score of 0 ("clear") or 1 ("almost clear") with at least a 2-grade reduction from baseline.
[2] Intent-to-Treat (ITT) population: all randomized subjects. Missing data was imputed using NRI-C.
Source: Statistical Reviewer's analysis; ADEFF.xpt, ADSL.xpt

Table 115. Results for EASI-75 at Week 16 by Sex, Race, Baseline Body Weight, Country, and Baseline IGA score for Trial M16-045 (ITT[1])

	Placebo (N=281)	Upadacitinib 15 mg (N=281)	Upadacitinib 30 mg (N=285)	Difference 15 mg vs. Placebo (95% CI)	Difference 30 mg vs. Placebo (95% CI)
Sex					
Male (144, 157, 155)	15%	65%	79%	50% (41%, 60%)	64% (55%, 73%)
Female (137, 124, 130)	18%	75%	81%	57% (47%, 67%)	63% (53%, 72%)
Race					
White (182, 182, 191)	18%	68%	81%	51% (42%, 60%)	63% (55%, 71%)
Asian (69, 63, 71)	11%	73%	75%	62% (49%, 76%)	64% (51%, 76%)
Black or African American (21, 26, 8)	19%	62%	63%	42% (17%, 68%)	43% (6%, 81%)
Other (9, 10, 15)	26%	90%	98%	64% (28%, 100%)	73% (41%, 100%)
Baseline Body Weight					
< 70 kg (119, 136, 138)	18%	77%	84%	59% (49%, 69%)	66% (57%, 75%)
70 – 100 kg (129, 115, 126)	18%	61%	76%	43% (32%, 54%)	58% (48%, 68%)
> 100 kg (33, 30, 21)	6%	70%	76%	64% (46%, 82%)	70% (50%, 90%)
Country					
United States (76, 84, 71)	20%	67%	83%	46% (33%, 60%)	63% (50%, 75%)
Outside United States (205, 197, 214)	15%	71%	79%	56% (48%, 64%)	64% (56%, 71%)
Baseline IGA Score					
3 – Moderate (154, 120, 129)	21%	71%	81%	50% (40%, 60%)	60% (51%, 69%)
4 – Severe (127, 129, 129)	11%	68%	78%	57% (48%, 67%)	68% (59%, 77%)
Overall	16%	70%	80%	53% (46%, 60%)	63% (57%, 70%)

[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data was imputed using NRI-C.
Source: Statistical Reviewer's analysis; ADEFF.xpt, ADSL.xpt

Table 116. Results for EASI-75 at Week 16 by Sex, Race, Baseline Body Weight, Country, and Baseline IGA score for Trial M18-891 (ITT[1])

		Upadacitinib		Difference	
	Placebo (N=278)	15 mg (N=276)	30 mg (N=282)	15 mg vs. Placebo (95% CI)	30 mg vs. Placebo (95% CI)
Sex					
Male (154, 155, 162)	12%	61%	73%	49% (40%, 58%)	61% (52%, 69%)
Female (124, 121, 120)	15%	59%	73%	44% (33%, 55%)	58% (48%, 68%)
Race					
White (195, 184, 198)	10%	60%	73%	50% (42%, 58%)	62% (55%, 70%)
Asian (56, 65, 62)	16%	62%	74%	45% (30%, 61%)	58% (43%, 72%)
Black or African American (16, 17, 18)	25%	47%	78%	22% (-10%, 54%)	53% (24%, 81%)
Other (11, 10, 4)	36%	70%	61%	34% (7%, 74%)	24% (35%, 84%)
Baseline Body Weight					
< 70 kg (116, 130, 124)	14%	66%	76%	52% (42%, 63%)	63% (53%, 72%)
70 – 100 kg (132, 122, 134)	13%	54%	69%	41% (31%, 52%)	57% (47%, 66%)
> 100 kg (30, 24, 24)	13%	58%	75%	45% (22%, 68%)	62% (41%, 83%)
Country					
United States (76, 78, 82)	16%	60%	64%	44% (31%, 58%)	48% (35%, 61%)
Outside United States (202, 198, 200)	12%	60%	77%	48% (40%, 56%)	64% (57%, 72%)
Baseline IGA Score					
3 – Moderate (125, 125, 125)	16%	60%	69%	44% (33%, 55%)	53% (43%, 64%)
4 – Severe (153, 151, 157)	11%	60%	76%	49% (40%, 58%)	65% (56%, 73%)
Overall	13%	60%	73%	47% (40%, 54%)	60% (53%, 66%)

[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data was imputed using NRI-C.
Source: Statistical Reviewer's analysis; ADEFF.xpt, ADSL.xpt

Table 117. Results for EASI-75 at Week 16 by Sex, Race, Baseline Body Weight, Country, and Baseline IGA score for Trial M16-047 (ITT[1])

		Upadacitinib		Difference	
	Placebo (N=304)	15 mg (N=300)	30 mg (N=297)	15 mg vs. Placebo (95% CI)	30 mg vs. Placebo (95% CI)
Sex					
Male (178, 179, 190)	23%	61%	75%	38% (29%, 48%)	52% (43%, 61%)
Female (126, 121, 107)	31%	69%	81%	38% (27%, 50%)	49% (38%, 61%)
Race					
White (225, 204, 218)	26%	66%	78%	39% (31%, 48%)	52% (44%, 60%)
Asian (60, 64, 61)	22%	63%	78%	40% (24%, 56%)	55% (40%, 70%)
Black or African American (18, 19, 13)	44%	61%	54%	17% (-15%, 49%)	9% (-26%, 45%)

	Placebo (N=304)	Upadacitinib 15 mg (N=300)	Upadacitinib 30 mg (N=297)	Difference 15 mg vs. Placebo (95% CI)	Difference 30 mg vs. Placebo (95% CI)
Other (1, 13, 5)	0%	62%	80%	62% (35%, 88%)	80% (45%, 100%)
Baseline Body Weight					
< 70 kg (120, 133, 127)	28%	63%	85%	36% (24%, 47%)	58% (47%, 68%)
70 – 100 kg (154, 140, 139)	26%	66%	71%	40% (29%, 51%)	45% (35%, 55%)
> 100 kg (30, 27, 31)	23%	63%	72%	40% (16%, 63%)	49% (27%, 71%)
Country					
United States (56, 57, 53)	36%	63%	65%	27% (10%, 45%)	29% (11%, 47%)
Outside United States (248, 243, 244)	24%	65%	80%	41% (33%, 49%)	56% (48%, 63%)
Baseline IGA Score					
3 – Moderate (143, 141, 140)	30%	67%	85%	37% (26%, 48%)	55% (45%, 64%)
4 – Severe (161, 159, 157)	23%	62%	70%	39% (29%, 49%)	47% (37%, 57%)
Overall	26%	65%	77%	38% (31%, 45%)	51% (44%, 58%)

[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data was imputed using NRI-C.
Source: Statistical Reviewer's analysis; ADEFF.xpt, ADSL.xpt

18.6. Additional Clinical Outcome Assessment Analyses

Refer to the consult review by Mira Patel on December 2, 2021 filed in DARRTS.

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YANGBING LI
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MATTHEW W GUERRA
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