CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

211675Orig1s004

Trade Name:	RINVOQ
Generic or Proper Name:	upadacitinib
Sponsor:	AbbVie Inc.
Approval Date:	January 14, 2022
Indication:	RINVOQ is a Janus kinase (JAK) inhibitor indicated for the treatment of • Adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more TNF blockers. • Adults with active psoriatic arthritis who have had an inadequate response or intolerance to one or more TNF blockers. • 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 drug products, including biologics, or when use of those therapies are inadvisable.

CENTER FOR DRUG EVALUATION AND RESEARCH

211675Orig1s004

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Officer/Employee List	
Multidiscipline Review(s) • **Summary Review** • **Office Director** • **Cross Discipline Team Leader** • **Clinical** • **Non-Clinical** • **Statistical** • **Clinical Pharmacology**	**X**
Product Quality Review(s)	
Clinical Microbiology / Virology Review(s)	
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211675Orig1s004

APPROVAL LETTER

NDA 211675/S-004

SUPPLEMENT APPROVAL

AbbVie Inc.
Attention: Viraj Gandhi, MS, MBA, RAC
Associate Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA72/Bldg. AP30-4
North Chicago, IL 60064

Dear Mr. Gandhi:

Please refer to your supplemental new drug application (sNDA) dated and received October 15, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Rinvoq (upadacitinib) extended-release tablets.

We acknowledge receipt of your major amendments dated March 26, 2021, which extended the goal date by three months.

This Prior Approval supplemental new drug application provides for the new indication of 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 drug products, including biologics, or when use of those therapies are inadvisable.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (Prescribing Information, and Medication Guide), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling and carton and container labeling submitted on June 30, 2021, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 211675/S-004**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for patients less than 6 months of age because necessary studies are impossible or highly impracticable. This is because of the diagnostic uncertainty especially in children below 3 months of age.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

We are deferring submission of your pediatric studies for ages 6 months to 11 years for this application because this product is ready for approval for use in adults and adolescents 12 years and older and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

4212-1 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 lower 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 4212-1 for pediatric subjects 6-11 years of age will inform our 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 ages 6 months to 5 years and on the type of data that would be required.

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 128180 with a cross-reference letter to this NDA. Reports of this required pediatric postmarketing study must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the unexpected serious risk of long term use of upadacitinib and the effect on women exposed to upadacitinib during pregnancy and /or lactation.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

4212-2 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.

The timetable you submitted on December 20, 2021, states that you will conduct this study according to the following schedule:

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

4212-3 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.

The timetable you submitted on December 20, 2021, states that you will conduct this study according to the following schedule:

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

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Submit the protocol(s) to your IND 128180 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[5]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

As required under 21 CFR 314.80, report each adverse drug experience that is both serious and unexpected within 15 days from initial receipt of the information. You are also required to report cases of drug-induced liver injury (DILI) and retinal detachment regardless of whether it was assessed as serious or non-serious within 15 days from initial receipt of the information. Every effort should be made to obtain thorough and complete follow-up of events related to DILI or retinal detachment, including results from specialist consults (e.g., hepatology, ophthalmology). The clinical information collected in this manner will enhance the quality of adverse event reports submitted to the FDA and facilitate our assessment of these reports.

If you have any questions, call Craig Johnson, Regulatory Project Manager, at 301-796-3921.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KENDALL A MARCUS
01/14/2022 11:46:48 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211675Orig1s004

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RINVOQ safely and effectively. See full prescribing information for RINVOQ.

RINVOQ® (upadacitinib) extended-release tablets, for oral use
Initial U.S. Approval: 2019

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE), AND THROMBOSIS

See full prescribing information for complete boxed warning.

- **Increased risk of serious bacterial, fungal, viral, and opportunistic infections leading to hospitalization or death, including tuberculosis (TB). Interrupt treatment with RINVOQ if serious infection occurs until the infection is controlled. Test for latent TB before and during therapy; treat latent TB prior to use. Monitor all patients for active TB during treatment, even patients with initial negative, latent TB test. (5.1)**
- **Higher rate of all-cause mortality, including sudden cardiovascular death with another Janus kinase (JAK) inhibitor vs. tumor necrosis factor (TNF) blockers in rheumatoid arthritis (RA) patients. (5.2)**
- **Malignancies have occurred in patients treated with RINVOQ. Higher rate of lymphomas and lung cancers with another JAK inhibitor vs. TNF blockers in RA patients. (5.3)**
- **Higher rate of MACE (defined as cardiovascular death, myocardial infarction, and stroke) with another JAK inhibitor vs. TNF blockers in RA patients. (5.4)**
- **Thrombosis has occurred in patients treated with RINVOQ. Increased incidence of pulmonary embolism, venous and arterial thrombosis with another JAK inhibitor vs. TNF blockers. (5.5)**

RECENT MAJOR CHANGES

Boxed Warning	12/2021
Indications and Usage, Rheumatoid Arthritis (1.1)	12/2021
Indications and Usage, Psoriatic Arthritis (1.2)	12/2021
Indications and Usage, Atopic Dermatitis (1.3)	1/2022
Dosage and Administration	
Recommended Evaluations and Immunizations Prior to Treatment Initiation (2.1)	1/2022
Recommended Dosage in Psoriatic Arthritis (2.4)	12/2021
Recommended Dosage in Atopic Dermatitis (2.5)	1/2022
Recommended Dosage in Patients with Renal Impairment or Severe Hepatic Impairment (2.6)	1/2022
Dosage Modifications Due to Drug Interactions (2.7)	1/2022
Contraindications (4)	1/2022
Warnings and Precautions	
Serious Infections (5.1)	12/2021
Mortality (5.2)	12/2021
Malignancy and Lymphoproliferative Disorders (5.3)	12/2021
Major Adverse Cardiovascular Events (5.4)	12/2021
Thrombosis (5.5)	12/2021
Hypersensitivity Reactions (5.6)	1/2022
Gastrointestinal Perforations (5.7)	12/2021
Embryo-Fetal Toxicity (5.9)	1/2022

INDICATIONS AND USAGE

RINVOQ is a Janus kinase (JAK) inhibitor indicated for the treatment of

- Adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more TNF blockers. (1.1)

  Limitations of Use

  Use of RINVOQ in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended. (1.1)
- Adults with active psoriatic arthritis who have had an inadequate response or intolerance to one or more TNF blockers. (1.2)

  Limitations of Use

  Use of RINVOQ in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended. (1.2)
- 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 drug products, including biologics, or when use of those therapies are inadvisable. (1.3)

  Limitations of Use

  RINVOQ is not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, or with other immunosuppressants. (1.3)

DOSAGE AND ADMINISTRATION

- Prior to treatment update immunizations and consider evaluating for active and latent tuberculosis, viral hepatitis, hepatic function, and pregnancy status (2.1)
- Avoid initiation or interrupt RINVOQ if absolute lymphocyte count is less than 500 cells/mm^3, absolute neutrophil count is less than 1000 cells/mm^3, or hemoglobin level is less than 8 g/dL. (2.1, 2.8)

Rheumatoid Arthritis

- The recommended dosage of RINVOQ is 15 mg once daily. (2.3)

Psoriatic Arthritis

- The recommended dosage of RINVOQ is 15 mg once daily. (2.4)

Atopic Dermatitis

- *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 orally once daily. If an adequate response is not achieved, consider increasing the dosage to 30 mg orally once daily. (2.5)
- *Adults 65 Years of Age and Older*: Recommended dosage is 15 mg once daily. (2.5)
- *Severe Renal Impairment*: Recommended dosage is 15 mg once daily. (2.6)

DOSAGE FORMS AND STRENGTHS

Extended-release tablets: 15 mg and 30 mg (3)

CONTRAINDICATIONS

Known hypersensitivity to upadacitinib or any of the excipients in RINVOQ. (4)

WARNINGS AND PRECAUTIONS

- Serious Infections: Avoid use of RINVOQ in patients with active, serious infection, including localized infections. (5.1)
- Hypersensitivity: Serious hypersensitivity reactions (e.g., anaphylaxis) have been reported. Discontinue RINVOQ if a serious hypersensitivity reaction occurs. (5.6)
- Gastrointestinal (GI) Perforations: Monitor patients at risk for GI perforations and promptly evaluate patients with symptoms. (5.7)
- Laboratory Abnormalities: Monitoring recommended due to potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes and lipids. (5.8)
- Embryo-Fetal Toxicity: RINVOQ may cause fetal harm based on animal studies. Advise female patients of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.9, 8.1, 8.3)
- Vaccinations: Avoid use of RINVOQ with live vaccines. (5.10)

ADVERSE REACTIONS

- Rheumatoid arthritis and psoriatic arthritis: Adverse reactions (≥ 1%) were: upper respiratory tract infections, herpes zoster, herpes simplex, bronchitis, nausea, cough, pyrexia and acne. (6.1)
- Atopic Dermatitis: Adverse reactions (≥ 1%) are: upper respiratory tract infections, acne, herpes simplex, headache, blood creatine phosphokinase increased, cough, hypersensitivity, folliculitis, nausea, abdominal pain, pyrexia, increased weight, herpes zoster, influenza, fatigue, neutropenia, myalgia, and influenza like illness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong CYP3A4 Inhibitors: Recommended dosage of RINVOQ in patients taking strong CYP3A4 inhibitors is 15 mg once daily. (7.1)
- Strong CYP3A4 Inducers: Coadministration of RINVOQ with strong CYP3A4 inducers is not recommended. (7.2)

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)
- Hepatic Impairment: RINVOQ is not recommended in patients with severe hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 1/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS, AND THROMBOSIS

SERIOUS INFECTIONS

Patients treated with RINVOQ are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions (5.1), Adverse Reactions (6.1)]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

If a serious infection develops, interrupt RINVOQ until the infection is controlled.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before RINVOQ use and during therapy. Treatment for latent infection should be considered prior to RINVOQ use.**
- **Invasive fungal infections, including cryptococcosis and pneumocystosis.**
- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

The risks and benefits of treatment with RINVOQ should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with RINVOQ, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy *[see Warnings and Precautions (5.1)]*.

MORTALITY

In a large, randomized, postmarketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor comparing another Janus kinase (JAK) inhibitor to tumor necrosis factor (TNF) blockers, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with the JAK inhibitor *[see Warnings and Precautions (5.2)]*.

MALIGNANCIES

Lymphoma and other malignancies have been observed in patients treated with RINVOQ. In RA patients treated with another JAK inhibitor, a higher rate of malignancies (excluding non-melanoma skin cancer (NMSC)) was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk *[see Warnings and Precautions (5.3)]*.

MAJOR ADVERSE CARDIOVASCULAR EVENTS

In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with another JAK inhibitor, a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke), was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue RINVOQ in patients that have experienced a myocardial infarction or stroke *[see Warnings and Precautions (5.4)]*.

THROMBOSIS

Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis have occurred in patients treated with JAK inhibitors used to treat inflammatory conditions. Many of these adverse events were serious and some resulted in death. In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with another JAK inhibitor, a higher rate of thrombosis was observed when compared with TNF blockers. Avoid RINVOQ in patients at risk. Patients with symptoms of thrombosis should discontinue RINVOQ and be promptly evaluated *[see Warnings and Precautions (5.5)]*.

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis

RINVOQ® (upadacitinib) is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more TNF blockers.

- Limitations of Use: Use of RINVOQ in combination with other JAK inhibitors, biologic disease-modifying antirheumatic drugs (DMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine, is not recommended.

1.2 Psoriatic Arthritis

RINVOQ is indicated for the treatment of adults with active psoriatic arthritis who have had an inadequate response or intolerance to one or more TNF blockers.

- Limitations of Use: Use of RINVOQ in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine, is not recommended.

1.3 Atopic Dermatitis

RINVOQ is indicated 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 drug products, including biologics, or when use of those therapies are inadvisable.

- Limitations of Use: RINVOQ is not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, or with other immunosuppressants.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Evaluations and Immunizations Prior to Treatment Initiation

Prior to RINVOQ treatment initiation, consider performing the following evaluations:

- Active and latent tuberculosis (TB) infection evaluation - If positive, treat for TB prior to RINVOQ use *[see Warnings and Precautions (5.1)]*.
- Viral hepatitis screening in accordance with clinical guidelines - RINVOQ initiation is not recommended in patients with active hepatitis B or hepatitis C *[see Warnings and Precautions (5.1)]*.
- A complete blood count - RINVOQ initiation is not recommended in patients with an absolute lymphocyte count less than 500 cells/mm^3, absolute neutrophil count less than 1000 cells/mm^3, or hemoglobin level less than 8 g/dL *[see Dosage and Administration (2.8) and Warnings and Precautions (5.8)]*.
- Baseline hepatic function: RINVOQ initiation is not recommended for patients with severe hepatic impairment (Child-Pugh C) *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.
- Pregnancy Status: Verify the pregnancy status of females of reproductive potential prior to starting treatment *[see Warnings and Precautions (5.9) and Use in Specific Populations (8.1, 8.3)]*.

Update immunizations according to current immunization guidelines *[see Warnings and Precautions (5.10)]*.

2.2 Important Administration Instructions

- RINVOQ tablets should be taken orally with or without food *[see Clinical Pharmacology (12.3)]*.
- RINVOQ tablets should be swallowed whole. RINVOQ should not be split, crushed, or chewed.

2.3 Recommended Dosage in Rheumatoid Arthritis

The recommended dosage of RINVOQ is 15 mg once daily.

2.4 Recommended Dosage in Psoriatic Arthritis

The recommended dosage of RINVOQ is 15 mg once daily.

2.5 Recommended Dosage in Atopic Dermatitis

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.

2.6 Recommended Dosage in Patients with Renal Impairment or Severe Hepatic Impairment

Renal Impairment

Rheumatoid Arthritis and Psoriatic Arthritis:

- No dosage adjustment is needed for patients with mild, moderate, or severe renal impairment.

Atopic Dermatitis:

- For patients with severe renal impairment [creatinine clearance (CrCL) < 30 mL/min] the recommended dosage is 15 mg once daily *[see Use in Specific Populations (8.6)]*.
- No dosage adjustment is needed for patients with mild or moderate renal impairment [(CrCL) > 30 mL/min)].

Hepatic Impairment

RINVOQ is not recommended for use in patients with severe hepatic impairment *[see Use in Specific Populations (8.7)]*.

2.7 Dosage Modifications Due to Drug Interactions

The recommended dosage in patients receiving strong CYP3A4 inhibitors is 15 mg once daily *[see Drug Interactions (7.1)]*.

2.8 Dosage Interruption

Infections

If a patient develops a serious infection, including serious opportunistic infection, interrupt RINVOQ treatment until the infection is controlled *[see Warnings and Precautions (5.1)]*.

Laboratory Abnormalities

Interruption of dosing may be needed for management of laboratory abnormalities as described in Table 1 *[see Warnings and Precautions (5.8)]*.

Table 1: Recommended Dosage Interruptions for Laboratory Abnormalities

Laboratory Measure	Action
Absolute Neutrophil Count (ANC)	Interrupt treatment if ANC is less than 1000 cells/mm^3; treatment may be restarted once ANC returns above this value
Absolute Lymphocyte Count (ALC)	Interrupt treatment if ALC is less than 500 cells/mm^3; treatment may be restarted once ALC returns above this value
Hemoglobin (Hb)	Interrupt treatment if Hb is less than 8 g/dL; treatment may be restarted once Hb returns above this value

Hepatic transaminases	Interrupt treatment if drug-induced liver injury is suspected, until this diagnosis is excluded.

3 DOSAGE FORMS AND STRENGTHS

Extended-release tablets:

- 15 mg: purple, biconvex oblong, with dimensions of 14 x 8 mm, and debossed with ‘a15’ on one side.
- 30 mg: red, biconvex oblong, with dimensions of 14 x 8 mm, and debossed with ‘a30’ on one side.

4 CONTRAINDICATIONS

RINVOQ is contraindicated in patients with known hypersensitivity to upadacitinib or any of its excipients *[see Warnings and Precautions (5.6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Serious and sometimes fatal infections have been reported in patients receiving RINVOQ. The most frequent serious infections reported with RINVOQ included pneumonia and cellulitis *[see Adverse Reactions (6.1)]*. Among opportunistic infections, tuberculosis, multidermatomal herpes zoster, oral/esophageal candidiasis, and cryptococcosis, were reported with RINVOQ.

Avoid use of RINVOQ in patients with an active, serious infection, including localized infections. Consider the risks and benefits of treatment prior to initiating RINVOQ in patients:

- with chronic or recurrent infection
- who have been exposed to tuberculosis
- with a history of a serious or an opportunistic infection
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with RINVOQ. Interrupt RINVOQ if a patient develops a serious or opportunistic infection.

A patient who develops a new infection during treatment with RINVOQ should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, the patient should be closely monitored, and RINVOQ should be interrupted if the patient is not responding to antimicrobial therapy. RINVOQ may be resumed once the infection is controlled.

Tuberculosis

Evaluate and test patients for latent and active tuberculosis (TB) infection prior to administration of RINVOQ. Patients with latent TB should be treated with standard antimycobacterial therapy

before initiating RINVOQ. RINVOQ should not be given to patients with active TB. Consider anti-TB therapy prior to initiation of RINVOQ in patients with previously untreated latent TB or active TB in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent TB but who have risk factors for TB infection.

Consultation with a physician with expertise in the treatment of TB is recommended to aid in the decision about whether initiating anti-TB therapy is appropriate for an individual patient.

During RINVOQ use, monitor patients for the development of signs and symptoms of TB, including patients who tested negative for latent TB infection prior to initiating therapy.

Viral Reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster) and hepatitis B virus reactivation, were reported in clinical trials with RINVOQ *[see Adverse Reactions (6.1)]*. The risk of herpes zoster appears to be higher in patients treated with RINVOQ in Japan. If a patient develops herpes zoster, consider temporarily interrupting RINVOQ until the episode resolves.

Screening for viral hepatitis and monitoring for reactivation should be performed in accordance with clinical guidelines before starting and during therapy with RINVOQ. Patients who were positive for hepatitis C antibody and hepatitis C virus RNA, were excluded from clinical trials. Patients who were positive for hepatitis B surface antigen or hepatitis B virus DNA were excluded from clinical trials. However, cases of hepatitis B reactivation were still reported in patients enrolled in the Phase 3 trials of RINVOQ. If hepatitis B virus DNA is detected while receiving RINVOQ, a liver specialist should be consulted.

5.2 Mortality

In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed in patients treated with the JAK inhibitor compared with TNF blockers.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ.

5.3 Malignancy and Lymphoproliferative Disorders

Malignancies, including lymphomas, were observed in clinical trials of RINVOQ *[see Adverse Reactions (6.1)]*.

In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients, a higher rate of malignancies (excluding non-melanoma skin cancer (NMSC)) was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. A higher rate of lymphomas was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. A higher rate of lung cancers was observed in current or past smokers treated with the JAK inhibitor compared to those treated with TNF blockers. In this study, current or past smokers had an additional increased risk of overall malignancies.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ, particularly in patients with a known malignancy (other than a successfully

treated NMSC), patients who develop a malignancy when on treatment, and patients who are current or past smokers.

Non-Melanoma Skin Cancer

NMSCs have been reported in patients treated with RINVOQ. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Exposure to sunlight and UV light should be limited by wearing protective clothing and using a broad-spectrum sunscreen.

5.4 Major Adverse Cardiovascular Events

In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of major adverse cardiovascular events (MACE) defined as cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke was observed with the JAK inhibitor compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur. Discontinue RINVOQ in patients that have experienced a myocardial infarction or stroke.

5.5 Thrombosis

Thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis, have occurred in patients treated for inflammatory conditions with JAK inhibitors, including RINVOQ. Many of these adverse events were serious and some resulted in death.

In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, higher rates of overall thrombosis, DVT, and PE were observed compared to those treated with TNF blockers.

If symptoms of thrombosis occur, patients should discontinue RINVOQ and be evaluated promptly and treated appropriately. Avoid RINVOQ in patients that may be at increased risk of thrombosis.

5.6 Hypersensitivity Reactions

Serious hypersensitivity reactions such as anaphylaxis and angioedema were reported in patients receiving RINVOQ in clinical trials. If a clinically significant hypersensitivity reaction occurs, discontinue RINVOQ and institute appropriate therapy *[see Adverse Reactions (6.1)]*.

5.7 Gastrointestinal Perforations

Gastrointestinal perforations have been reported in clinical trials with RINVOQ. In these trials, many patients with rheumatoid arthritis were receiving background therapy with nonsteroidal anti-inflammatory drugs (NSAIDs).

Monitor RINVOQ-treated patients who may be at risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis or taking NSAIDs). Evaluate promptly patients presenting with new onset abdominal pain for early identification of gastrointestinal perforation.

5.8 Laboratory Abnormalities

Neutropenia

Treatment with RINVOQ was associated with an increased incidence of neutropenia (ANC less than 1000 cells/mm^3).

Evaluate neutrophil counts at baseline and thereafter according to routine patient management. Avoid RINVOQ initiation and interrupt RINVOQ treatment in patients with a low neutrophil count (i.e., ANC less than 1000 cells/mm^3) *[see Dosage and Administration (2.1, 2.8)]*.

Lymphopenia

ALC less than 500 cells/mm^3 were reported in RINVOQ-treated patients in clinical trials.

Evaluate lymphocyte counts at baseline and thereafter according to routine patient management. Avoid RINVOQ initiation or interrupt RINVOQ treatment in patients with a low lymphocyte count (i.e., less than 500 cells/mm^3) *[see Dosage and Administration (2.1, 2.8)]*.

Anemia

Decreases in hemoglobin levels to less than 8 g/dL were reported in RINVOQ-treated patients in clinical trials.

Evaluate hemoglobin at baseline and thereafter according to routine patient management. Avoid RINVOQ initiation or interrupt RINVOQ treatment in patients with a low hemoglobin level (i.e., less than 8 g/dL) *[see Dosage and Administration (2.1, 2.8)]*.

Lipids

Treatment with RINVOQ was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol *[see Adverse Reactions (6.1)]*. Elevations in LDL cholesterol decreased to pre-treatment levels in response to statin therapy. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

Assess lipid parameters approximately 12 weeks after initiation of treatment, and thereafter according to the clinical guidelines for hyperlipidemia. Manage patients according to clinical guidelines for the management of hyperlipidemia.

Liver Enzyme Elevations

Treatment with RINVOQ was associated with increased incidence of liver enzyme elevations compared to treatment with placebo.

Evaluate liver enzymes at baseline and thereafter according to routine patient management. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury.

If increases in ALT or AST are observed during routine patient management and drug-induced liver injury is suspected, RINVOQ should be interrupted until this diagnosis is excluded.

5.9 Embryo-Fetal Toxicity

Based on findings in animal studies, RINVOQ may cause fetal harm when administered to a pregnant woman. Administration of upadacitinib to rats and rabbits during organogenesis caused increases in fetal malformations. Verify the pregnancy status of patients of reproductive potential prior to starting treatment. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception during treatment with RINVOQ and for 4 weeks following completion of therapy *[see Use in Specific Populations (8.1, 8.3)]*.

5.10 Vaccinations

Avoid use of live vaccines during, or immediately prior to, RINVOQ therapy. Prior to initiating RINVOQ, it is recommended that patients be brought up to date with all immunizations, including varicella zoster or prophylactic herpes zoster vaccinations, in agreement with current immunization guidelines.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Serious Infections *[see Warnings and Precautions (5.1)]*
- Mortality *[see Warnings and Precautions (5.2)]*
- Malignancy and Lymphoproliferative Disorders *[see Warnings and Precautions (5.3)]*
- Major Adverse Cardiovascular Events *[see Warnings and Precautions (5.4)]*
- Thrombosis *[see Warnings and Precautions (5.5)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.6)]*
- Gastrointestinal Perforations *[see Warnings and Precautions (5.7)]*
- Laboratory Abnormalities *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Patients with Rheumatoid Arthritis

A total of 3833 patients with rheumatoid arthritis were treated with upadacitinib in the Phase 3 clinical trials of whom 2806 were exposed for at least one year.

Patients could advance or switch to RINVOQ 15 mg from placebo, or be rescued to RINVOQ from active comparator or placebo from as early as Week 12 depending on the trial design.

A total of 2630 patients received at least 1 dose of RINVOQ 15 mg, of whom 1860 were exposed for at least one year. In trials RA-I, RA-II, RA-III and RA-V, 1213 patients received at least 1 dose of RINVOQ 15 mg, of which 986 patients were exposed for at least one year, and

1203 patients received at least 1 dose of upadacitinib 30 mg, of which 946 were exposed for at least one year.

Table 2: Adverse Reactions Reported in ≥ 1% of Rheumatoid Arthritis Patients Treated with RINVOQ 15 mg in Placebo-controlled Trials

Adverse Reaction	Placebo	RINVOQ 15 mg
	n=1042 (%)	n=1035 (%)
Upper respiratory tract infection (URTI)*	9.5	13.5
Nausea	2.2	3.5
Cough	1.0	2.2
Pyrexia	0	1.2
*URTI includes: acute sinusitis, laryngitis, nasopharyngitis, oropharyngeal pain, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, tonsillitis, viral upper respiratory tract infection		

Other adverse reactions reported in less than 1% of patients in the RINVOQ 15 mg group and at a higher rate than in the placebo group through Week 12 included pneumonia, herpes zoster, herpes simplex (includes oral herpes), and oral candidiasis.

Four integrated datasets are presented in the Specific Adverse Reaction section:

Placebo-controlled Trials: Trials RA-III, RA-IV, and RA-V were integrated to represent safety through 12/14 weeks for placebo (n=1042) and RINVOQ 15 mg (n=1035). Trials RA-III and RA-V were integrated to represent safety through 12 weeks for placebo (n=390), RINVOQ 15 mg (n=385), and upadacitinib 30 mg (n=384). Trial RA-IV did not include the 30 mg dose and, therefore, safety data for upadacitinib 30 mg can only be compared with placebo and RINVOQ 15 mg rates from pooling trials RA-III and RA-V.

MTX-controlled Trials: Trials RA-I and RA-II were integrated to represent safety through 12/14 weeks for MTX (n=530), RINVOQ 15 mg (n=534), and upadacitinib 30 mg (n=529).

12-Month Exposure Dataset: Trials RA-I, II, III, and V were integrated to represent the long-term safety of RINVOQ 15 mg (n=1213) and upadacitinib 30 mg (n=1203).

Exposure adjusted incidence rates were adjusted by trial for all the adverse events reported in this section.

Specific Adverse Reactions

Infections

Placebo-controlled Trials: In RA-III, RA-IV, and RA-V, infections were reported in 218 patients (95.7 per 100 patient-years) treated with placebo and 284 patients (127.8 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, infections were reported in 99 patients (136.5 per 100 patient-years) treated with placebo, 118 patients (164.5 per 100 patient-years) treated with RINVOQ 15 mg, and 126 patients (180.3 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Trials: Infections were reported in 127 patients (119.5 per 100 patient-years) treated with MTX monotherapy, 104 patients (91.8 per 100 patient-years) treated with RINVOQ 15 mg monotherapy, and 128 patients (115.1 per 100 patient-years) treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Infections were reported in 615 patients (83.8 per 100 patient-years) treated with RINVOQ 15 mg and 674 patients (99.7 per 100 patient-years) treated with upadacitinib 30 mg.

Serious Infections

Placebo-controlled Trials: In RA-III, RA-IV, and RA-V, serious infections were reported in 6 patients (2.3 per 100 patient-years) treated with placebo, and 12 patients (4.6 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, serious infections were reported in 1 patient (1.2 per 100 patient-years) treated with placebo, 2 patients (2.3 per 100 patient-years) treated with RINVOQ 15 mg, and 7 patients (8.2 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Trials: Serious infections were reported in 2 patients (1.6 per 100 patient-years) treated with MTX monotherapy, 3 patients (2.4 per 100 patient-years) treated with RINVOQ 15 mg monotherapy, and 8 patients (6.4 per 100 patient-years) treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Serious infections were reported in 38 patients (3.5 per 100 patient-years) treated with RINVOQ 15 mg and 59 patients (5.6 per 100 patient-years) treated with upadacitinib 30 mg.

The most frequently reported serious infections were pneumonia and cellulitis.

Tuberculosis

Placebo-controlled Trials and MTX-controlled Trials: In the placebo-controlled period, there were no active cases of tuberculosis reported in the placebo, RINVOQ 15 mg, and upadacitinib 30 mg groups. In the MTX-controlled period, there were no active cases of tuberculosis reported in the MTX monotherapy, RINVOQ 15 mg monotherapy, and upadacitinib 30 mg monotherapy groups.

12-Month Exposure Dataset: Active tuberculosis was reported for 2 patients treated with RINVOQ 15 mg and 1 patient treated with upadacitinib 30 mg. Cases of extra-pulmonary tuberculosis were reported.

Opportunistic Infections (excluding tuberculosis)

Placebo-controlled Trials: In RA-III, RA-IV, and RA-V, opportunistic infections were reported in 3 patients (1.2 per 100 patient-years) treated with placebo, and 5 patients (1.9 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, opportunistic infections were reported in 1 patient (1.2 per 100 patient-years) treated with placebo, 2 patients (2.3 per 100 patient-years) treated with RINVOQ 15 mg, and 6 patients (7.1 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Trials: Opportunistic infections were reported in 1 patient (0.8 per 100 patient-years) treated with MTX monotherapy, 0 patients treated with RINVOQ 15 mg monotherapy, and 4 patients (3.2 per 100 patient-years) treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Opportunistic infections were reported in 7 patients (0.6 per 100 patient-years) treated with RINVOQ 15 mg and 15 patients (1.4 per 100 patient-years) treated with upadacitinib 30 mg.

Malignancies

Placebo-controlled Trials: In RA-III, RA-IV, and RA-V, malignancies excluding NMSC were reported in 1 patient (0.4 per 100 patient-years) treated with placebo, and 1 patient (0.4 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, malignancies excluding NMSC were reported in 0 patients treated with placebo, 1 patient (1.1 per 100 patient-years) treated with RINVOQ 15 mg, and 3 patients (3.5 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Trials: Malignancies excluding NMSC were reported in 1 patient (0.8 per 100 patient-years) treated with MTX monotherapy, 3 patients (2.4 per 100 patient-years) treated with RINVOQ 15 mg monotherapy, and 0 patients treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Malignancies excluding NMSC were reported in 13 patients (1.2 per 100 patient-years) treated with RINVOQ 15 mg and 14 patients (1.3 per 100 patient-years) treated with upadacitinib 30 mg.

Gastrointestinal Perforations

Placebo-controlled Trials: There were no gastrointestinal perforations (based on medical review) reported in patients treated with placebo, RINVOQ 15 mg, and upadacitinib 30 mg.

MTX-controlled Trials: There were no cases of gastrointestinal perforations reported in the MTX and RINVOQ 15 mg group through 12/14 weeks. Two cases of gastrointestinal perforations were observed in the upadacitinib 30 mg group.

12-Month Exposure Dataset: Gastrointestinal perforations were reported in 1 patient treated with RINVOQ 15 mg and 4 patients treated with upadacitinib 30 mg.

Thrombosis

Placebo-controlled Trials: In RA-IV, venous thrombosis (pulmonary embolism or deep vein thrombosis) was observed in 1 patient treated with placebo and 1 patient treated with RINVOQ 15 mg. In RA-V, venous thrombosis was observed in 1 patient treated with RINVOQ 15 mg. There were no observed cases of venous thrombosis reported in RA-III. No cases of arterial thrombosis were observed through 12/14 weeks.

MTX-controlled Trials: In RA-II, venous thrombosis was observed in 0 patients treated with MTX monotherapy, 1 patient treated with RINVOQ 15 mg monotherapy and 0 patients treated with upadacitinib 30 mg monotherapy through Week 14. In RA-II, no cases of arterial thrombosis were observed through 12/14 weeks. In RA-I, venous thrombosis was observed in 1 patient treated with MTX, 0 patients treated with RINVOQ 15 mg and 1 patient treated with upadacitinib 30 mg through Week 24. In RA-I, arterial thrombosis was observed in 1 patient treated with upadacitinib 30 mg through Week 24.

12-Month Exposure Dataset: Venous thrombosis events were reported in 5 patients (0.5 per 100 patient-years) treated with RINVOQ 15 mg and 4 patients (0.4 per 100 patient-years) treated with upadacitinib 30 mg. Arterial thrombosis events were reported in 0 patients treated with RINVOQ 15 mg and 2 patients (0.2 per 100 patient-years) treated with upadacitinib 30 mg.

Laboratory Abnormalities

Hepatic Transaminase Elevations

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, alanine transaminase (ALT) and aspartate transaminase (AST) elevations ≥ 3 x upper limit of normal (ULN) in at least one measurement were observed in 2.1% and 1.5% of patients treated with RINVOQ 15 mg, and in 1.5% and 0.7% of patients treated with placebo, respectively. In RA-III and RA-V, ALT and AST elevations ≥ 3 x ULN in at least one measurement were observed in 0.8% and 1.0% of patients treated with RINVOQ 15 mg, 1.0% and 0% of patients treated with upadacitinib 30 mg and in 1.3% and 1.0% of patients treated with placebo, respectively.

In MTX-controlled trials, for up to 12/14 weeks, ALT and AST elevations ≥ 3 x ULN in at least one measurement were observed in 0.8% and 0.4% of patients treated with RINVOQ 15 mg, 1.7% and 1.3% of patients treated with upadacitinib 30 mg and in 1.9% and 0.9% of patients treated with MTX, respectively.

Lipid Elevations

Upadacitinib treatment was associated with dose-related increases in total cholesterol, triglycerides and LDL cholesterol. Upadacitinib was also associated with increases in HDL cholesterol. Elevations in LDL and HDL cholesterol peaked by Week 8 and remained stable thereafter. In controlled trials, for up to 12/14 weeks, changes from baseline in lipid parameters in patients treated with RINVOQ 15 mg and upadacitinib 30 mg, respectively, are summarized below:

- Mean LDL cholesterol increased by 14.81 mg/dL and 17.17 mg/dL.
- Mean HDL cholesterol increased by 8.16 mg/dL and 9.01 mg/dL.
- The mean LDL/HDL ratio remained stable.
- Mean triglycerides increased by 13.55 mg/dL and 14.44 mg/dL.

Creatine Phosphokinase Elevations

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, dose-related increases in creatine phosphokinase (CPK) values were observed. CPK elevations > 5 x ULN were reported in 1.0%, and 0.3% of patients over 12/14 weeks in the RINVOQ 15 mg and placebo groups, respectively. Most elevations >5 x ULN were transient and did not require treatment discontinuation. In RA-III and RA-V, CPK elevations > 5 x ULN were observed in 0.3% of patients treated with placebo, 1.6% of patients treated with RINVOQ 15 mg, and none in patients treated with upadacitinib 30 mg.

Neutropenia

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, dose-related decreases in neutrophil counts, below 1000 cells/mm^3 in at least one measurement occurred in 1.1% and <0.1% of patients in the RINVOQ 15 mg and placebo

groups, respectively. In RA-III and RA-V, decreases in neutrophil counts below 1000 cells/mm^3 in at least one measurement occurred in 0.3% of patients treated with placebo, 1.3% of patients treated with RINVOQ 15 mg, and 2.4% of patients treated with upadacitinib 30 mg. In clinical trials, treatment was interrupted in response to ANC less than 1000 cells/mm^3.

Lymphopenia

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, dose-related decreases in lymphocyte counts below 500 cells/mm^3 in at least one measurement occurred in 0.9% and 0.7% of patients in the RINVOQ 15 mg and placebo groups, respectively. In RA-III and RA-V, decreases in lymphocyte counts below 500 cells/mm^3 in at least one measurement occurred in 0.5% of patients treated with placebo, 0.5% of patients treated with RINVOQ 15 mg, and 2.4% of patients treated with upadacitinib 30 mg.

Anemia

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, hemoglobin decreases below 8 g/dL in at least one measurement occurred in <0.1% of patients in both the RINVOQ 15 mg and placebo groups. In RA-III and RA-V, hemoglobin decreases below 8 g/dL in at least one measurement were observed in 0.3% of patients treated with placebo, and none in patients treated with RINVOQ 15 mg and upadacitinib 30 mg.

Adverse Reactions in Patients with Psoriatic Arthritis

A total of 1827 patients with psoriatic arthritis were treated with upadacitinib in clinical studies representing 1639.2 patient-years of exposure, of whom 722 were exposed to upadacitinib for at least one year. In the two Phase 3 studies, 907 patients received at least 1 dose of RINVOQ 15 mg, of whom 359 were exposed for at least one year.

Two placebo-controlled studies were integrated (640 patients on RINVOQ 15 mg once daily and 635 patients on placebo) to evaluate the safety of RINVOQ 15 mg in comparison to placebo for up to 24 weeks after treatment initiation.

Overall, the safety profile observed in patients with active psoriatic arthritis treated with RINVOQ 15 mg was consistent with the safety profile observed in patients with rheumatoid arthritis. During the 24-week placebo-controlled period, the frequencies of herpes zoster and herpes simplex were >1% (1.1% and 1.4%, respectively) with RINVOQ 15 mg and 0.8% and 1.3%, respectively with placebo. A higher incidence of acne and bronchitis was also observed in patients treated with RINVOQ 15 mg (1.3% and 3.9%, respectively) compared to placebo (0.3% and 2.7%, respectively).

Adverse Reactions in Patients with Atopic Dermatitis

Three Phase 3 (AD-1, AD-2, and AD-3) and one Phase 2b (AD-4) randomized, double-blind, placebo-controlled, multicenter trials evaluated the safety of RINVOQ in patients with moderate-to-severe atopic dermatitis. The majority of patients were White (68%) and male (57%). The mean age was 34 years (ranged from 12 to 75 years) and 13% of the patients were 12 to less than 18 years. In these 4 trials, 2612 patients were treated with RINVOQ 15 mg or 30 mg orally once daily, with or without concomitant topical corticosteroids (TCS).

In the Phase 3 clinical trials (AD-1, AD-2, and AD-3), a total of 1239 patients received RINVOQ 15 mg, of whom 791 were exposed for at least one year and 1246 patients received RINVOQ 30 mg, of whom 826 were exposed for at least one year.

Trials AD-1, AD-2, and AD-4 compared the safety of RINVOQ monotherapy to placebo through Week 16. Trial AD-3 compared the safety of RINVOQ + TCS to placebo + TCS through Week 16.

Weeks 0 to 16 (Trials AD-1 to AD-4)

In RINVOQ trials with and without TCS (Trials AD-1, 2, 3 and 4) through Week 16, the proportion of patients who discontinued treatment because of adverse reactions in the RINVOQ 15 mg, 30 mg and placebo groups were 2.3%, 2.9% and 3.8%, respectively. Table 3 summarizes the adverse reactions that occurred at a rate of at least 1% in the RINVOQ 15 mg or 30 mg groups during the first 16 weeks of treatment.

Table 3: Adverse Reactions Reported in ≥ 1% of Patients with Atopic Dermatitis Treated with RINVOQ 15 mg or 30 mg

Adverse Reaction	**Placebo**	**RINVOQ 15 mg**	**RINVOQ 30 mg**
	n=902 (%)	n=899 (%)	n=906 (%)
Upper respiratory tract infection (URTI)*	17	23	25
Acne**	2	10	16
Herpes simplex***	2	4	8
Headache	4	6	6
Increased blood creatine phosphokinase	2	5	6
Cough	1	3	3
Hypersensitivity****	2	2	3
Folliculitis	1	2	3
Nausea	1	3	3
Abdominal pain*****	1	3	2
Pyrexia	1	2	2
Increased Weight	1	2	2
Herpes zoster******	1	2	2
Influenza	<1	2	2
Fatigue	1	1	2
Neutropenia	<1	1	2
Myalgia	1	1	2
Influenza like illness	1	1	2

* 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
** Includes: acne and dermatitis acneiform
*** Includes: genital herpes, genital herpes simplex, herpes dermatitis, herpes ophthalmic, herpes simplex, nasal herpes, ophthalmic herpes simplex, herpes virus infection, oral herpes
**** Includes anaphylactic reaction, anaphylactic shock, angioedema, dermatitis exfoliative generalized, drug hypersensitivity, eyelid oedema, face oedema, hypersensitivity, periorbital swelling, pharyngeal swelling, swelling face, toxic skin eruption, type I hypersensitivity, urticaria
***** Includes abdominal pain and abdominal pain upper
****** Includes herpes zoster and varicella

Other adverse reactions reported in less than 1% of patients in the RINVOQ 15 mg and/or 30 mg group and at a higher rate than in the placebo group through Week 16 included anemia, oral candidiasis, pneumonia, and the adverse event of retinal detachment.

The safety profile of RINVOQ through Week 52 was generally consistent with the safety profile observed at Week 16.

Overall, the safety profile observed in patients with AD treated with RINVOQ was similar to the safety profile in patients with RA. Other specific adverse reactions that were reported in patients with AD included eczema herpeticum/Kaposi's varicelliform eruption.

Eczema Herpeticum/Kaposi's Varicelliform Eruption

Placebo-controlled Period (16 weeks): Eczema herpeticum was reported in 4 patients (1.6 per 100 patient-years) treated with placebo, 6 patients (2.2 per 100 patient-years) treated with RINVOQ 15 mg and 7 patients (2.6 per 100 patient-years) treated with RINVOQ 30 mg.

12-Month Exposure (Weeks 0 to 52): Eczema herpeticum was reported in 18 patients (1.6 per 100 patient-years) treated with RINVOQ 15 mg and 17 patients (1.5 per 100 patient-years) treated with RINVOQ 30 mg.

7 DRUG INTERACTIONS

7.1 Strong CYP3A4 Inhibitors

Upadacitinib exposure is increased when RINVOQ is co-administered with a strong CYP3A4 inhibitor (such as ketoconazole), which may increase the risk of RINVOQ adverse reactions *[see Clinical Pharmacology (12.3)]*. Monitor patients closely for adverse reactions when co-administering RINVOQ 15 mg once daily with strong CYP3A4 inhibitors. Coadministration of RINVOQ 30 mg once daily with strong CYP3A4 inhibitors is not recommended.

7.2 Strong CYP3A4 Inducers

Upadacitinib exposure is decreased when RINVOQ is co-administered with strong CYP3A4 inducers (such as rifampin), which may lead to reduced therapeutic effect of RINVOQ *[see Clinical Pharmacology (12.3)]*. Coadministration of RINVOQ with strong CYP3A4 inducers is not recommended.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from the pharmacovigilance safety database and postmarketing case reports on use of RINVOQ in pregnant women are not sufficient to evaluate a drug-associated risk for major birth defects or miscarriage. Based on animal studies, RINVOQ has the potential to adversely affect a developing fetus. Advise patients of reproductive potential and pregnant patients of the potential risk to the fetus.

In animal embryo-fetal development studies, oral upadacitinib administration to pregnant rats and rabbits at exposures equal to or greater than approximately 2 and 17 times the 15 mg dose and 0.9 and 8.5 times the maximum recommended human dose (MRHD) of 30 mg, respectively, resulted in dose-related increases in skeletal malformations (rats only), an increased incidence of cardiovascular malformations (rabbits only), increased post-implantation loss (rabbits only), and decreased fetal body weights in both rats and rabbits. No developmental toxicity was observed in pregnant rats and rabbits treated with oral upadacitinib during organogenesis at approximately 0.3 and 2.5 times the 15 mg dose and 0.2 and 1.3 times the MRHD of 30 mg, respectively. In a pre- and post-natal development study in pregnant female rats, oral upadacitinib administration at exposures approximately 1.6 times the MRHD of 30 mg resulted in no maternal or developmental toxicity (*see Data)*.

The background risks of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriages are 2-4% and 15-20%, respectively.

Report pregnancies to the AbbVie Inc.'s Adverse Event reporting line at 1-888-633-9110, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data suggest that increased disease activity is associated with the risk of developing adverse pregnancy outcomes in women with rheumatoid arthritis. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Data

Animal Data

In an oral embryo-fetal development study, pregnant rats received upadacitinib at doses of 5, 25, and 75 mg/kg/day during the period of organogenesis from gestation day 6 to 17. Upadacitinib was teratogenic (skeletal malformations that consisted of misshapen humerus and bent scapula) at exposures equal to or greater than approximately 1.0 times the MRHD of 30 mg (on an AUC basis at maternal oral doses of 5 mg/kg/day and higher). Additional skeletal malformations (bent forelimbs/hindlimbs and rib/vertebral defects) and decreased fetal body weights were observed

in the absence of maternal toxicity at an exposure approximately 48 times the MRHD of 30 mg (on an AUC basis at a maternal oral dose of 75 mg/kg/day).

In a second oral embryo-fetal development study, pregnant rats received upadacitinib at doses of 1.5 and 4 mg/kg/day during the period of organogenesis from gestation day 6 to 17. Upadacitinib was teratogenic (skeletal malformations that included bent humerus and scapula) at exposures approximately 0.9 times the MRHD of 30 mg (on an AUC basis at maternal oral doses of 4 mg/kg/day). No developmental toxicity was observed in rats at an exposure approximately 0.2 times the MRHD of 30 mg (on an AUC basis at a maternal oral dose of 1.5 mg/kg/day).

In an oral embryo-fetal developmental study, pregnant rabbits received upadacitinib at doses of 2.5, 10, and 25 mg/kg/day during the period of organogenesis from gestation day 7 to 19. Embryolethality, decreased fetal body weights, and cardiovascular malformations were observed in the presence of maternal toxicity at an exposure approximately 8.5 times the MRHD of 30 mg (on an AUC basis at a maternal oral dose of 25 mg/kg/day). Embryolethality consisted of increased post-implantation loss that was due to elevated incidences of both total and early resorptions. No developmental toxicity was observed in rabbits at an exposure approximately 1.3 times the MRHD of 30 mg (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

In an oral pre- and post-natal development study, pregnant female rats received upadacitinib at doses of 2.5, 5, and 10 mg/kg/day from gestation day 6 through lactation day 20. No maternal or developmental toxicity was observed in either mothers or offspring, respectively, at an exposure approximately 1.6 times the MRHD of 30 mg (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

8.2 Lactation

Risk Summary

There are no data on the presence of upadacitinib in human milk, the effects on the breastfed infant, or the effects on milk production. Available pharmacodynamic/toxicological data in animals have shown excretion of upadacitinib in milk *(see Data)*. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the potential for serious adverse reactions in the breastfed infant, advise patients that breastfeeding is not recommended during treatment with RINVOQ, and for 6 days (approximately 10 half-lives) after the last dose.

Data

A single oral dose of 10 mg/kg radiolabeled upadacitinib was administered to lactating female Sprague-Dawley rats on post-partum days 7-8. Drug exposure was approximately 30-fold greater in milk than in maternal plasma based on $AUC_{0\text{-}t}$ values. Approximately 97% of drug-related material in milk was parent drug.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to starting treatment with RINVOQ *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Based on animal studies, upadacitinib may cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*. Advise female patients of reproductive potential to use effective contraception during treatment with RINVOQ and for 4 weeks after the final dose.

8.4 Pediatric Use

Juvenile Idiopathic Arthritis and Psoriatic Arthritis

The safety and effectiveness of RINVOQ in pediatric patients with juvenile idiopathic arthritis and psoriatic arthritis have not been established.

Atopic Dermatitis

The safety and effectiveness of RINVOQ in pediatric patients 12 years of age and older weighing at least 40 kg with atopic dermatitis have been established. A total of 344 pediatric patients aged 12 to 17 years with moderate to severe atopic dermatitis were randomized across three trials (AD-1, AD-2 and AD-3) to receive either RINVOQ 15 mg (N=114) or 30 mg (N=114) or matching placebo (N=116) in monotherapy or combination with topical corticosteroids. Efficacy was consistent between the pediatric patients and adults *[see Clinical Studies (14.3)]*. The adverse reaction profile in the pediatric patients was similar to the adults *[see Adverse Reactions (6.1)]*.

The safety and effectiveness of RINVOQ in pediatric patients less than 12 years of age with atopic dermatitis have not been established.

8.5 Geriatric Use

Rheumatoid Arthritis and Psoriatic Arthritis

Of the 4381 patients treated in the five clinical studies, a total of 906 rheumatoid arthritis patients were 65 years of age or older, including 146 patients 75 years and older. Of the 1827 patients treated in the two psoriatic arthritis Phase 3 clinical studies, a total of 274 patients were 65 years of age or older, including 34 patients 75 years and older. No differences in effectiveness were observed between these patients and younger patients; however, there was a higher rate of overall adverse events, including serious infections, in patients 65 years of age and older.

Atopic Dermatitis

Of the 2583 patients treated in the three Phase 3 clinical trials, a total of 120 patients with atopic dermatitis were 65 years of age or older, including 6 patients 75 years of age. No differences in effectiveness were observed between these patients and younger patients; however, there was a higher rate of serious infections and malignancies in those patients 65 years of age or older in the 30 mg dosing group in the long-term trials.

8.6 Renal Impairment

For patients with rheumatoid arthritis and psoriatic arthritis, no dosage adjustment is needed in patients with mild, moderate or severe renal impairment.

For patients with atopic dermatitis, the maximum recommended dosage is 15 mg once daily for patients with severe renal impairment (CrCL < 30 mL/min). No dosage adjustment is needed in patients with mild or moderate renal impairment.

The use of RINVOQ has not been studied in patients with end stage renal disease, and therefore not recommended for use in this population *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dosage adjustment is needed in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. The use of RINVOQ has not been studied in patients with severe hepatic impairment (Child Pugh C), and therefore not recommended for use in this population *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)]*.

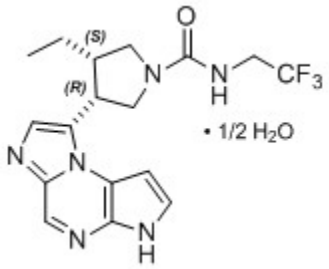
11 DESCRIPTION

RINVOQ is formulated with upadacitinib, a JAK inhibitor.

Upadacitinib has the following chemical name: (3*S*,4*R*)-3-Ethyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-*N*-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide hydrate (2:1).

The strength of upadacitinib is based on anhydrous upadacitinib. The solubility of upadacitinib in water is 38 to less than 0.2 mg/mL across a pH range of 2 to 9 at 37 °C.

Upadacitinib has a molecular weight of 389.38 g/mol and a molecular formula of $C_{17}H_{19}F_3N_6O \cdot ½\ H_2O$. The chemical structure of upadacitinib is:



RINVOQ 15 mg extended-release tablets for oral administration are purple, biconvex oblong, with dimensions of 14 x 8 mm, and debossed with ‘a15’ on one side. Each tablet contains the following inactive ingredients: colloidal silicon dioxide, ferrosoferric oxide, hypromellose, iron oxide red, magnesium stearate, mannitol, microcrystalline cellulose, polyvinyl alcohol, polyethylene glycol, talc, tartaric acid and titanium dioxide.

RINVOQ 30 mg extended-release tablets for oral administration are red, biconvex oblong, with dimensions of 14 x 8 mm, and debossed with ‘a30’ on one side. Each tablet contains the following inactive ingredients: colloidal silicon dioxide, hypromellose, iron oxide red, magnesium stearate, mannitol, microcrystalline cellulose, polyvinyl alcohol, polyethylene glycol, talc, tartaric acid and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Upadacitinib is 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. 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.

JAK enzymes transmit cytokine signaling through their pairing (e.g., JAK1/JAK2, JAK1/JAK3, JAK1/TYK2, JAK2/JAK2, JAK2/TYK2). 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. However, the relevance of inhibition of specific JAK enzymes to therapeutic effectiveness is not currently known.

12.2 Pharmacodynamics

Inhibition of IL-6 Induced STAT3 and IL-7 Induced STAT5 Phosphorylation

In healthy volunteers, the administration of upadacitinib (immediate release formulation) resulted in a dose- and concentration-dependent inhibition of IL-6 (JAK1/JAK2)-induced STAT3 and IL-7 (JAK1/JAK3)-induced STAT5 phosphorylation in whole blood. The maximal inhibition was observed 1 hour after dosing which returned to near baseline by the end of dosing interval.

Lymphocytes

In patients with rheumatoid arthritis, treatment with upadacitinib was associated with a small, transient increase in mean ALC from baseline up to Week 36 which gradually returned to, at or near baseline levels with continued treatment.

Immunoglobulins

In patients with rheumatoid arthritis, small decreases from baseline in mean IgG and IgM levels were observed with upadacitinib treatment in the controlled period; however, the mean values at baseline and at all visits were within the normal reference range.

Cardiac Electrophysiology

At 6 times the mean maximum exposure of the 15 mg once daily dose, there was no clinically relevant effect on the QTc interval.

12.3 Pharmacokinetics

Upadacitinib plasma exposures are proportional to dose over the therapeutic dose range. Steady-state plasma concentrations are achieved within 4 days with minimal accumulation after multiple

once-daily administrations. Upadacitinib pharmacokinetics are similar between rheumatoid arthritis, psoriatic arthritis, and atopic dermatitis patients.

Absorption

Following oral administration of upadacitinib extended-release formulation, upadacitinib is absorbed with a median T_{max} of 2 to 4 hours.

Coadministration of upadacitinib with a high-fat/ high-calorie meal had no clinically relevant effect on upadacitinib exposures (increased AUC_{inf} by 29% and C_{max} by 39%). In clinical trials, upadacitinib was administered without regard to meals *[see Dosage and Administration (2.2)]*.

Distribution

Upadacitinib is 52% bound to plasma proteins. Upadacitinib partitions similarly between plasma and blood cellular components with a blood to plasma ratio of 1.0.

Elimination

Metabolism

Upadacitinib metabolism is mediated by mainly CYP3A4 with a potential minor contribution from CYP2D6. The pharmacologic activity of upadacitinib is attributed to the parent molecule. In a human radiolabeled study, unchanged upadacitinib accounted for 79% of the total radioactivity in plasma while the main metabolite detected (product of monooxidation followed by glucuronidation) accounted for 13% of the total plasma radioactivity. No active metabolites have been identified for upadacitinib.

Excretion

Following single dose administration of [^{14}C]-upadacitinib immediate-release solution, upadacitinib was eliminated predominantly as the unchanged parent substance in urine (24%) and feces (38%). Approximately 34% of upadacitinib dose was excreted as metabolites. Upadacitinib mean terminal elimination half-life ranged from 8 to 14 hours.

Specific Populations

Body Weight, Gender, Race, and Age

Body weight, gender, race, ethnicity, and age did not have a clinically meaningful effect on upadacitinib exposure *[see Use in Specific Populations (8.5)]*.

Patients with Renal Impairment

Upadacitinib AUC_{inf} was 18%, 33%, and 44% higher in patients with mild, moderate, and severe renal impairment, respectively, compared to patients with normal renal function. Upadacitinib C_{max} was similar in patients with normal and impaired renal function. Mild or moderate renal impairment has no clinically relevant effect on upadacitinib exposure for the 15 or 30 mg once daily dosing regimens. Severe renal impairment is likely to increase the systemic exposure of upadacitinib after 30 mg once daily dosing in patients with atopic dermatitis. This may increase the risk of adverse reactions; therefore, dosage modification in patients with severe renal impairment is recommended *[see Dosage and Administration (2.6) and Use in Specific Populations (8.6)]*.

Patients with Hepatic Impairment

Mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment has no clinically relevant effect on upadacitinib exposure. Upadacitinib AUC_{inf} was 28% and 24% higher in patients with mild and moderate hepatic impairment, respectively, compared to patients with normal liver function. Upadacitinib C_{max} was unchanged in patients with mild hepatic impairment and 43% higher in patients with moderate hepatic impairment compared to patients with normal liver function. Upadacitinib was not studied in patients with severe hepatic impairment (Child-Pugh C) *[see Dosage and Administration (2.6) and Use in Specific Populations (8.7)]*.

Drug Interaction Studies

Potential for Other Drugs to Influence the Pharmacokinetics of Upadacitinib

Upadacitinib is metabolized *in vitro* by CYP3A4 with a minor contribution from CYP2D6. The effect of co-administered drugs on upadacitinib plasma exposures is provided in Table 4 *[see Drug Interactions (7)]*.

Table 4: Change in Pharmacokinetics of Upadacitinib in the Presence of Co-administered Drugs

Co-administered Drug	Regimen of Co-administered Drug	Ratio (90% CI)[a]	
		C_{max}	AUC
Methotrexate	10 to 25 mg/week	0.97 (0.86-1.09)	0.99 (0.93- 1.06)
Strong CYP3A4 inhibitor: Ketoconazole	400 mg once daily x 6 days	1.70 (1.55-1.89)	1.75 (1.62-1.88)
Strong CYP3A4 inducer: Rifampin	600 mg once daily x 9 days	0.49 (0.44-0.55)	0.39 (0.37-0.42)
OATP1B inhibitor: Rifampin	600 mg single dose	1.14 (1.02-1.28)	1.07 (1.01-1.14)

CI: Confidence interval
[a] Ratios for C_{max} and AUC compare co-administration of the medication with upadacitinib vs. administration of upadacitinib alone.

pH modifying medications (e.g., antacids or proton pump inhibitors) are not expected to affect upadacitinib plasma exposures based on *in vitro* assessments and population pharmacokinetic analyses. CYP2D6 metabolic phenotype had no effect on upadacitinib pharmacokinetics (based on population pharmacokinetic analyses), indicating that inhibitors of CYP2D6 have no clinically relevant effect on upadacitinib exposures.

Potential for Upadacitinib to Influence the Pharmacokinetics of Other Drugs

In vitro studies indicate that upadacitinib does not inhibit or induce the activity of cytochrome P450 (CYP) enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at clinically relevant concentrations. *In vitro* studies indicate that upadacitinib does not

inhibit the transporters P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, and MATE2K at clinically relevant concentrations.

Clinical studies indicate that upadacitinib has no clinically relevant effects on the pharmacokinetics of co-administered drugs. Summary of results from clinical studies which evaluated the effect of upadacitinib on other drugs is provided in Table 5.

Table 5: Change in Pharmacokinetics of Co-administered Drugs or In Vivo Markers of CYP Activity in the Presence of Upadacitinib

Co-administered Drug or CYP Activity Marker	**Multiple-Dose Regimen of Upadacitinib**	**Ratio (90% CI)[a]**	
		C_{max}	**AUC**
Methotrexate	6 mg to 24 mg BID[b]	1.03 (0.86-1.23)	1.14 (0.91-1.43)
Sensitive CYP1A2 Substrate: Caffeine	30 mg QD[c]	1.13 (1.05-1.22)	1.22 (1.15-1.29)
Sensitive CYP3A Substrate: Midazolam	30 mg QD[c]	0.74 (0.68-0.80)	0.74 (0.68-0.80)
Sensitive CYP2D6 Substrate: Dextromethorphan	30 mg QD[c]	1.09 (0.98-1.21)	1.07 (0.95-1.22)
Sensitive CYP2C9 Substrate: S-Warfarin	30 mg QD[c]	1.07 (1.02-1.11)	1.11 (1.07-1.15)
Sensitive CYP2C19 Marker: 5-OH Omeprazole to Omeprazole metabolic ratio	30 mg QD[c]	--	1.09 (1.00-1.19)
CYP2B6 Substrate: Bupropion	30 mg QD[c]	0.87 (0.79-0.96)	0.92 (0.87-0.98)
Rosuvastatin	30 mg QD[c]	0.77 (0.63-0.94)	0.67 (0.56-0.82)
Atorvastatin	30 mg QD[c]	0.88 (0.79-0.97)	0.77 (0.70-0.85)
Ethinylestradiol	30 mg QD[c]	0.96 (0.89-1.02)	1.11 (1.04-1.19)
Levonorgestrel	30 mg QD[c]	0.96 (0.87-1.06)	0.96 (0.85-1.07)

CYP: cytochrome P450; CI: Confidence interval; BID: twice daily; QD: once daily
[a] Ratios for C_{max} and AUC compare co-administration of the medication with upadacitinib vs. administration of medication alone.
[b] Immediate-release formulation
[c] Extended-release formulation

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of upadacitinib was evaluated in Sprague-Dawley rats and Tg.rasH2 mice. No evidence of tumorigenicity was observed in male or female rats that received upadacitinib for up to 101 weeks at oral doses up to 15 or 20 mg/kg/day, respectively (approximately 2.4 and 6.0 times the MRHD of 30 mg on an AUC basis, respectively). No evidence of tumorigenicity was observed in male or female Tg.rasH2 mice that received upadacitinib for 26 weeks at oral doses up to 20 mg/kg/day.

Mutagenesis

Upadacitinib tested negatively in the following genotoxicity assays: the *in vitro* bacterial mutagenicity assay (Ames assay), *in vitro* chromosome aberration assay in human peripheral blood lymphocytes, and *in vivo* rat bone marrow micronucleus assay.

Impairment of Fertility

Upadacitinib had no effect on fertility in male or female rats at oral doses up to 50 mg/kg/day in males and 75 mg/kg/day in females (approximately 24 and 48 times the MRHD of 30 mg in males and females, respectively, on an AUC basis). However, maintenance of pregnancy was adversely affected at oral doses of 25 mg/kg/day and 75 mg/kg/day based upon dose-related findings of increased post-implantation losses (increased resorptions) and decreased numbers of mean viable embryos per litter (approximately 13 and 48 times the MRHD of 30 mg on an AUC basis, respectively). The number of viable embryos was unaffected in female rats that received upadacitinib at an oral dose of 5 mg/kg/day and were mated to males that received the same dose (approximately 1.0 times the MRHD of 30 mg on an AUC basis).

14 CLINICAL STUDIES

14.1 Rheumatoid Arthritis

The efficacy and safety of RINVOQ 15 mg once daily were assessed in five Phase 3 randomized, double-blind, multicenter trials in patients with moderately to severely active rheumatoid arthritis and fulfilling the ACR/EULAR 2010 classification criteria. Patients 18 years of age and older were eligible to participate. The presence of at least 6 tender and 6 swollen joints and evidence of systemic inflammation based on elevation of hsCRP was required at baseline. Although other doses have been studied, the recommended dosage of RINVOQ is 15 mg once daily.

Trial RA-I (NCT02706873) was a 24-week monotherapy trial in 947 patients with moderately to severely active rheumatoid arthritis who were naïve to methotrexate (MTX). Patients received RINVOQ 15 mg or upadacitinib 30 mg orally once daily or MTX as monotherapy. At Week 26, non-responding patients on upadacitinib could be rescued with the addition of MTX, while patients on MTX could be rescued with the addition of blinded RINVOQ 15 mg or upadacitinib 30 mg once daily. The primary endpoint was the proportion of patients who achieved an ACR50 response at Week 12. Key secondary endpoints included disease activity score (DAS28-CRP)

≤3.2 at Week 12, DAS28-CRP <2.6 at Week 24, change from baseline in HAQ-DI at Week 12, and change from baseline in van der Heijde-modified total Sharp Score (mTSS) at Week 24.

Trial RA-II (NCT02706951) was a 14-week monotherapy trial in 648 patients with moderately to severely active rheumatoid arthritis who had an inadequate response to MTX. Patients received RINVOQ 15 mg or upadacitinib 30 mg once daily monotherapy or continued their stable dose of MTX monotherapy. At Week 14, patients who were randomized to MTX were advanced to RINVOQ 15 mg or upadacitinib 30 mg once daily monotherapy in a blinded manner based on pre-determined assignment at baseline. The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 14. Key secondary endpoints included DAS28-CRP ≤3.2, DAS28-CRP <2.6, and change from baseline in HAQ-DI at Week 14.

Trial RA-III (NCT02675426) was a 12-week trial in 661 patients with moderately to severely active rheumatoid arthritis who had an inadequate response to conventional disease modifying anti-rheumatic drugs (cDMARDs). Patients received RINVOQ 15 mg or upadacitinib 30 mg once daily or placebo added to background cDMARD therapy. At Week 12, patients who were randomized to placebo were advanced to RINVOQ 15 mg or upadacitinib 30 mg once daily in a blinded manner based on pre-determined assignment at baseline. The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 12. Key secondary endpoints included DAS28-CRP ≤3.2, DAS28-CRP<2.6, and change from baseline in HAQ-DI at Week 12.

Trial RA-IV (NCT02629159) was a 48-week trial in 1629 patients with moderately to severely active rheumatoid arthritis who had an inadequate response to MTX. Patients received RINVOQ 15 mg once daily, active comparator, or placebo added to background MTX. From Week 14, non-responding patients on RINVOQ 15 mg could be rescued to active comparator in a blinded manner, and non-responding patients on active comparator or placebo could be rescued to RINVOQ 15 mg in a blinded manner. At Week 26, all patients randomized to placebo were switched to RINVOQ 15 mg once daily in a blinded manner. The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 12 versus placebo. Key secondary endpoints versus placebo included DAS28-CRP ≤3.2, DAS28-CRP <2.6, change from baseline in HAQ-DI at Week 12, and change from baseline in mTSS at Week 26.

Trial RA-V (NCT02706847) was a 12-week trial in 499 patients with moderately to severely active rheumatoid arthritis who had an inadequate response or intolerance to biologic DMARDs. Patients received RINVOQ 15 mg or upadacitinib 30 mg once daily or placebo added to background cDMARD therapy. At Week 12, patients who were randomized to placebo were advanced to RINVOQ 15 mg or upadacitinib 30 mg once daily in a blinded manner based on pre-determined assignment at baseline. The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 12. Key secondary endpoints included DAS28-CRP ≤3.2 and change from baseline in HAQ-DI at Week 12.

Clinical Response

The percentages of RINVOQ-treated patients achieving ACR20, ACR50, and ACR70 responses, and DAS28(CRP) < 2.6 in all trials are shown in Table 6.

Patients treated with RINVOQ 15 mg, alone or in combination with cDMARDs, achieved higher ACR response rates compared to MTX monotherapy or placebo, respectively, at the primary efficacy timepoint (Table 6).

In Trial IV, the percent of patients achieving ACR20 response by visit is shown in Figure 1.

In Trials RA-III and RA-V, higher ACR20 response rates were observed at 1 week with RINVOQ 15 mg versus placebo.

Treatment with RINVOQ 15 mg, alone or in combination with cDMARDs, resulted in greater improvements in the ACR components compared to MTX or placebo at the primary efficacy timepoint (Table 7).

Table 6: Clinical Response in RA Patients in Trials RA-I, RA-II, RA-III, RA-IV and RA V

	Trial RA-I MTX-Naïve		**Trial RA-II MTX-IR**		**Trial RA-III cDMARD-IR**		**Trial RA-IV MTX-IR**		**Trial RA-V bDMARD-IR**	
	Monotherapy		Monotherapy		Background cDMARDs		Background MTX		Background cDMARDs	
	MTX	RINVOQ 15 mg % Δ (95% CI)	MTX	RINVOQ 15 mg % Δ (95% CI)	PBO	RINVOQ 15 mg % Δ (95% CI)	PBO	RINVOQ 15 mg % Δ (95% CI)	PBO	RINVOQ 15 mg % Δ (95% CI)
N	314	317	216	217	221	221	651	651	169	164
Week										
ACR20										
12[a]/14[b]	54	76 22 (14, 29)	41	68 26 (17, 36)	36	64 28 (19, 37)	36	71 34 (29, 39)	28	65 36 (26, 46)
24[c]/26[d]	59	79 20 (13, 27)					36	67 32 (27, 37)		
ACR50										
12[a]/14[b]	28	52 24 (16, 31)	15	42 27 (18, 35)	15	38 23 (15, 31)	15	45 30 (26, 35)	12	34 22 (14, 31)
24[c]/26[d]	33	60 27 (19, 34)					21	54 33 (28, 38)		
ACR70										
12[a]/14[b]	14	32 18 (12, 25)	3	23 20 (14, 26)	6	21 15 (9, 21)	5	25 20 (16, 24)	7	12 5 (-1, 11)
24[c]/26[d]	18	44 26 (19, 33)					10	35 25 (21, 29)		
DAS28-CRP <2.6										
12[a]/14[b]	14	36 22 (15, 28)	8	28 20 (13, 27)	10	31 21 (14, 28)	6	29 23 (19, 27)	9	29 19 (11, 27)
24[c]/26[d]	18	48 30 (23, 37)					9	41 32 (27, 36)		

Abbreviations: ACR20 (or 50 or 70) = American College of Rheumatology ≥20% (or ≥50% or ≥70%) improvement; bDMARD = biologic disease-modifying anti-rheumatic drug; CRP = c-reactive protein; DAS28 = Disease Activity Score 28 joints; cDMARDs = conventional disease-modifying anti-rheumatic drugs; MTX = methotrexate; PBO = placebo; IR = inadequate responder

Patients who discontinued randomized treatment, or had cross-over between randomized

treatments, or were missing data at week of evaluation were imputed as non-responders in the analyses.
[a] Trial RA-I, Trial RA-III, Trial RA-IV, Trial RA-V
[b] Trial RA-II
[c] Trial RA-I
[d] Trial RA-IV

Table 7: Components of ACR Response at Primary Efficacy Timepoint[a]

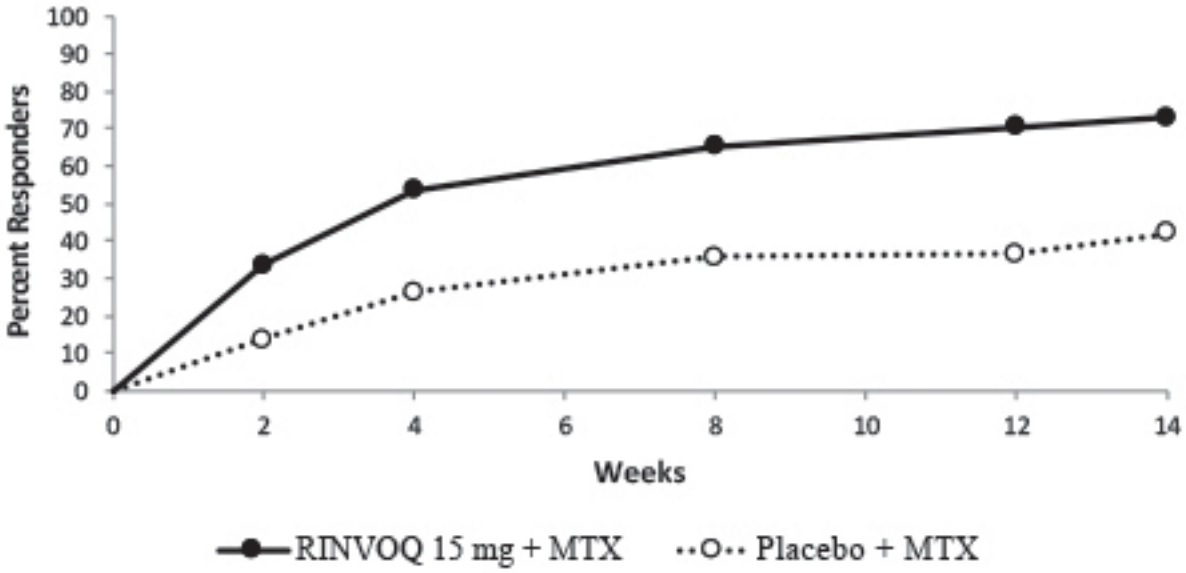
	Trial RA-I MTX-Naïve		**Trial RA-II[b] MTX-IR**		**Trial RA-III cDMARD-IR**		**Trial RA-IV MTX-IR**		**Trial RA-V bDMARD-IR**	
	Monotherapy		Monotherapy		Background cDMARDs		Background MTX		Background cDMARDs	
	MTX	RINVOQ 15 mg	MTX	RINVOQ 15 mg	PBO	RINVOQ 15 mg	PBO	RINVOQ 15 mg	PBO	RINVOQ 15 mg
N	314	317	216	217	221	221	651	651	169	164
Number of tender joints (0-68)										
Baseline	26 (16)	25 (14)	25 (16)	24 (15)	25 (15)	25 (14)	26 (14)	26 (15)	28 (15)	28 (16)
Week 12/14	13 (15)	9 (12)	15 (16)	10 (13)	16 (17)	12 (14)	16 (15)	10 (13)	18 (17)	11 (14)
Number of swollen joints (0-66)										
Baseline	17 (11)	17 (10)	17 (12)	16 (11)	15 (9)	16 (10)	16 (9)	17 (10)	16 (10)	17 (11)
Week 12/14	6 (8)	5 (7)	9 (11)	6 (9)	9 (10)	7 (10)	9 (9)	5 (7)	9 (10)	6 (8)
Pain[c]										
Baseline	66 (21)	68 (21)	63 (21)	62 (23)	62 (21)	64 (19)	65 (21)	66 (21)	69 (21)	68 (20)
Week 12/14	41 (25)	31 (25)	49 (25)	36 (27)	51 (26)	33 (24)	49 (25)	33 (24)	55 (28)	41 (28)
Patient global assessment[c]										
Baseline	66 (21)	67 (22)	60 (22)	62 (22)	60 (20)	63 (22)	64 (21)	64 (22)	66 (23)	67 (20)
Week 12/14	42 (25)	31 (24)	48 (26)	37 (27)	50 (26)	32 (24)	48 (24)	33 (24)	54 (28)	40 (26)
Disability Index (HAQ-DI)[d]										
Baseline	1.60 (0.67)	1.60 (0.67)	1.47 (0.66)	1.47 (0.66)	1.42 (0.63)	1.48 (0.61)	1.61 (0.61)	1.63 (0.64)	1.56 (0.60)	1.67 (0.64)
Week 12/14	1.08 (0.72)	0.76 (0.69)	1.19 (0.69)	0.86 (0.67)	1.13 (0.70)	0.85 (0.66)	1.28 (0.67)	0.98 (0.68)	1.33 (0.66)	1.24 (0.77)
Physician global assessment[c]										
Baseline	69 (16)	67 (17)	62 (17)	66 (18)	64 (18)	64 (16)	66 (18)	66 (17)	67 (17)	69 (17)

Week 12/14	32 (22)	22 (19)	37 (24)	26 (21)	41 (24)	26 (21)	41 (25)	27 (21)	39 (25)	29 (22)
CRP (mg/L)										
Baseline	21.2 (22.1)	23.0 (27.4)	14.5 (17.3)	14.0 (16.5)	12.6 (14.0)	16.6 (19.2)	18.0 (21.5)	17.9 (22.5)	16.3 (21.1)	16.3 (18.6)
Week 12/14	10.9 (14.9)	4.2 (8.8)	12.8 (21.4)	3.7 (7.8)	13.1 (15.5)	4.6 (9.6)	16.2 (19.8)	5.5 (10.9)	13.9 (17.3)	5.0 (14.0)

Abbreviations: ACR = American College of Rheumatology; bDMARD = biologic disease-modifying anti-rheumatic drug; CRP = c-reactive protein; cDMARDs = conventional disease-modifying anti-rheumatic drugs; HAQ-DI = Health Assessment Questionnaire Disability Index; IR = inadequate responder; MTX = methotrexate; PBO = placebo

[a] Data shown are mean (standard deviation).
[b] Primary efficacy timepoint is at Week 14.
[c] Visual analog scale: 0 = best, 100 = worst.
[d] Health Assessment Questionnaire-Disability Index: 0=best, 3=worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

Figure 1. Percent of Patients Achieving ACR20 in Trial RA-IV



Abbreviations: ACR20 = American College of Rheumatology ≥20% improvement; MTX = methotrexate
Patients who discontinued randomized treatment, or were missing ACR20 results, or were lost-to-follow-up or withdrawn from the trial were imputed as non-responders.

In RA-I and RA-IV, a higher proportion of patients treated with RINVOQ 15 mg alone or in combination with MTX, achieved DAS28-CRP < 2.6 compared to MTX or placebo at the primary efficacy timepoint (Table 8).

Table 8: Proportion of Patients with DAS28-CRP Less Than 2.6 with Number of Residual Active Joints at Primary Efficacy Timepoint

	Trial RA-I MTX-Naive	
	Monotherapy	
DAS28-CRP Less Than 2.6	**MTX** N = 314	**RINVOQ 15 mg** N = 317
Proportion of responders at Week 12 (n)	14% (43)	36% (113)
Of responders, proportion with 0 active joints (n)	51% (22)	45% (51)
Of responders, proportion with 1 active joint (n)	35% (15)	23% (26)
Of responders, proportion with 2 active joints (n)	9% (4)	17% (19)
Of responders, proportion with 3 or more active joints (n)	5% (2)	15% (17)
	Trial RA-IV MTX-IR	
	Background MTX	
DAS28-CRP Less Than 2.6	**PBO** N = 651	**RINVOQ 15 mg** N = 651
Proportion of responders at Week 12 (n)	6% (40)	29% (187)
Of responders, proportion with 0 active joints (n)	60% (24)	48% (89)
Of responders, proportion with 1 active joint (n)	20% (8)	23% (43)
Of responders, proportion with 2 active joints (n)	15% (6)	13% (25)
Of responders, proportion with 3 or more active joints (n)	5% (2)	16% (30)
Abbreviations: CRP = c-reactive protein; DAS28 = Disease Activity Score 28 joints; MTX = methotrexate; PBO = placebo; IR = inadequate responder		

Radiographic response

Inhibition of progression of structural joint damage was assessed using the modified Total Sharp Score (mTSS) and its components, the erosion score and joint space narrowing score, at Week 26 in Trial RA-IV and Week 24 in Trial RA-I. The proportion of patients with no radiographic progression (mTSS change from baseline ≤ 0) was also assessed.

In Trial RA-IV, treatment with RINVOQ 15 mg inhibited the progression of structural joint damage compared to placebo in combination with cDMARDs at Week 26 (Table 9). Analyses of erosion and joint space narrowing scores were consistent with overall results.

In the placebo plus MTX group, 76% of the patients experienced no radiographic progression at Week 26 compared to 83% of the patients treated with RINVOQ 15 mg.

In Trial RA-I, treatment with RINVOQ 15 mg monotherapy inhibited the progression of structural joint damage compared to MTX monotherapy at Week 24 (Table 9). Analyses of erosion and joint space narrowing scores were consistent with overall results.

In the MTX monotherapy group, 78% of the patients experienced no radiographic progression at Week 24 compared to 87% of the patients treated with RINVOQ 15 mg monotherapy.

Table 9: Radiographic Changes

	Trial RA-IV MTX-IR		
	Background MTX		
mTSS	PBO (N=651) Mean (SD)	RINVOQ 15 mg (N=651) Mean (SD)	Estimated Difference vs PBO at Week 26 (95% CI)[a]
Baseline	35.9 (52)	34.0 (50)	
Week 26[b]	0.78 (0.1)	0.15 (0.1)	-0.63 (-0.92, -0.34)
	Trial RA-I MTX-naïve		
	Monotherapy		
	MTX (N=309) Mean (SD)	RINVOQ 15 mg (N=309) Mean (SD)	Estimated Difference vs MTX at Week 24 (95% CI)[c]
Baseline	13.3 (31)	18.1 (38)	
Week 24[d]	0.67 (2.8)	0.14 (1.4)	-0.53 (-0.85, -0.20)

Abbreviations: mTSS = modified Total Sharp Score, MTX = methotrexate; PBO = placebo; SD = standard deviation; IR = inadequate responders; bDMARDs = biologic disease modifying anti-rheumatic drugs; LS = least squares; CI = confidence intervals

[a] LS means and 95% CI based on a random coefficient model fit to the mTSS value adjusting for time, treatment group, prior bDMARDs use, treatment group-by-time interaction, with random slopes and random intercept.

[b] Estimated linear rate of structural progression by Week 26 and standard errors are presented.

[c] LS means and 95% CI based on a linear regression model fit to change from baseline in mTSS adjusting for treatment group, baseline mTSS, and geographic region.

[d] Mean change from baseline and standard deviation are presented.

Physical Function Response

Treatment with RINVOQ 15 mg, alone or in combination with cDMARDs, resulted in a greater improvement in physical function at Week 12/14 compared to all comparators as measured by HAQ-DI.

Other Health-Related Outcomes

In all trials except for Trial RA-V, patients receiving RINVOQ 15 mg had greater improvement from baseline in physical component summary (PCS) score, mental component summary (MCS) scores, and in all 8 domains of the Short Form Health Survey (SF-36) compared to placebo in combination with cDMARDs or MTX monotherapy at Week 12/14.

Fatigue was assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue score (FACIT-F) in Trials RA-I, RA-III, and RA-IV. Improvement in fatigue at Week 12 was observed in patients treated with RINVOQ 15 mg compared to patients on placebo in combination with cDMARDs or MTX monotherapy.

14.2 Psoriatic Arthritis

The efficacy and safety of RINVOQ 15 mg once daily were assessed in two Phase 3 randomized, double-blind, multicenter, placebo-controlled studies in patients 18 years of age or older with moderately to severely active psoriatic arthritis. All patients had active psoriatic arthritis for at least 6 months based upon the Classification Criteria for Psoriatic Arthritis (CASPAR), at least 3 tender joints and at least 3 swollen joints, and active plaque psoriasis or history of plaque psoriasis. Although another dose has been studied, the recommended dose of RINVOQ is 15 mg once daily for psoriatic arthritis.

Study PsA-I (NCT03104400) was a 24-week trial in 1705 patients with moderately to severely active psoriatic arthritis who had an inadequate response or intolerance to at least one non-biologic DMARD. Patients received RINVOQ 15 mg or upadacitinib 30 mg once daily, adalimumab, or placebo, alone or in combination with background non-biologic DMARDs. At Week 24, all patients randomized to placebo were switched to RINVOQ 15 mg or upadacitinib 30 mg once daily in a blinded manner. The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 12.

Study PsA-II (NCT03104374) was a 24-week trial in 642 patients with moderately to severely active psoriatic arthritis who had an inadequate response or intolerance to at least one biologic DMARD. Patients received RINVOQ 15 mg or upadacitinib 30 mg once daily or placebo, alone or in combination with background non-biologic DMARDs. At Week 24, all patients randomized to placebo were switched to RINVOQ 15 mg or upadacitinib 30 mg once daily in a blinded manner. The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 12.

Clinical Response

In both studies, patients treated with RINVOQ 15 mg achieved significantly higher ACR20 responses compared to placebo at Week 12 (Table 10, Figure 2). A higher proportion of patients treated with RINVOQ 15 mg achieved ACR50 and ACR70 responses at Week 12 compared to placebo.

Treatment with RINVOQ 15 mg resulted in improvements in the ACR components compared to placebo at the primary efficacy timepoint (Table 11).

Table 10: Clinical Response

Study	**Study PsA-I non-biologic DMARD-IR**		**Study PsA-II bDMARD-IR**	
Treatment Group	PBO %	RINVOQ 15 mg % Δ (95% CI)	PBO %	RINVOQ 15 mg % Δ (95% CI)
N	423	429	212	211
ACR20				
Week 12	36	71 35 (28, 41)	24	57 33 (24, 42)
ACR50				
Week 12	13	38 24 (19, 30)	5	32 27 (20, 34)

ACR70				
Week 12	2	16 13 (10, 17)	1	9 8 (4, 12)

Abbreviations: ACR20 (or 50 or 70) = American College of Rheumatology ≥20% (or ≥50% or ≥70%) improvement, bDMARD = biologic disease-modifying anti-rheumatic drug; IR = inadequate responder; PBO = placebo
Patients who discontinued randomized treatment or were missing data at week of evaluation were imputed as non-responders in the analyses.

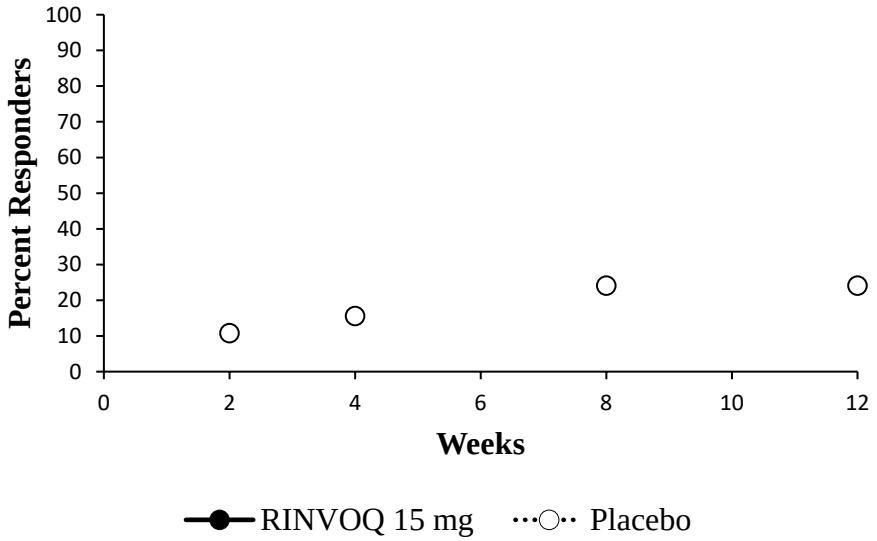
Table 11: Components of ACR Response[a]

Study	**Study PsA-I non-biologic DMARD-IR**		**Study PsA-II bDMARD-IR**	
Treatment Group	PBO (N=423)	RINVOQ 15 mg (N=429)	PBO (N=212)	RINVOQ 15 mg (N=211)
Number of tender/painful joints (0-68)				
Baseline	20.0 (14.3)	20.4 (14.7)	25.3 (17.6)	24.9 (17.3)
Week 12	12.5 (13.3)	8.8 (12.5)	19.3 (18.5)	12.6 (15.6)
Number of swollen joints (0-66)				
Baseline	11.0 (8.2)	11.6 (9.3)	12.0 (8.9)	11.3 (8.2)
Week 12	5.6 (7.2)	3.5 (6.0)	7.3 (9.4)	4.4 (5.7)
Patient assessment of pain[b]				
Baseline	6.1 (2.1)	6.2 (2.1)	6.6 (2.1)	6.4 (2.1)
Week 12	5.1 (2.3)	3.8 (2.4)	5.9 (2.3)	4.4 (2.5)
Patient global assessment[b]				
Baseline	6.3 (2.0)	6.6 (2.0)	6.8 (2.0)	6.8 (1.9)
Week 12	5.2 (2.2)	3.8 (2.3)	6.1 (2.3)	4.5 (2.5)
Disability index (HAQ-DI)[c]				
Baseline	1.1 (0.6)	1.2 (0.7)	1.2 (0.7)	1.1 (0.6)
Week 12	1.0 (0.7)	0.7 (0.6)	1.1 (0.6)	0.8 (0.7)
Physician global assessment[b]				
Baseline	6.5 (1.6)	6.7 (1.6)	6.5 (1.8)	6.5 (1.8)
Week 12	4.3 (2.2)	3.1 (2.0)	5.0 (2.2)	3.4 (2.1)
hsCRP (mg/L)				
Baseline	11.5 (15.8)	11.0 (14.9)	10.4 (18.5)	11.2 (18.6)
Week 12	10.1 (15.2)	4.2 (9.9)	9.4 (13.4)	4.3 (7.9)

Abbreviations: ACR = American College of Rheumatology; hsCRP = high sensitivity c-reactive protein; HAQ-DI = Health Assessment Questionnaire-Disability Index; IR = inadequate responder; PBO = placebo
[a] Data shown are mean (standard deviation).
[b] Numeric rating scale (NRS): 0 = best, 10 = worst
[c] Health Assessment Questionnaire-Disability Index: 0=best, 3=worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

The percentage of patients achieving ACR20 response by visit is shown in Figure 2.

Figure 2. Percent of Patients Achieving ACR20 in Study PsA-II



Abbreviations: ACR20 = American College of Rheumatology ≥20% improvement
Patients who discontinued randomized treatment, or were missing ACR20 results, or were lost-to-follow-up or withdrawn from the study were imputed as non-responders.

Treatment with RINVOQ 15 mg resulted in improvement in dactylitis and enthesitis in patients with pre-existing dactylitis or enthesitis.

Treatment with RINVOQ 15 mg resulted in improvement in skin manifestations in patients with PsA. However, RINVOQ has not been studied in and is not indicated for the treatment of plaque psoriasis.

Physical Function Response

In both studies, patients treated with RINVOQ 15 mg showed significant improvement in physical function from baseline compared to placebo as assessed by HAQ-DI at Week 12 (Table 10). The mean difference (95% CI) from placebo in HAQ-DI change from baseline at Week 12 was -0.28 (-0.35, -0.22) in Study PsA-I and -0.21 (-0.30, -0.12) in Study PsA-II.

The proportion of HAQ-DI responders (≥ 0.35 improvement from baseline in HAQ-DI score) at Week 12 in Study PsA-I and Study PsA-II was 58% and 45%, respectively, in patients receiving RINVOQ 15 mg and 33% and 27%, respectively, in patients receiving placebo.

Radiographic Response

In Study PsA-I, inhibition of progression of structural damage was assessed radiographically and expressed as the change from baseline in modified Total Sharp Score (mTSS) and its components, the erosion score and the joint space narrowing score, at Week 24.

Treatment with RINVOQ 15 mg inhibited progression of structural joint damage compared to placebo at Week 24 (Table 12). Analyses of erosion and joint space narrowing scores were consistent with overall results. The proportion of patients with no radiographic progression (mTSS change ≤ 0) at Week 24 was 93% in patients receiving RINVOQ 15 mg and 89% in patients receiving placebo.

Table 12: Radiographic Changes in Study PsA-I

	PBO (N=392) Mean (SD)	**RINVOQ 15 mg** (N=407) Mean (SD)	Estimated Difference vs PBO at Week 24 (95% CI)[a]
mTSS			
Baseline	13.32 (31.2)	13.14 (42.4)	
Week 24[b]	0.23 (0.07)	-0.02 (0.04)	-0.25 (-0.41, -0.09)

Abbreviations: CI = confidence intervals; LS = least squares; mTSS = modified Total Sharp Score; PBO = placebo; SD = standard deviation
[a] LS means and 95% CI based on a random coefficient model fit to the mTSS value adjusting for time, treatment group, current DMARD use (yes/no), treatment group-by-time interaction, with random slopes and random intercept.
[b] Estimated linear rate of structural progression by Week 24 and standard errors are presented.

Other Health-Related Outcomes

Health-related quality of life was assessed by SF-36. In both studies, patients receiving RINVOQ 15 mg experienced significantly greater improvement from baseline in the Physical Component Summary score compared to placebo at Week 12. Greater improvement was also observed in the Mental Component Summary score and all 8 domains of SF-36 compared to placebo.

Patients receiving RINVOQ 15 mg showed greater improvement from baseline in fatigue, as measured by FACIT-F score, at Week 12 compared to placebo in both studies.

14.3 Atopic Dermatitis

The efficacy of RINVOQ 15 mg and 30 mg once daily, was assessed in three Phase 3 randomized, double-blind, multicenter trials (AD-1, AD-2, AD-3; NCT03569293, NCT03607422, and NCT03568318, respectively) in a total of 2584 patients (12 years of age and older). RINVOQ was evaluated in 344 pediatric patients and 2240 adult patients with moderate to severe atopic dermatitis (AD) not adequately controlled by topical medication(s).

Disease severity at baseline was defined by a validated Investigator's Global Assessment (vIGA-AD) score ≥3 in the overall assessment of AD on a severity scale of 0 to 4, an Eczema Area and Severity Index (EASI) score ≥16, a minimum body surface area (BSA) involvement of ≥10%, and weekly average Worst Pruritus Numerical Rating Scale (NRS) score ≥4. Overall, 57% of the patients were male and 69% were white. The mean age at baseline was 34 years (ranged from 12 to 75 years) and 13% of the patients were 12 to less than 18 years. At baseline, 49% of patients had a vIGA-AD score of 3 (moderate AD), and 51% of patients had a vIGA-AD score of 4 (severe AD). The baseline mean EASI score was 29 and the baseline weekly average Worst

Pruritus NRS score was 7. Approximately 52% of the patients had prior exposure to systemic AD treatment.

In all three trials, patients received RINVOQ once daily oral doses of 15 mg, 30 mg, or matching placebo for 16 weeks. In Trial AD-3, patients also received RINVOQ or placebo with concomitant topical corticosteroids (TCS) for 16 weeks.

All three trials assessed the co-primary endpoints of the proportion of patients with a vIGA-AD score of 0 (clear) or 1 (almost clear) with at least a 2-point improvement and the proportion of patients with EASI-75 (improvement of at least 75% in EASI score from baseline) at Week 16. Secondary endpoints included EASI-90 and EASI-100 at Week 16, and the proportion of patients with reduction in itch (≥4-point improvement from baseline in the Worst Pruritus NRS) at Weeks 1, 4, and 16. In Trials AD-1 and AD-2, the proportion of patients with reduction in pain (≥4-point improvement in the Atopic Dermatitis Symptom Scale [ADerm-SS] Skin Pain NRS) from baseline to Week 16 was a secondary endpoint.

Clinical Response

Monotherapy Trials (AD-1 and AD-2)

The results of RINVOQ monotherapy trials (AD-1 and AD-2) are presented in Table 13. Figure 3 presents the proportion of patients with ≥ 4-point improvement in Worst Pruritus NRS at Weeks 1, 4, and 16 for Trials AD-1 and AD-2.

Table 13: Efficacy Results of Monotherapy Trials at Week 16 in Patients with Moderate to Severe AD

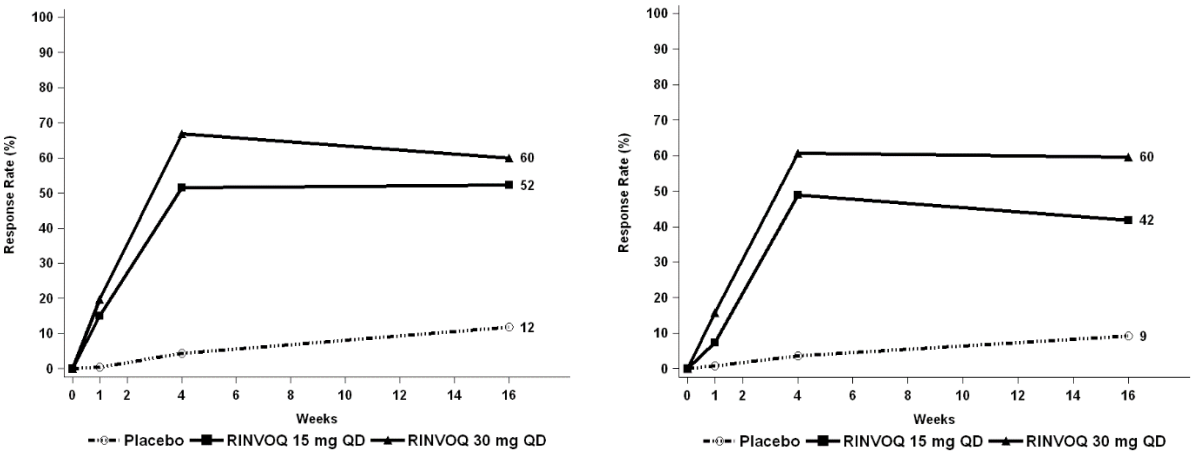
	Trial AD-1			**Trial AD-2**		
	PBO	**RINVOQ 15 mg**	**RINVOQ 30 mg**	**PBO**	**RINVOQ 15 mg**	**RINVOQ 30 mg**
Number of patients randomized	281	281	285	278	276	282
vIGA-AD 0/1[a,b]	8%	48%	62%	5%	39%	52%
Difference from PBO (95% CI)		40% (33%, 46%)	54% (47%, 60%)		34% (28%, 40%)	47% (41%, 54%)
EASI-75[a]	16%	70%	80%	13%	60%	73%
Difference from PBO (95% CI)		53% (46%, 60%)	63% (57%, 70%)		47% (40%, 54%)	60% (53%, 66%)
EASI-90[a]	8%	53%	66%	5%	42%	58%
Difference from PBO (95% CI)		45% (39%, 52%)	58% (51%, 64%)		37% (31%, 43%)	53% (47%, 59%)
EASI-100[a]	2%	17%	27%	1%	14%	19%
Difference from PBO (95% CI)		15% (10%, 20%)	25% (20%, 31%)		13% (9%, 18%)	18% (13%, 23%)
Number of patients with baseline Worst Pruritus NRS score ≥ 4	272	274	280	274	270	280
≥ 4-point improvement in Worst Pruritus NRS[c]	12%	52%	60%	9%	42%	60%

Difference from PBO (95% CI)		40% (33%, 48%)	48% (41%, 55%)		33% (26%, 39%)	50% (44%, 57%)
Number of patients with baseline ADerm-SS Skin Pain NRS score ≥ 4	233	237	249	247	237	238
≥ 4-point improvement in ADerm-SS Skin Pain NRS[d]	15%	54%	63%	13%	49%	65%
Difference from PBO (95% CI)		39% (31%, 47%)	49% (41%, 56%)		36% (28%, 43%)	52% (44%, 59%)

Abbreviations: ADerm-SS = Atopic Dermatitis Symptom Scale; PBO = placebo
[a] Based on number of patients randomized
[b] Responder was defined as a patient with vIGA-AD 0 or 1 ("clear" or "almost clear") with a reduction of ≥ 2 points on a 0-4 ordinal scale
[c] Based on number of patients whose baseline Worst Pruritus NRS is ≥ 4
[d] Based on number of patients whose baseline ADerm-SS Skin Pain NRS is ≥ 4

Figure 3: Proportion of Patients with Moderate to Severe AD with ≥4-point Improvement in the Worst Pruritus NRS in Monotherapy Trials

Trial AD-1 **Trial AD-2**



Examination of age, gender, race, weight, and prior systemic treatment with immunosuppressants did not identify differences in response to RINVOQ among these subgroups in Trials AD-1 and AD-2.

Concomitant TCS Trial (AD-3)

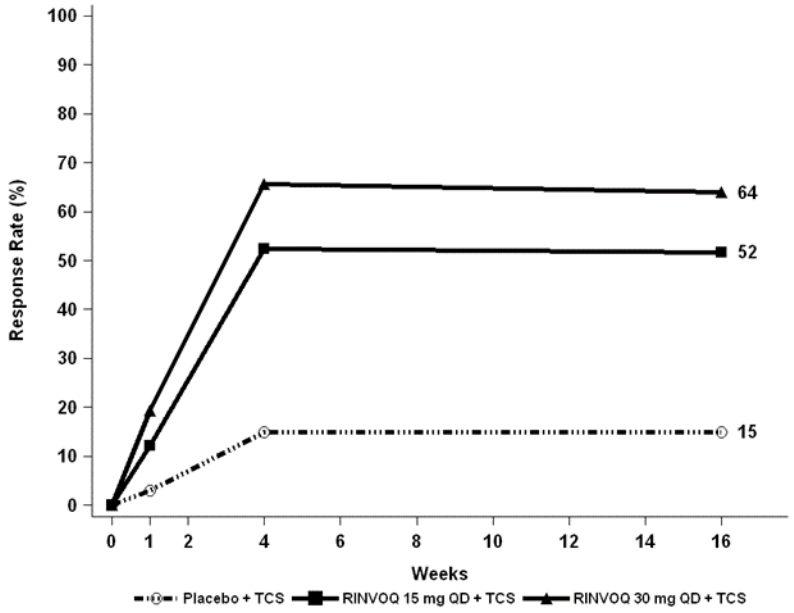
The results of the RINVOQ with concomitant TCS trial (AD-3) are presented in Table 14. Figure 4 presents the proportion of patients with ≥ 4-point improvement in Worst Pruritus NRS at Weeks 1, 4, and 16 for Trial AD-3.

Table 14: Efficacy Results with Concomitant TCS at Week 16 in Patients with Moderate to Severe AD

	Trial AD-3		
	PBO + TCS	**RINVOQ 15 mg + TCS**	**RINVOQ 30 mg + TCS**
Number of patients randomized	304	300	297
vIGA-AD 0/1[a,b]	11%	40%	59%
Difference from PBO (95% CI)		29% (22%, 35%)	48% (41%, 54%)
EASI-75[a,]	26%	65%	77%
Difference from PBO (95% CI)		38% (31%, 45%)	51% (44%, 57%)
EASI-90[a]	13%	43%	63%
Difference from PBO (95% CI)		30% (23%, 36%)	50% (43%, 56%)
EASI-100[a]	1%	12%	23%
Difference from PBO (95% CI)		11% (7%, 14%)	21% (16%, 26%)
Number of patients with baseline Worst Pruritus NRS score ≥ 4	294	288	291
≥ 4-point improvement in Worst Pruritus NRS[c]	15%	52%	64%
Difference from PBO (95% CI)		37% (30%, 44%)	49% (42%, 56%)

Abbreviations: PBO = placebo
[a] Based on number of patients randomized
[b] Responder was defined as a patient with vIGA-AD 0 or 1 ("clear" or "almost clear") with a reduction of ≥ 2 points on a 0-4 ordinal scale
[c] Based on number of patients whose baseline Worst Pruritus NRS is ≥ 4

Figure 4: Proportion of Patients with Moderate to Severe AD with ≥4-point Improvement in the Worst Pruritus NRS in Concomitant TCS Trial



Examination of age, gender, race, weight, and prior systemic treatment with immunosuppressants did not identify differences in response to RINVOQ among these subgroups in Trial AD-3.

Pediatric Patient Population

The efficacy results of the RINVOQ monotherapy trials (AD-1 and AD-2) and the RINVOQ with concomitant TCS trial (AD-3) at Week 16 for pediatric patients 12 years of age and older are presented in Table 15 and Table 16, respectively.

Table 15: Efficacy Results of Monotherapy Trials for Pediatric Patients 12 Years of Age and Older with Moderate to Severe AD at Week 16

	Trial AD-1			Trial AD-2		
	PBO	**RINVOQ 15 mg**	**RINVOQ 30 mg**	**PBO**	**RINVOQ 15 mg**	**RINVOQ 30 mg**
Number of pediatric patients randomized	40	42	42	36	33	35
vIGA-AD 0/1[a,b]	8%	38%	69%	3%	42%	62%
Difference from PBO (95% CI)		31% (14%, 47%)	62% (45%, 78%)		40% (22%, 57%)	60% (42%, 77%)
EASI-75[a]	8%	71%	83%	14%	67%	74%
Difference from PBO (95% CI)		63% (47%, 79%)	75% (61%, 89%)		53% (33%, 72%)	61% (42%, 79%)
Number of pediatric patients with baseline Worst Pruritus NRS score ≥ 4	39	40	42	36	30	34
≥ 4-point improvement in Worst Pruritus NRS[c]	15%	45%	55%	3%	33%	50%

Difference from PBO (95% CI)	30% (10%, 49%)	39% (21%, 58%)		31% (13%, 48%)	47% (30%, 65%)

Abbreviations: PBO = placebo
[a] Based on number of pediatric patients randomized
[b] Responder was defined as a patient with vIGA-AD 0 or 1 ("clear" or "almost clear") with a reduction of ≥ 2 points on a 0-4 ordinal scale
[c] Based on number of pediatric patients whose baseline Worst Pruritus NRS is ≥ 4

Table 16: Efficacy Results with Concomitant TCS for Pediatric Patients 12 Years of Age and Older with Moderate to Severe AD at Week 16

	Trial AD-3		
	PBO + TCS	**RINVOQ 15 mg + TCS**	**RINVOQ 30 mg + TCS**
Number of pediatric patients randomized	40	39	37
vIGA-AD 0/1[a,b]	8%	31%	65%
Difference from PBO (95% CI)		23% (7%, 40%)	57% (40%, 75%)
EASI-75[a]	30%	56%	76%
Difference from PBO (95% CI)		26% (5%, 47%)	46% (26%, 65%)
Number of pediatric patients with baseline Worst Pruritus NRS score ≥ 4	38	36	33
≥ 4-point improvement in Worst Pruritus NRS[c]	13%	42%	55%
Difference from PBO (95% CI)		29% (9%, 48%)	41% (21%, 61%)

Abbreviations: PBO = placebo
[a] Based on number of pediatric patients randomized
[b] Responder was defined as a patient with vIGA-AD 0 or 1 ("clear" or "almost clear") with a reduction of ≥ 2 points on a 0-4 ordinal scale
[c] Based on number of pediatric patients whose baseline Worst Pruritus NRS is ≥ 4

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

RINVOQ extended-release tablets are supplied as:

- 15 mg: purple, biconvex oblong, with dimensions of 14 x 8 mm, and debossed with 'a15' on one side.

  30 tablets in a bottle; NDC: 0074-2306-30

- 30 mg: red, biconvex oblong, with dimensions of 14 x 8 mm, and debossed with 'a30' on one side.

30 tablets in a bottle; NDC: 0074-2310-30

Storage and Handling

Store at 2˚C to 25˚C (36˚F to 77˚F).

Store in the original bottle in order to protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Serious Infections

Inform patients that they may be more likely to develop infections when taking RINVOQ. Instruct patients to contact their healthcare provider immediately during treatment if they develop any signs or symptoms of an infection *[see Warnings and Precautions (5.1)]*.

Advise patients that the risk of herpes zoster is increased in patients taking RINVOQ and in some cases can be serious *[see Warnings and Precautions (5.1)]*.

Malignancies

Inform patients that RINVOQ may increase their risk of certain cancers and that periodic skin examinations should be performed while using RINVOQ.

Advise patients that exposure to sunlight and UV light should be limited by wearing protective clothing and using a broad-spectrum sunscreen *[see Warnings and Precautions (5.3)]*.

Major Adverse Cardiovascular Events

Inform patients that RINVOQ may increase their risk of major adverse cardiovascular events (MACE) including myocardial infarction, stroke, and cardiovascular death. Instruct all patients, especially current or past smokers or patients with other cardiovascular risk factors, to be alert for the development of signs and symptoms of cardiovascular events *[see Warnings and Precautions (5.4)]*.

Thrombosis

Inform patients that events of deep venous thrombosis and pulmonary embolism have been reported in clinical trials with RINVOQ. Instruct patients to seek immediate medical attention if they develop any signs or symptoms of a DVT or PE *[see Warnings and Precautions (5.5)]*.

Hypersensitivity Reactions

Advise patients to discontinue RINVOQ and seek immediate medical attention if they develop any signs and symptoms of allergic reactions *[see Warnings and Precautions (5.6)]*.

Gastrointestinal Perforations

Inform patients that gastrointestinal perforations have been reported in clinical trials with RINVOQ and that risk factors include the use of NSAIDS or history of diverticulitis. Instruct patients to seek medical care immediately if they experience new onset of abdominal pain, fever, chills, nausea, or vomiting *[see Warnings and Precautions (5.7)]*.

Retinal Detachment

Inform patients that retinal detachment has been reported in clinical trials with RINVOQ. Advise patients to immediately inform their healthcare provider if they develop any sudden changes in vision while receiving RINVOQ *[see Adverse Reactions (6.1)]*.

Laboratory Abnormalities

Inform patients that RINVOQ may affect certain lab tests, and that blood tests are required before and during RINVOQ treatment *[see Warnings and Precautions (5.8)]*.

Vaccinations

Advise patients to avoid use of live vaccines with RINVOQ. Instruct patients to inform their healthcare practitioner that they are taking RINVOQ prior to a potential vaccination *[see Warnings and Precautions (5.10)]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential that exposure to RINVOQ during pregnancy may result in fetal harm. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.9) and Use in Specific Populations (8.1)]*.

Advise females of reproductive potential that effective contraception should be used during treatment and for 4 weeks following the final dose of upadacitinib *[see Use in Specific Populations (8.3)]*.

Advise females patients who are exposed to RINVOQ during pregnancy to contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Lactation

Advise women not to breastfeed during treatment with RINVOQ and for 6 days after the last dose *[see Use in Specific Populations (8.2)]*.

Administration

Advise patients not to chew, crush, or split RINVOQ tablets *[see Dosage and Administration (2.2)]*.

Manufactured by: AbbVie Ireland NL B.V., Sligo, Ireland
Packed and Distributed by: AbbVie Inc., North Chicago, IL 60064

20066213 January 2022

MEDICATION GUIDE

RINVOQ® (RIN-VOKE)

extended-release tablets, for oral use

What is the most important information I should know about RINVOQ?

RINVOQ can cause serious side effects, including:

1. Serious Infections.

RINVOQ is a medicine that affects your immune system. RINVOQ can lower the ability of your immune system to fight infections. Some people have had serious infections while taking RINVOQ, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses that can spread throughout the body. Some people have died from these infections.

- Your healthcare provider should test you for TB before starting treatment with RINVOQ.
- Your healthcare provider should watch you closely for signs and symptoms of TB during treatment with RINVOQ.
- You should not start taking RINVOQ if you have any kind of infection unless your healthcare provider tells you it is okay. You may be at a higher risk of developing shingles (herpes zoster).
- **Before starting RINVOQ, tell your healthcare provider if you**:
  - o are being treated for an infection.
  - o have had an infection that does not go away or that keeps coming back.
  - o have diabetes, chronic lung disease, HIV, or a weak immune system.
  - o have TB or have been in close contact with someone with TB.
  - o have had shingles (herpes zoster).
  - o have or have had hepatitis B or C.
  - o live or have lived, or have traveled to certain parts of the country (such as the Ohio and Mississippi River valleys and the Southwest) where there is an increased chance for getting certain kinds of fungal infections. These infections may happen or become more severe if you use RINVOQ. Ask your healthcare provider if you do not know if you have lived in an area where these infections are common.
  - o think you have an infection or have symptoms of an infection such as:
    - fever, sweating, or chills
    - shortness of breath
    - warm, red, or painful skin or sores on your body
    - muscle aches
    - feeling tired
    - blood in your phlegm
    - diarrhea or stomach pain
    - cough
    - weight loss
    - burning when you urinate or urinating more often than usual

After starting RINVOQ, call your healthcare provider right away if you have any symptoms of an infection. RINVOQ can make you more likely to get infections or make worse any infections that you have. If you get a serious infection, your healthcare provider may stop your treatment with RINVOQ until your infection is controlled.

2. Increased risk of death in people 50 years of age and older who have at least 1 heart disease (cardiovascular) risk factor and are taking a medicine in the class of medicines called Janus kinase (JAK) inhibitors. RINVOQ is a JAK inhibitor medicine.

3. Cancer and immune system problems.

RINVOQ may increase your risk of certain cancers by changing the way your immune system works. Lymphoma and other cancers, including skin cancers can happen in people taking RINVOQ. People taking a medicine in the class of medicines called Janus kinase (JAK) inhibitors have a higher risk of certain cancers including lymphoma and lung cancer, especially if you are a current or past smoker. Tell your healthcare provider if you have ever had any type of cancer. Follow your healthcare provider's advice about having your skin checked for skin cancer during treatment with RINVOQ. Limit the amount of time you spend in sunlight. Avoid using tanning beds or sunlamps. Wear protective clothing when you are in the sun and use a sunscreen with a high protection factor (SPF 30 and above). This is especially important if your skin is very fair or if you have a family history of skin cancer.

4. Increased risk of major cardiovascular events such as heart attack, stroke or death in people 50 years of age and older who have at least 1 heart disease (cardiovascular) risk factor and taking a medicine in the class of medicines called JAK inhibitors, especially if you are a current or past smoker.

Get emergency help right away if you have any symptoms of a heart attack or stroke while taking RINVOQ, including:

- discomfort in the center of your chest that lasts for more than a few minutes, or that goes away and comes back
- severe tightness, pain, pressure, or heaviness in your chest, throat, neck, or jaw
- pain or discomfort in your arms, back, neck, jaw, or stomach
- shortness of breath with or without chest discomfort
- breaking out in a cold sweat
- nausea or vomiting
- feeling lightheaded
- weakness in one part or on one side of your body
- slurred speech

5. Blood Clots (thrombosis).
Blood clots in the veins of your legs (deep vein thrombosis, DVT) or lungs (pulmonary embolism, PE) and arteries (arterial thrombosis) can happen in some people taking RINVOQ. This may be life-threatening and cause death. Blood clots in the veins of the legs (DVT) and lungs (PE) have happened more often in people who are 50 years of age and older and with at least 1 heart disease (cardiovascular) risk factor taking a medicine in the class of medicines called Janus kinase (JAK) inhibitors.

- Tell your healthcare provider if you have had blood clots in the veins of your legs or lungs in the past.
- Get medical help right away if you have signs and symptoms of blood clots during treatment with RINVOQ, including:
  - swelling
  - pain or tenderness in one or both legs
  - sudden unexplained chest or upper back pain
  - shortness of breath or difficulty breathing

6. Allergic reactions. Symptoms such as rash (hives), trouble breathing, feeling faint or dizzy, or swelling of your lips, tongue, or throat, that may mean you are having an allergic reaction have been seen in people taking RINVOQ. Some of these reactions were serious. If any of these symptoms occur during treatment with RINVOQ, stop taking RINVOQ and get emergency medical help right away.

7. Tears (perforation) in the stomach or intestines.

- Tell your healthcare provider if you have had diverticulitis (inflammation in parts of the large intestine) or ulcers in your stomach or intestines. Some people taking RINVOQ can get tears in their stomach or intestines. This happens most often in people who take nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or methotrexate.
- Get medical help right away if you get stomach-area pain, fever, chills, nausea, or vomiting.

8. Changes in certain laboratory test results.
Your healthcare provider should do blood tests before you start taking RINVOQ and while you take RINVOQ to check for the following:

- **low neutrophil and lymphocyte counts.** Neutrophils and lymphocytes are types of white blood cells that help the body fight off infections.
- **low red blood cell counts.** Red blood cells carry oxygen. Low red blood cells means you may have anemia, which may make you feel weak and tired.
- **increased cholesterol levels.** Your healthcare provider should do blood tests to check your cholesterol levels approximately 12 weeks after you start taking RINVOQ, and as needed.
- **elevated liver enzymes.** Liver enzymes help to tell if your liver is functioning normally. Elevated liver enzymes may indicate that your healthcare provider needs to do additional tests on your liver.

You should not take RINVOQ if your neutrophil count, lymphocyte count, or red blood cell count is too low or your liver tests are too high. Your healthcare provider may stop your RINVOQ treatment for a period of time if needed because of changes in these blood test results.

See **"What are the possible side effects of RINVOQ?"** for more information about side effects.

What is RINVOQ?
RINVOQ is a prescription medicine that is a Janus kinase (JAK) inhibitor. RINVOQ is used:

- to treat adults with moderate to severe rheumatoid arthritis when 1 or more medicines called tumor necrosis factor (TNF) blockers have been used, and did not work well or could not be tolerated.
- to treat adults with active psoriatic arthritis when 1 or more medicines called tumor necrosis factor (TNF) blockers have been used, and did not work well or could not be tolerated.
- to treat adults and children 12 years of age and older with moderate to severe eczema (atopic dermatitis) that did not respond to previous treatment and their eczema is not well controlled with other pills or injections, including biologic medicines, or the use of other pills or injections is not recommended.

RINVOQ is safe and effective in children 12 years of age and older weighing at least 88 pounds (40 kg) with atopic dermatitis.

It is not known if RINVOQ is safe and effective in children under 18 years of age with juvenile idiopathic arthritis or with psoriatic arthritis.

It is not known if RINVOQ is safe and effective in children under 12 years of age with atopic dermatitis.

Do not take RINVOQ if you are allergic to upadacitinib or any of the ingredients in RINVOQ. See the end of this Medication Guide for a complete list of ingredients in RINVOQ.

Before taking RINVOQ, tell your healthcare provider about all of your medical conditions, including if you:

- See **"What is the most important information I should know about RINVOQ?"**
- have an infection.
- are a current or past smoker.
- have had a heart attack, other heart problems, or stroke.
- have liver problems.
- have kidney problems.
- have unexplained stomach (abdominal) pain, have a history of diverticulitis or ulcers in your stomach or intestines, or are taking NSAIDs.
- have low red or white blood cell counts.
- have recently received or are scheduled to receive an immunization (vaccine). People who take RINVOQ should not receive live vaccines.
- are pregnant or plan to become pregnant. Based on animal studies, RINVOQ may harm your unborn baby.

  Females who are able to become pregnant:
  - Your healthcare provider will check whether or not you are pregnant before you start treatment with RINVOQ.
  - You should use effective birth control (contraception) to avoid becoming pregnant during treatment with RINVOQ and for 4 weeks after your last dose of RINVOQ.
  - Tell your healthcare provider if you think you are pregnant or become pregnant during treatment with RINVOQ.
  - If you take RINVOQ during pregnancy, contact AbbVie Inc. at 1-800-633-9110, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch to provide information about the health of you and your baby.
- are breastfeeding or plan to breastfeed. RINVOQ may pass into your breast milk. You and your healthcare provider should decide if you will take RINVOQ or breastfeed. **Do not** breastfeed during treatment with RINVOQ and for 6 days after your last dose of RINVOQ.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. RINVOQ and other medicines may affect each other causing side effects.

Especially tell your healthcare provider if you take:

- medicines for fungal infections (such as ketoconazole, itraconazole, posaconazole or voriconazole) or clarithromycin (for bacterial infections) as these medicines may increase the amount of RINVOQ in your blood.
- rifampicin (for bacterial infections) or phenytoin (for neurological disorders) as these medicines may decrease the effect of RINVOQ.
- medicines that affect your immune system (such as azathioprine and cyclosporine) as these medicines may increase your risk of infection.

Ask your healthcare provider or pharmacist, if you are not sure if you are taking any of these medicines. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take RINVOQ?

- Take RINVOQ exactly as your healthcare provider tells you to use it.
- Take RINVOQ 1 time a day with or without food.
- Swallow RINVOQ tablets whole. Do not split, crush, or chew the tablets.
- If you take too much RINVOQ, call your healthcare provider or poison control center at 1-800-222-1222, or go to the nearest hospital emergency room right away.

What are the possible side effects of RINVOQ?

RINVOQ may cause serious side effects, including:

- See **"What is the most important information I should know about RINVOQ?"**

The most common side effects of RINVOQ in people treated for rheumatoid arthritis and psoriatic arthritis include:

- upper respiratory tract infections (common cold, sinus infections)
- shingles (herpes zoster)
- herpes simplex virus infections, including cold sores
- bronchitis
- nausea
- cough
- fever
- acne

The most common side effects of RINVOQ in people treated for atopic dermatitis include:

- upper respiratory tract infections (common cold, sinus infections)
- acne
- herpes simplex virus infections, including cold sores
- headache
- increased blood levels of creatine phosphokinase
- cough
- allergic reactions
- inflammation of hair follicles
- nausea
- stomach-area (abdominal) pain
- fever
- increased weight
- shingles (herpes zoster)
- flu
- tiredness
- low white blood cell count (neutropenia)
- muscle pain
- flu-like illness

Separation or tear to the lining of the back part of the eye (retinal detachment) has happened in people with atopic dermatitis treated with RINVOQ. Call your healthcare provider right away if you have any sudden changes in your vision during treatment with RINVOQ.

These are not all the possible side effects of RINVOQ.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store RINVOQ?

- Store RINVOQ at 36°F to 77°F (2°C to 25°C).
- Store RINVOQ in the original bottle to protect it from moisture.
- **Keep RINVOQ and all medicines out of the reach of children.**

General information about the safe and effective use of RINVOQ.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use RINVOQ for a condition for which it was not prescribed.

Do not give RINVOQ to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about RINVOQ that is written for health professionals.

What are the ingredients in RINVOQ 15 mg tablets?

Active ingredient: upadacitinib

Inactive ingredients: colloidal silicon dioxide, ferrosoferric oxide, hypromellose, iron oxide red, magnesium stearate, mannitol, microcrystalline cellulose, polyvinyl alcohol, polyethylene glycol, talc, tartaric acid and titanium dioxide.

What are the ingredients in RINVOQ 30 mg tablets?

Active ingredient: upadacitinib

Inactive ingredients: colloidal silicon dioxide, hypromellose, iron oxide red, magnesium stearate, mannitol, microcrystalline cellulose, polyvinyl alcohol, polyethylene glycol, talc, tartaric acid and titanium dioxide.

Manufactured by: AbbVie Ireland NL B.V., Sligo, Ireland
Packed and Distributed by: AbbVie Inc., North Chicago, IL 60064

For more information, call 1-800 2-RINVOQ (1-800-274-6867) or go to www.RINVOQ.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: 1/2022

20066213

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211675Orig1s004

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

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	(b) (4)
Applicant Proposed Indication(s)/Population(s)	(b) (4)
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.

Table of Contents

Table of Tables

Table of Figures

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Craig Johnson, PharmD
Clinical Pharmacology Reviewer	Soo Hyeon Shin, PharmD, PhD
Clinical Pharmacology Team Leader	Chinmay Shukla, PhD
Pharmacometrics Reviewer	Yangbing Li, PhD
Pharmacometrics Team Leader	Jiang Liu, PhD
Clinical Reviewer	Tong Li-Masters, MD, PhD
Clinical Team Leader	Snezana Trajkovic, MD
Statistical Reviewer	Matthew Guerra, PhD
Statistical Team Leader	Mohamed Alosh, PhD
Cross-Disciplinary Team Leader	Snezana Trajkovic, MD
Division Director (OB)	Laura Lee Johnson, PhD
Office Director (or designated signatory authority)	Kendall Marcus, MD

Additional Reviewers of Application

OPDP	Laurie Buonaccorsi, PharmD
DMPP	Jessica Chung, PharmD, MS
OSI	Phil Phuc Nguyen, MD
DPMH	Christos Mastroyannis, MD
OSE/DMEPA	Madhuri Patel, PharmD

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

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Soo Hyeon Shin, PharmD, PhD	OTS/OCP/DIIP	Section: 6, 18.4	**Select one:** _X_ Authored ___ Approved
	Signature: Please see signature in DARRTS			
Clinical Pharmacology Team Leader	Chinmay Shukla, PhD	OTS/OCP/DIIP	Section: 6, 18.4	**Select one:** ___ Authored _X_ Approved
	Signature: Please see signature in DARRTS			
Pharmacometrics Reviewer	Yangbing Li, PhD	OTS/OCP/DPM	Section: 6, 18.4	**Select one:** _X_ Authored ___ Approved
	Signature: Please see signature in DARRTS			
Pharmacometrics Team Leader	Jiang Liu, PhD	OTS/OCP/DPM	Section: 6, 18.4	**Select one:** ___ Authored _X_ Approved
	Signature: Please see signature in DARRTS			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Tong Li-Masters, MD, PhD	OND/OII/DDD	Sections: 1, 2, 3, 4, 5, 7, 8.2, 8.3.2, 9, 10, 11, 12, 13, 18.1, 18.2, 18.6	**Select one:** _X__ Authored ___ Approved
	Signature: Please see signature in DARRTS			
Clinical Team Leader	Snezana Trajkovic, MD	OND/OII/DDD	Sections: 1, 2, 3, 4, 5, 7, 8.2, 8.3.2, 9, 10, 11, 12, 13, 18.1, 18.2, 18.6	**Select one:** ___ Authored _X_ Approved
	Signature: Please see signature in DARRTS			
Statistical Reviewer	Matthew Guerra, PhD	OTS/OB/DBIII	Sections: 8.1, 8.3, 18.5	**Select one:** _X_ Authored ___ Approved
	Signature: Please see signature in DARRTS			
Statistical Team Leader	Mohamed Alosh, PhD	OTS/OB/DBIII	Sections: 8.1, 8.3, 18.5	**Select one:** ___ Authored _X_ Approved
	Signature: Please see signature in DARRTS			
Division Director (OB)	Laura Lee Johnson, PhD	OTS/OB/DBIII	Sections: 8.1, 8.3, 18.5	**Select one:** ___ Authored _X_ Approved
	Signature: Please see signature in DARRTS			
Division Director (Clinical)	Kendall Marcus, MD	OND/OII/DDD	Sections: All	**Select one:** ___ Authored _X_ Approved

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 treatment of (b) (4) (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.

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 the treatment of (b) (4) (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 (b) (4) (b) (4). 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, (b) (4)

The data on efficacy and safety for upadacitinib, in the treatment of moderate to severe AD in patients 12 years of age and older, 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 and patients ≥65 years of age. 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, some Council members recommended approving only the 15 mg dose, whereas others supported approving the 30 mg dose in this population, if needed. 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: ○ 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. ○ 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 (b) (4)

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. (b) (4) [redacted] • 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	(b) (4) [redacted] (b) (4) [redacted]. 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 defer submission of adolescent data until after submission of an sNDA with adult data only, citing inability to enroll the planned number of adolescents in their Phase 3 trials. 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 excludes pediatric patients.
- 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 excludes pediatric patients. 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 only adult data for the NDA submission. 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.

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 of atopic dermatitis (AD) in adults and adolescents 12 years of age and older.

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	(b) (4) 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), limiting the dose to 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 with a film coating, 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 core composition 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 (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

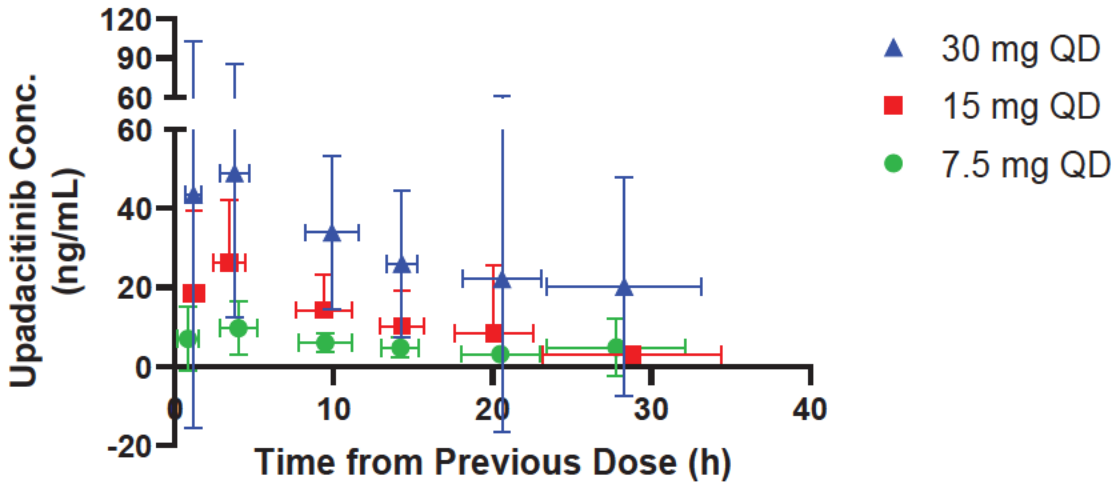
observed in clinical studies conducted under the original NDA submission and is stated in the currently approved RINVOQ labeling, plasma concentrations were analyzed by combining data from all visits. The mean upadacitinib plasma concentrations categorized by treatment group and time from previous dose 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

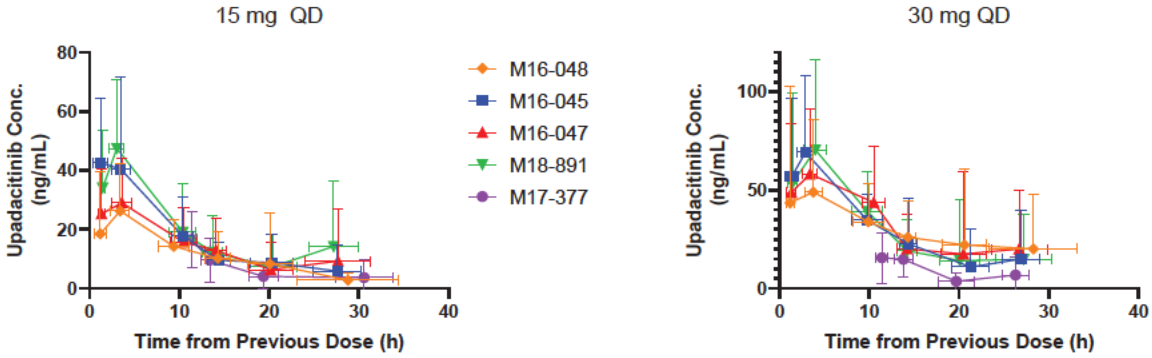
Table 7. Mean Plasma Upadacitinib Concentrations Categorized by Treatment Group and Time from Previous Dose from Study M17-377

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

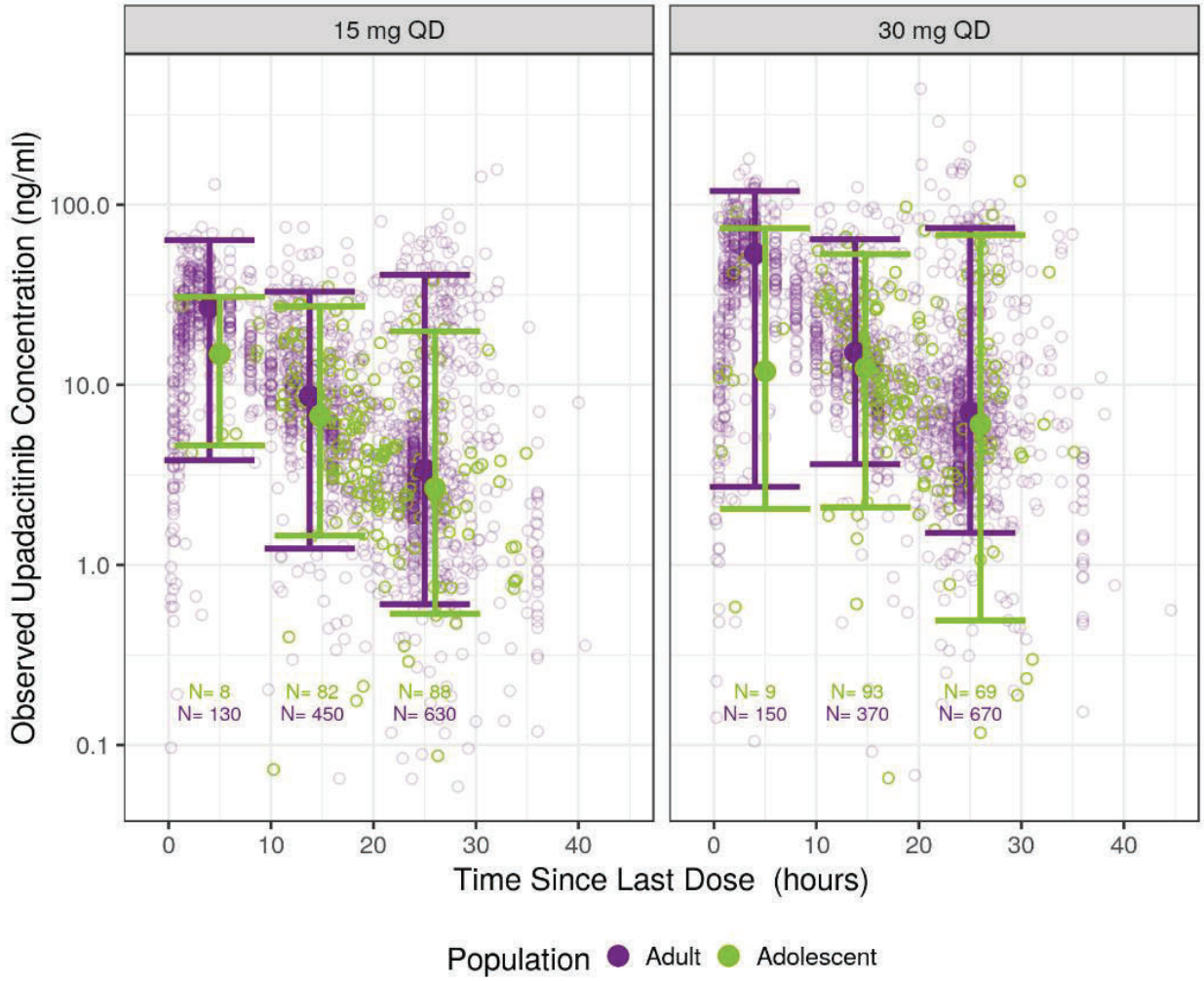
The recommendation is based on and is supported by the PK, efficacy and safety data obtained from the Phase 3 studies, as well as exposure-response analysis.

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.

(b) (4)

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.

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

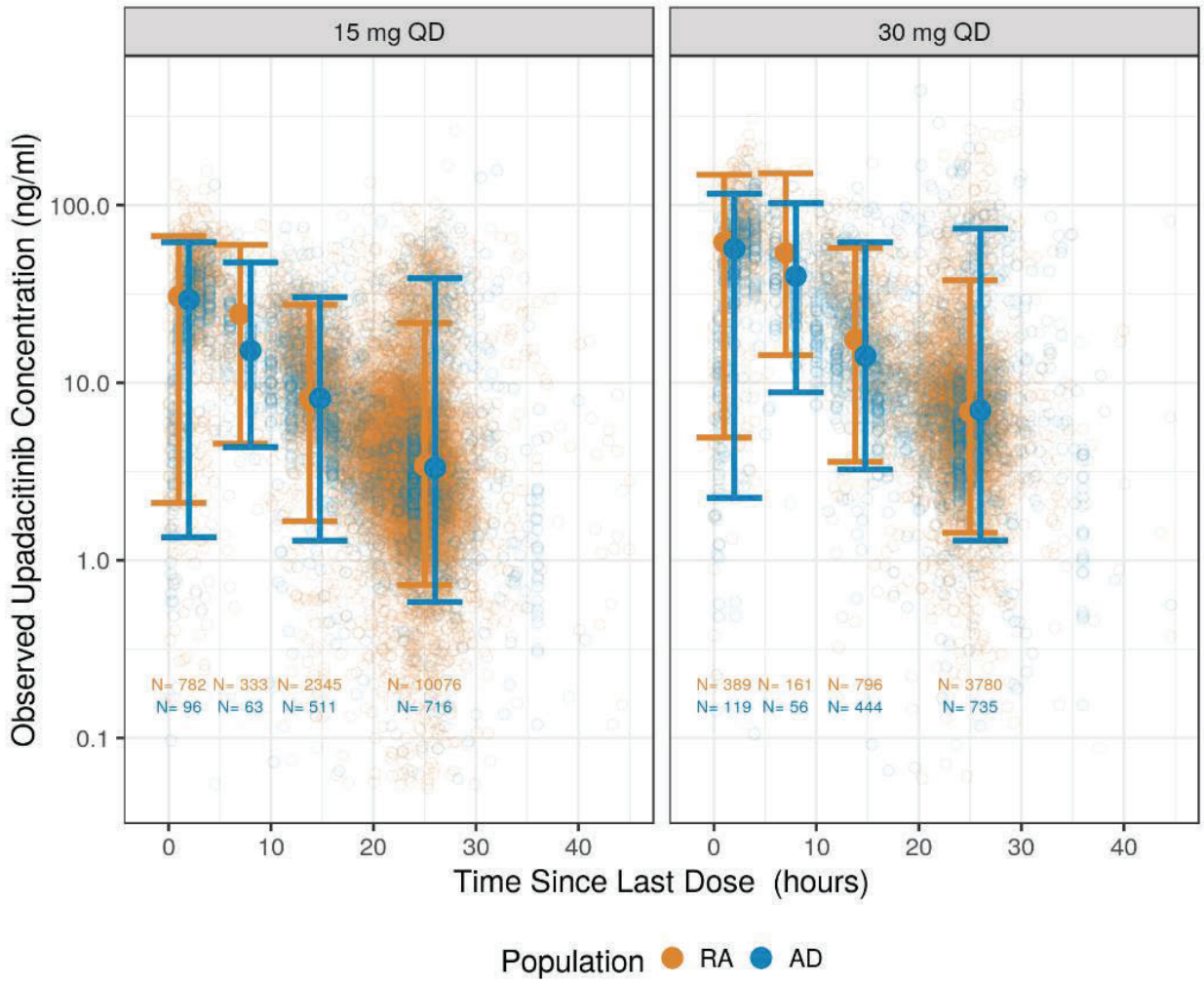


Purple circles represent observed upadacitinib concentrations from adult subjects (Studies M16-045, M16-047, M16-048, M17-377, M18-891). Green circles represent observed upadacitinib concentrations from adolescent subjects (Studies M16-045, M16-047, M17-377, M18-891). Closed circles and error bars represent 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

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.

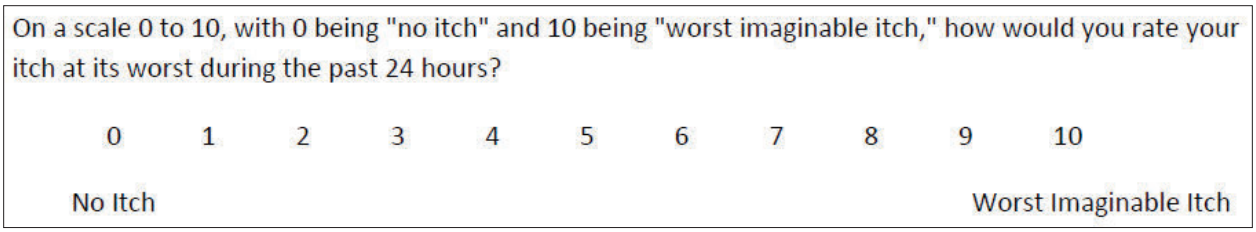
Table 14. Eczema Area and Severity Index (EASI)

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)



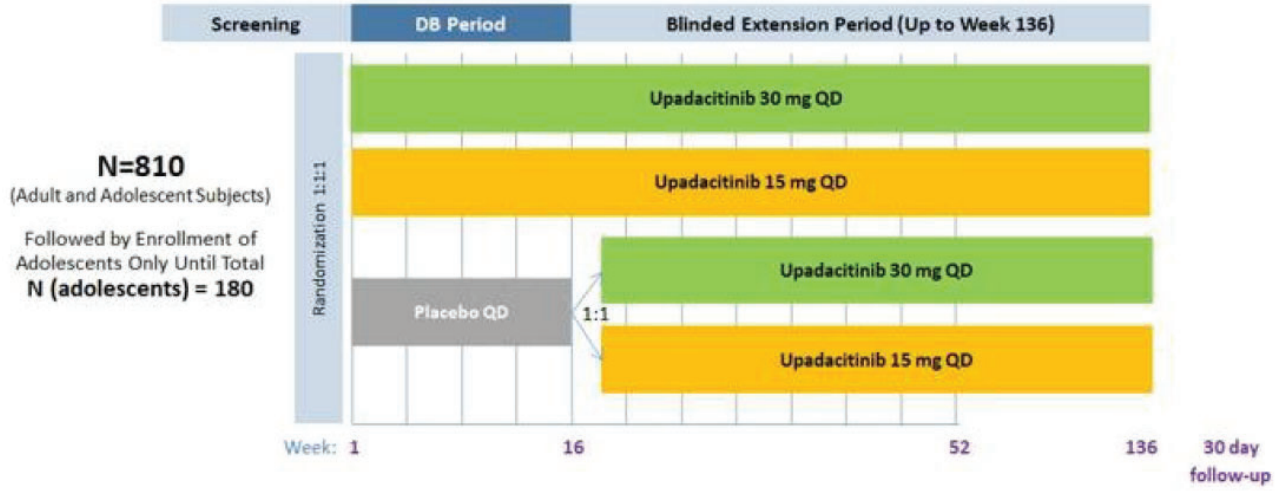
Source: page 120 of the protocol for Trial M16-045.

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

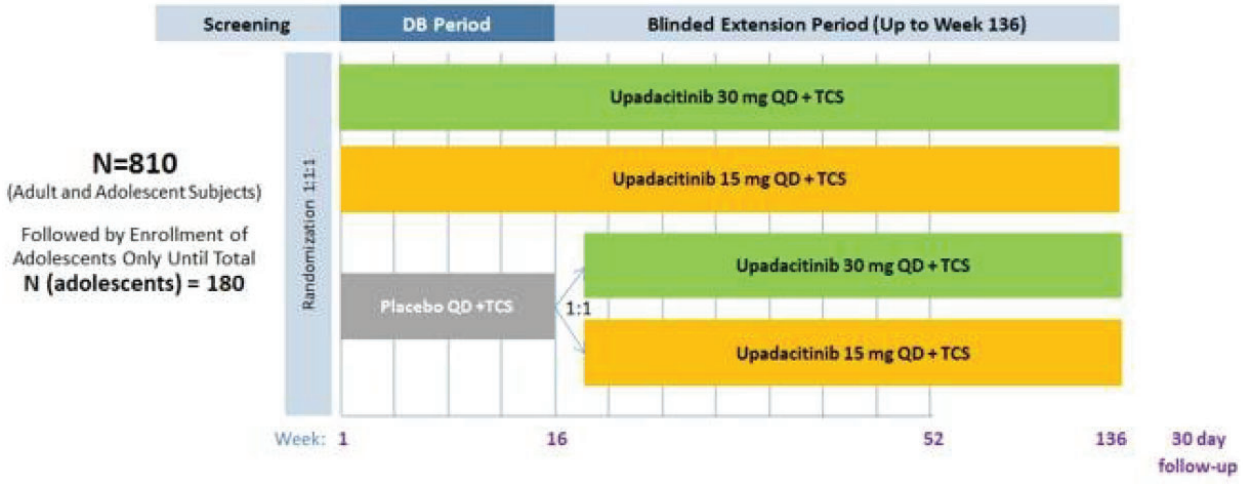
specified that subjects receiving rescue medications will be counted as nonresponders after the start of rescue medication for the primary analysis of the binary efficacy endpoints.

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

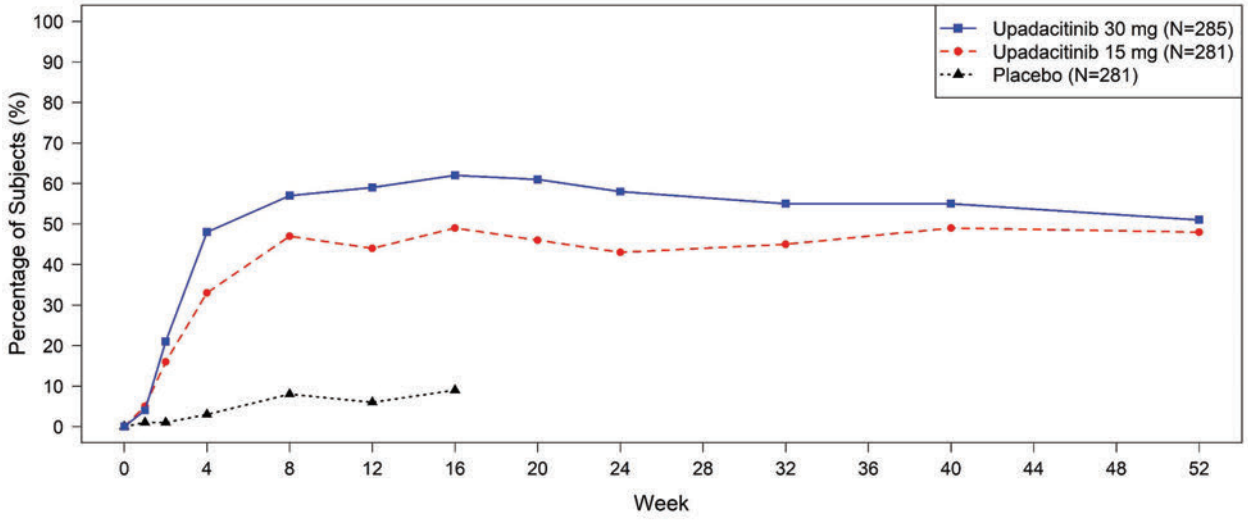
8.1.8. Efficacy Over Time

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.

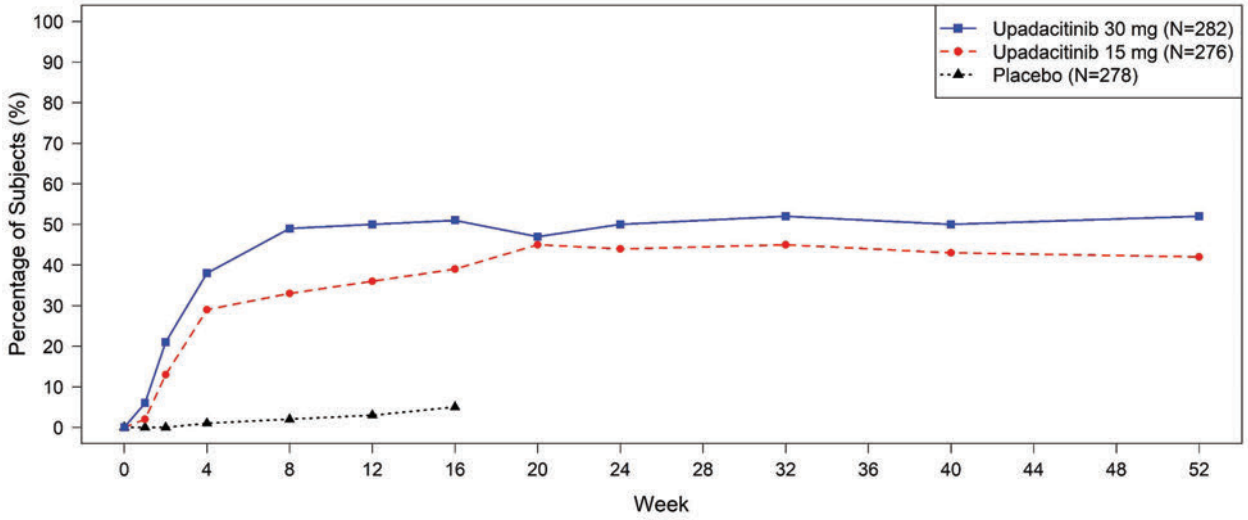
It should be noted that the original datasets (i.e., those submitted in the supplement on October 15, 2020) included data up to a specific cutoff date or a subject's Week 16 visit date, whichever was later. Therefore, in order evaluate efficacy up to Week 52, the Agency sent the Applicant an information 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])



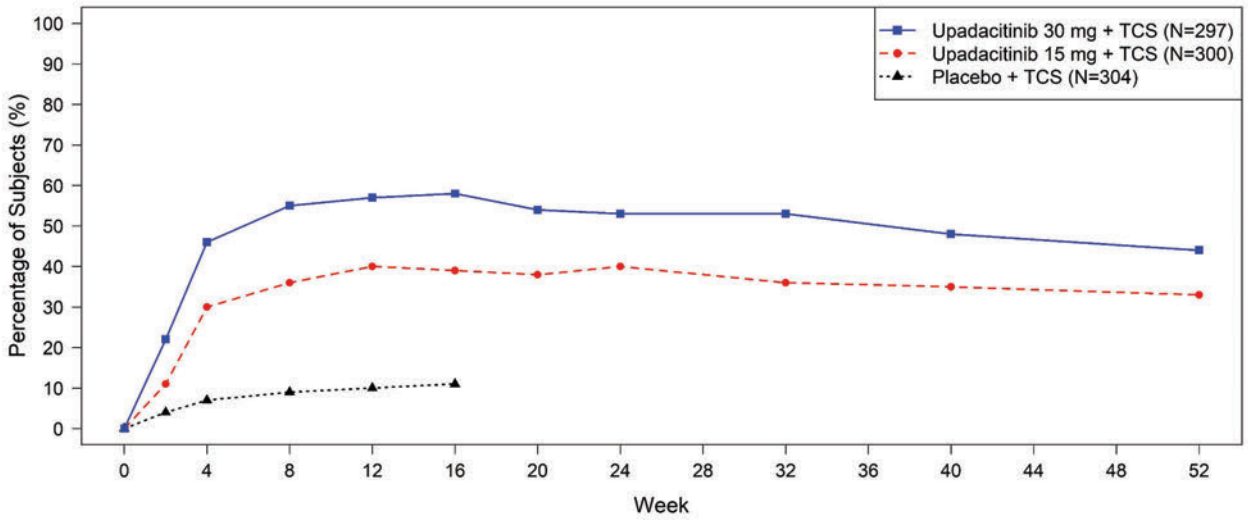
[1] Response was defined as a vIGA-AD score of 0 ("clear") or 1 ("almost clear") with at least a 2-grade reduction from baseline.
[2] ITT population: all randomized subjects. Missing data was imputed using NRI-NC.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADEFF.xpt (submitted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

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



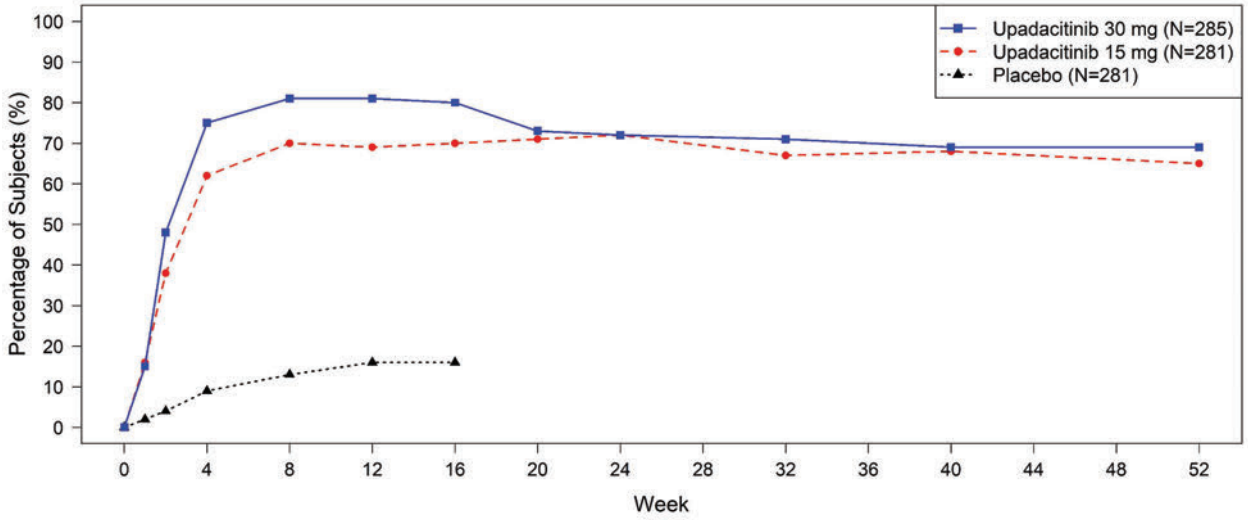
[1] Response was defined as a vIGA-AD score of 0 ("clear") or 1 ("almost clear") with at least a 2-grade reduction from baseline.
[2] ITT population: all randomized subjects. Missing data was imputed using NRI-NC.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADEFF.xpt (submitted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

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



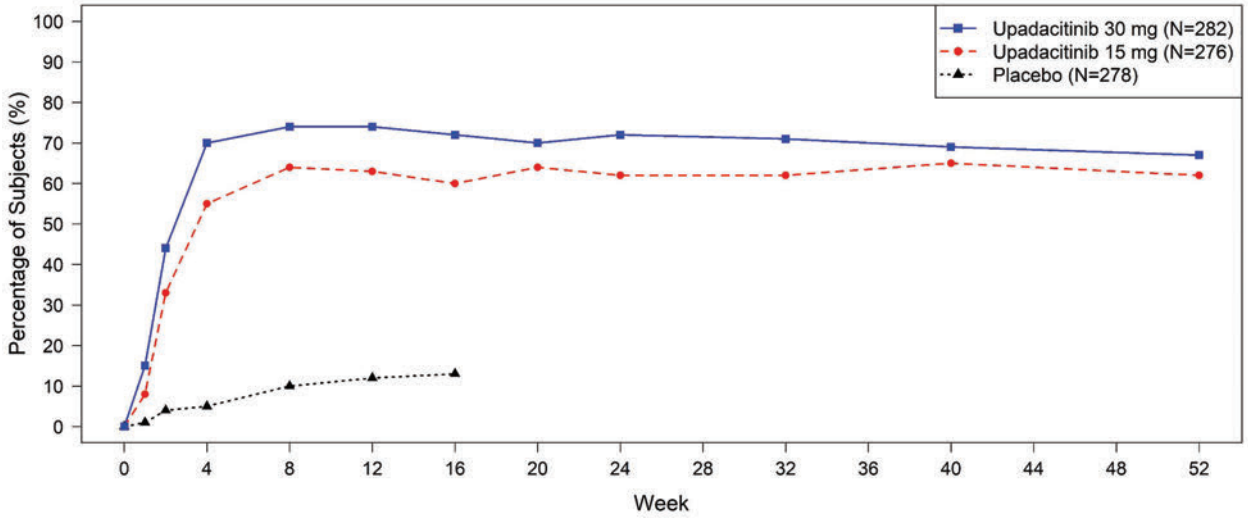
[1] Response was defined as a vIGA-AD score of 0 ("clear") or 1 ("almost clear") with at least a 2-grade reduction from baseline.
[2] ITT population: all randomized subjects. Missing data was imputed using NRI-NC.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADEFF.xpt (submitted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

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



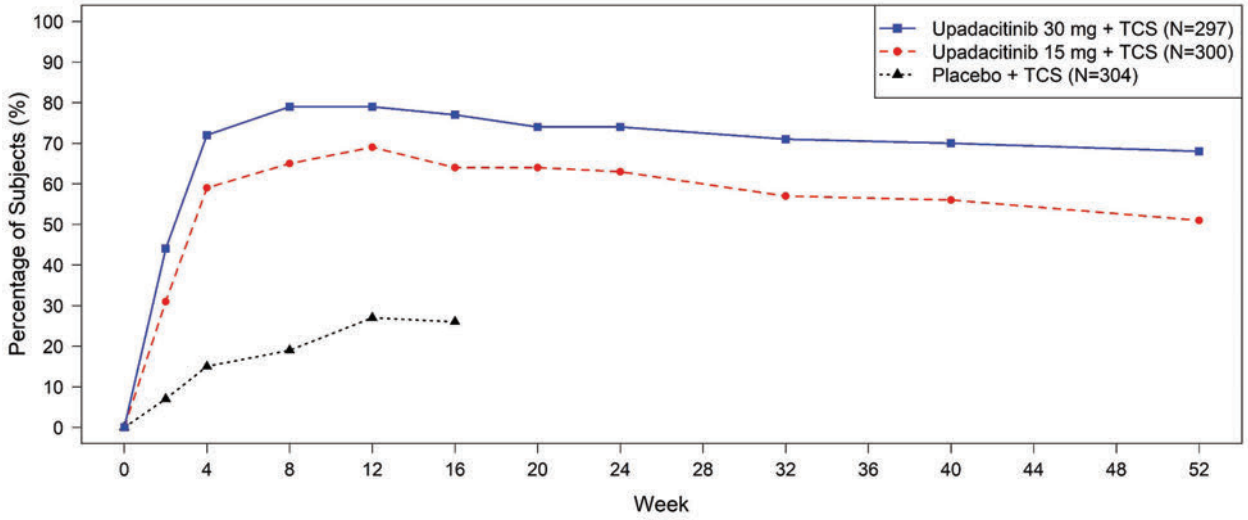
[1] ITT population: all randomized subjects. Missing data was imputed using NRI-NC.
Source: Statistical Reviewer's analysis (same as Applicant's analysis); ADEFF.xpt (submitted on June 22, 2021)

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%	52%	-	31%	62%
		(34%, 49%)	(45%, 59%)		(14%, 47%)	(45%, 78%)
EASI-75	18%	69%	79%	8%	71%	83%
Difference (95% CI)	-	52%	61%	-	63%	75%
		(44%, 59%)	(54%, 68%)		(47%, 79%)	(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%	46%	-	40%	60%
		(27%, 40%)	(39%, 52%)		(22%, 57%)	(42%, 77%)
EASI-75	13%	59%	73%	14%	67%	74%
Difference (95% CI)	-	46%	60%	-	53%	61%
		(39%, 54%)	(52%, 67%)		(33%, 72%)	(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 = upadacitinib
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 upadacitinib.
† 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 [redacted]/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.

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

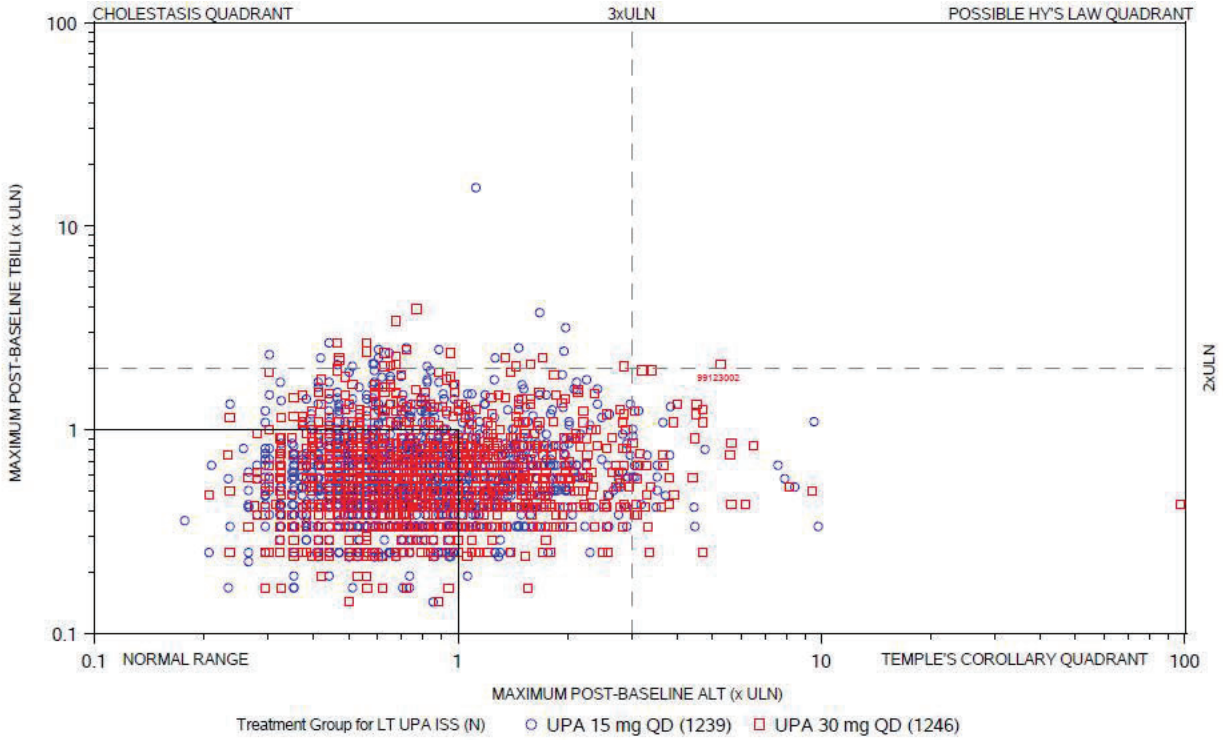
Source: SUR Table 19.

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 (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.

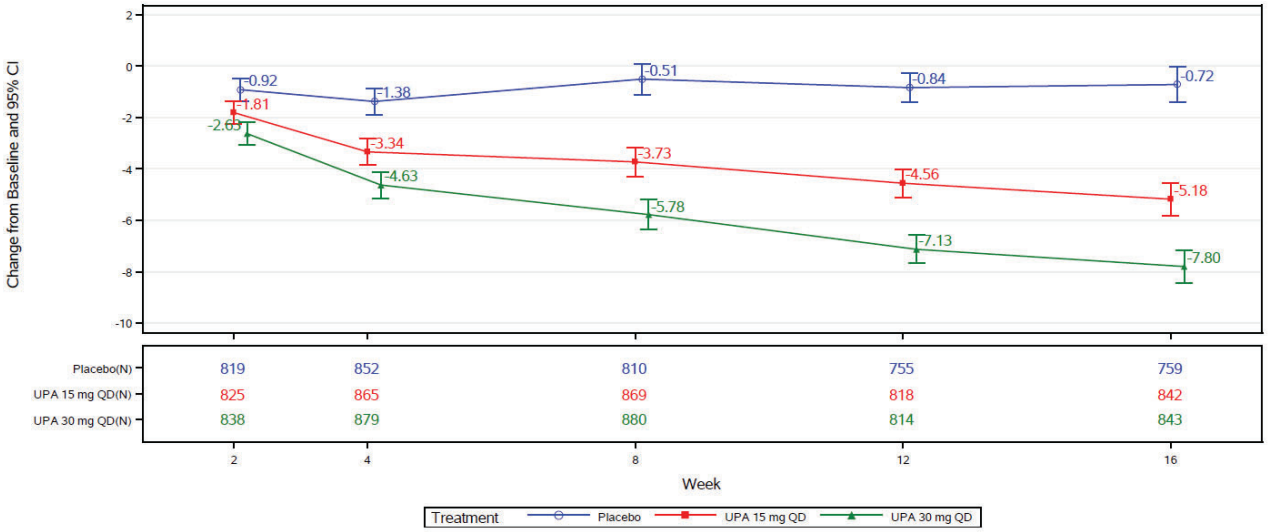
This reviewer assesses that although these subjects had significant medical co-morbidities, upadacitinib cannot be completely excluded as a cause or contributor of these MACE events.

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)

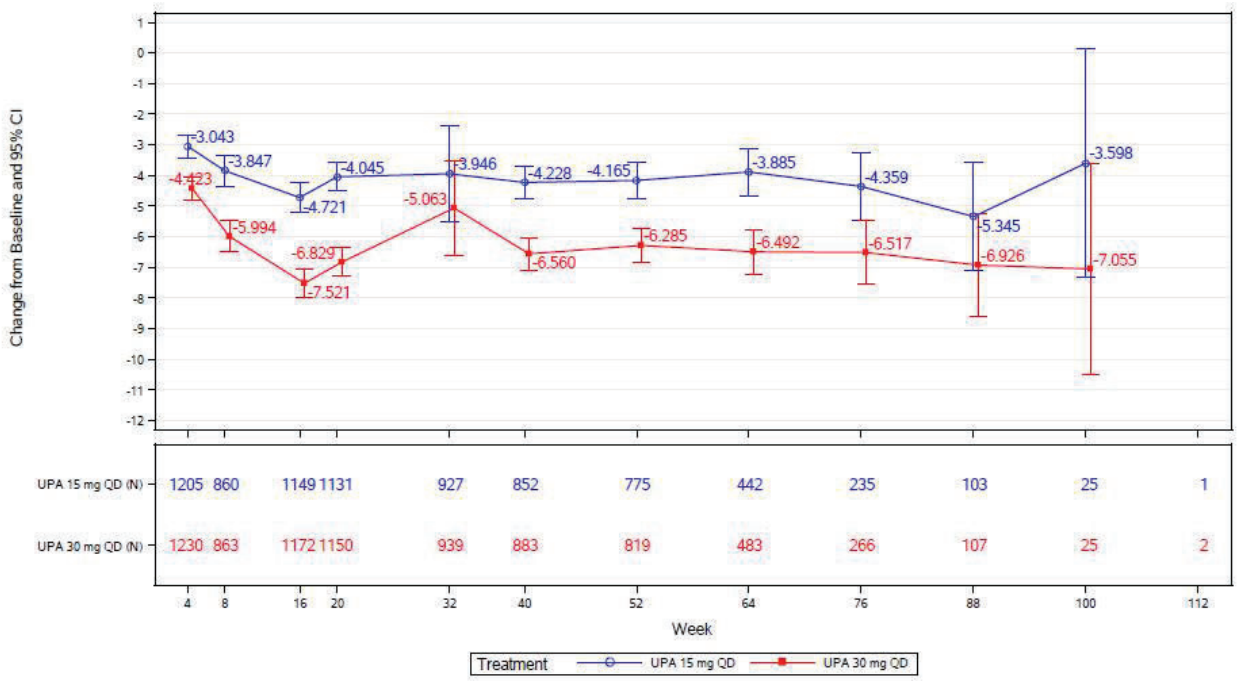
	Overall Population			Adolescent Population		
	Placebo (N=902) n (%)	UPA 15 mg (N=899) n (%)	UPA 30 mg (N=906) n (%)	Placebo (N=115) n (%)	UPA 15 mg (N=114) n (%)	UPA 30 mg (N=114) n (%)
Any adverse event	4 (0.4)	3 (0.3)	13 (1.4)	0	1 (0.9)	0
Anaemia	2 (0.2)	2 (0.2)	9 (1.0)	0	0	0
Iron deficiency anaemia	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-[redacted] (b) (6) 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.

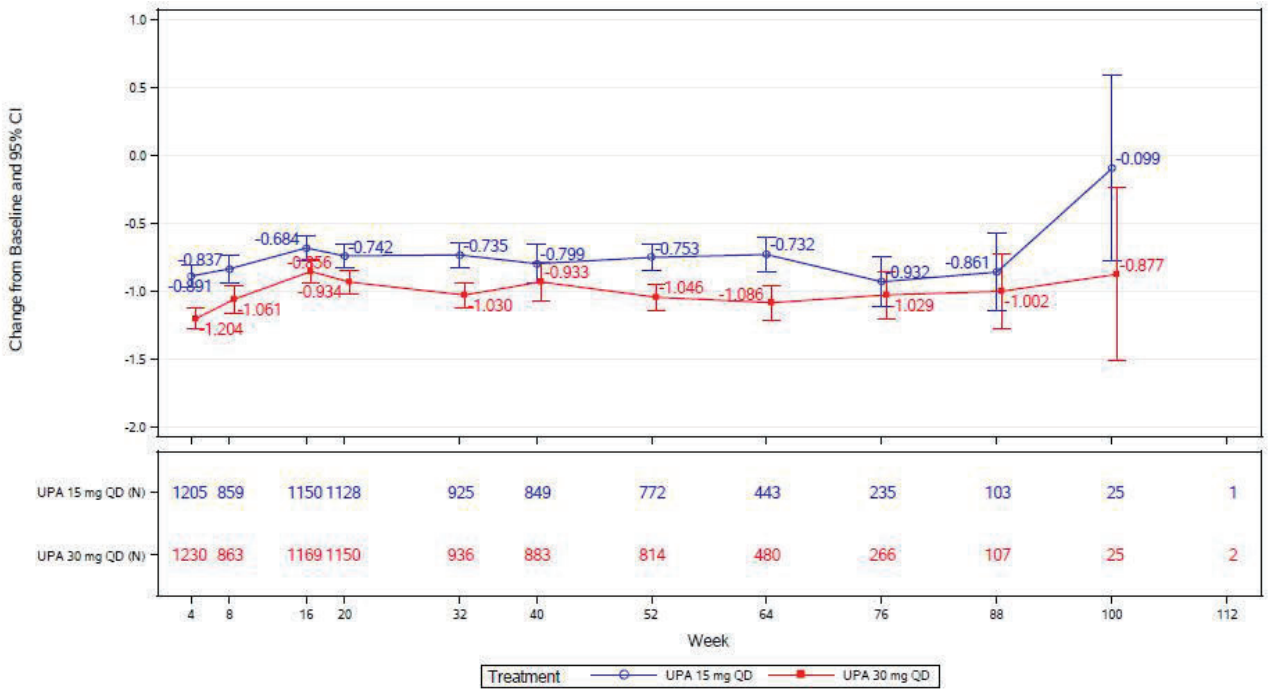
Table 60. Number and Percentage of Subjects with Treatment-Emergent Neutropenia (Placebo-Controlled AD Analysis Set)

	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.

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.

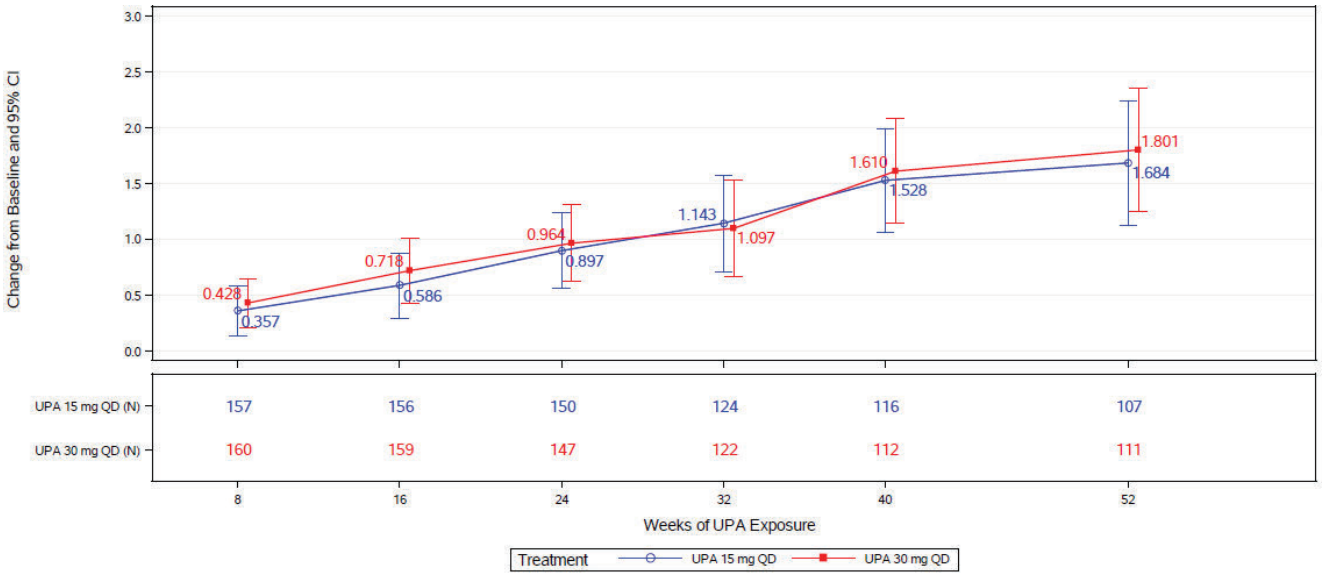
Reviewer's Comments:
This reviewer agrees that there was a dose-dependent association of weight gain with upadacitinib treatment.

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 pregnancies)	-	-	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

<u>Pregnancy</u>

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 21,838 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.

(b) (4)

- A Growth Study Among Adolescents: Observational cohort study of growth in adolescents weighing at least 30 kg. Using prospective patient data collected by the ongoing TREatment of ATopic eczema (TREAT) Registry in Germany.
    - Upadacitinib vs other systemic treatments.
    - Adolescents will be followed from initiation of upadacitinib (or comparator systemic treatment) until they reach 18 years of age, reach maximum height, or disenroll from the study or TREAT registry;
    - An additional 6 years of study follow-up is planned after the completion of the enrollment period.

- Drug utilization study in Denmark:
    - To understand characteristics of patients with AD who initiate upadacitinib and evaluate prescribing patterns during routine clinical care.
    - The potential of off label use of upadacitinib in patients with AD who are <12 years old will also be evaluated. All patients to be followed for a minimum of one year after upadacitinib initiation.

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 treatment of (b) (4) (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 (b) (4) (b) (4) (b) (4) 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, (b) (4)

The data on efficacy and safety for upadacitinib, for the treatment of moderate to severe AD in patients 12 years of age and older, 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, some Council members recommended approving only the 15 mg dose, whereas others supported approving the 30 mg dose in this population, if needed. Based on the higher risk for serious adverse reactions in adults >65 years of age, 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 than 2 years of age based on the rationale that trials are "impossible or highly impractical", and a deferral of pediatric studies in patients 2- 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.

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.

12 Risk Evaluation and Mitigation Strategies (REMS)

REMS will not be required for this application.

13 Postmarketing Requirements and Commitment

(b) (4)

[redacted]

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.

14 Division Director (DHOT) Comments

Not applicable.

15 Division Director (OCP) Comments

Not applicable.

16 Division Director (OB) Comments

Not applicable.

17 Division Director (Clinical) Comments

18 Appendices

18.1. References

Bao, K. and R. L. Reinhardt (2015). "The differential expression of IL-4 and IL-13 and its impact on type-2 immunity." Cytokine **75**(1): 25-37.

Czarnowicki, T., H. He, J. G. Krueger and E. Guttman-Yassky (2019). "Atopic dermatitis endotypes and implications for targeted therapeutics." J Allergy Clin Immunol **143**(1): 1-11.

Eichenfield, L. F., W. L. Tom, T. G. Berger, A. Krol, A. S. Paller, K. Schwarzenberger, J. N. Bergman, S. L. Chamlin, D. E. Cohen, K. D. Cooper, K. M. Cordoro, D. M. Davis, S. R. Feldman, J. M. Hanifin, D. J. Margolis, R. A. Silverman, E. L. Simpson, H. C. Williams, C. A. Elmets, J. Block, C. G. Harrod, W. Smith Begolka and R. Sidbury (2014). "Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies." J Am Acad Dermatol **71**(1): 116-132.

Eichenfield, L. F., W. L. Tom, S. L. Chamlin, S. R. Feldman, J. M. Hanifin, E. L. Simpson, T. G. Berger, J. N. Bergman, D. E. Cohen, K. D. Cooper, K. M. Cordoro, D. M. Davis, A. Krol, D. J. Margolis, A. S. Paller, K. Schwarzenberger, R. A. Silverman, H. C. Williams, C. A. Elmets, J. Block, C. G. Harrod, W. Smith Begolka and R. Sidbury (2014). "Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis." J Am Acad Dermatol **70**(2): 338-351.

Leung, D. Y. and E. Guttman-Yassky (2014). "Deciphering the complexities of atopic dermatitis: shifting paradigms in treatment approaches." J Allergy Clin Immunol **134**(4): 769-779.

May, R. D. and M. Fung (2015). "Strategies targeting the IL-4/IL-13 axes in disease." Cytokine **75**(1): 89-116.

Shaw, T. E., G. P. Currie, C. W. Koudelka and E. L. Simpson (2011). "Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health." J Invest Dermatol **131**(1): 67-73.

Sidbury, R., D. M. Davis, D. E. Cohen, K. M. Cordoro, T. G. Berger, J. N. Bergman, S. L. Chamlin, K. D. Cooper, S. R. Feldman, J. M. Hanifin, A. Krol, D. J. Margolis, A. S. Paller, K. Schwarzenberger, R. A. Silverman, E. L. Simpson, W. L. Tom, H. C. Williams, C. A. Elmets, J. Block, C. G. Harrod, W. S. Begolka, L. F. Eichenfield and D. American Academy of (2014). "Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents." J Am Acad Dermatol **71**(2): 327-349.

Weidinger, S. and N. Novak (2016). "Atopic dermatitis." Lancet **387**(10023): 1109-1122.

Weston, W. L. and W. How. (2020, Accessed Sept. 15, 2020). "Atopic dermatitis (eczema): Pathogenesis, clinical manifestations, and diagnosis of atopic dermatitis." UpToDate, R. P. Dellavalle, M. L. Levy and J. Fowler, eds, from http://www.uptodate.com.

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

Study (N[a])	Phase/ Population	Upadacitinib Regimen(s), Formulation	Pharmacokinetic Sampling and Assessment Times[b]
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.

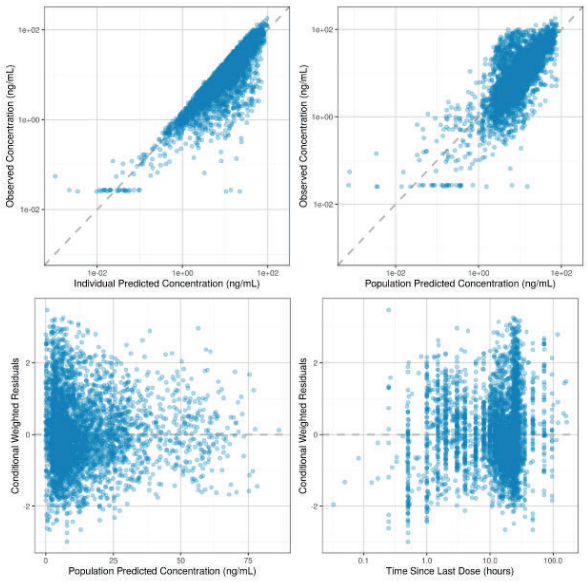
	Model Results		Bootstrap Results N = 430
Parameter	Population Estimate	Median	95% Confidence Interval
CL/F (L/h)	53.0	53.0	47.9 - 57.4
Vc/F (L)	145	148	111 - 192
KA (1/h)	0.0545	0.0545	0.0469 - 0.0699
Absorption Lag time (h)	0.232	0.232	0.219 - 0.242
Fraction of Dose Absorbed through Zero-Order Process (%)	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.

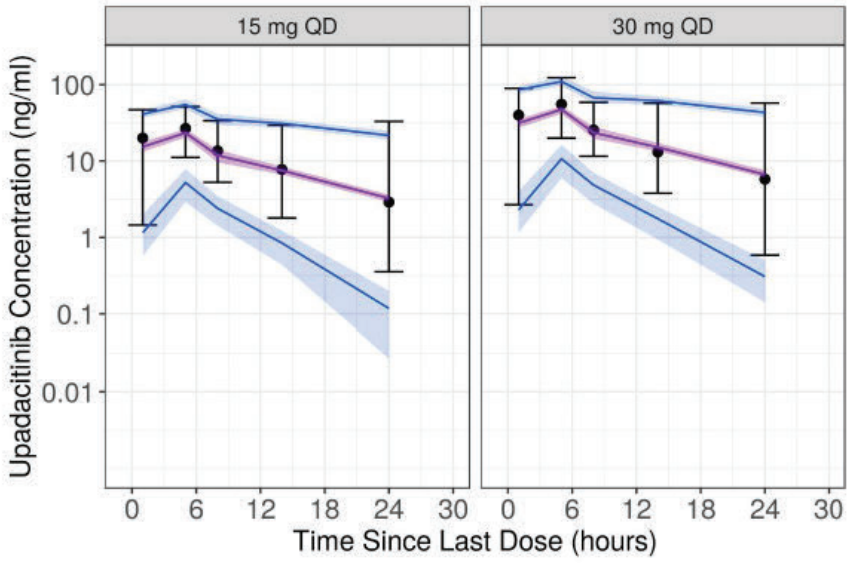
Goodness-of-fit plots for the final population PK model are shown in Figure 19. VPC (visual predictive check) stratified by dose and age groups (adolescents and adults) are shown in Figure 20 and Figure 21. The model described the observed data well and the model predictions were generally within the 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.

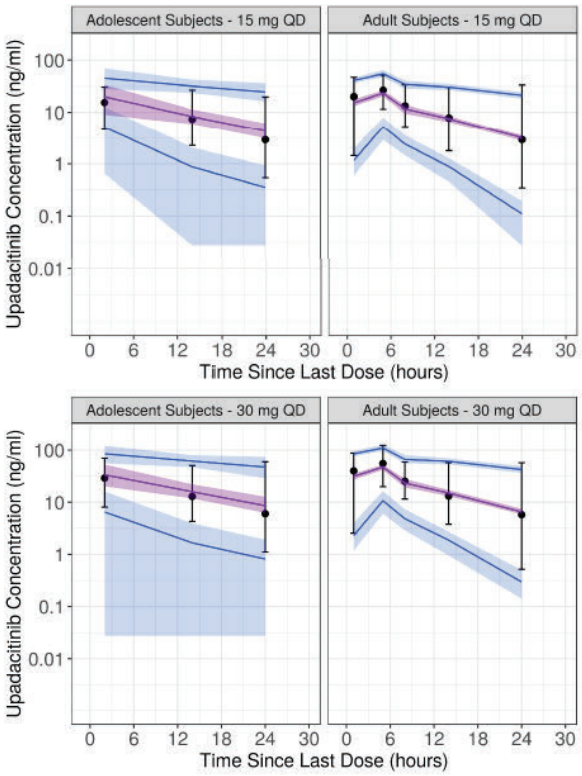
Figure 20. VPC for Subjects Receiving 15 mg QD and 30 mg QD.



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.

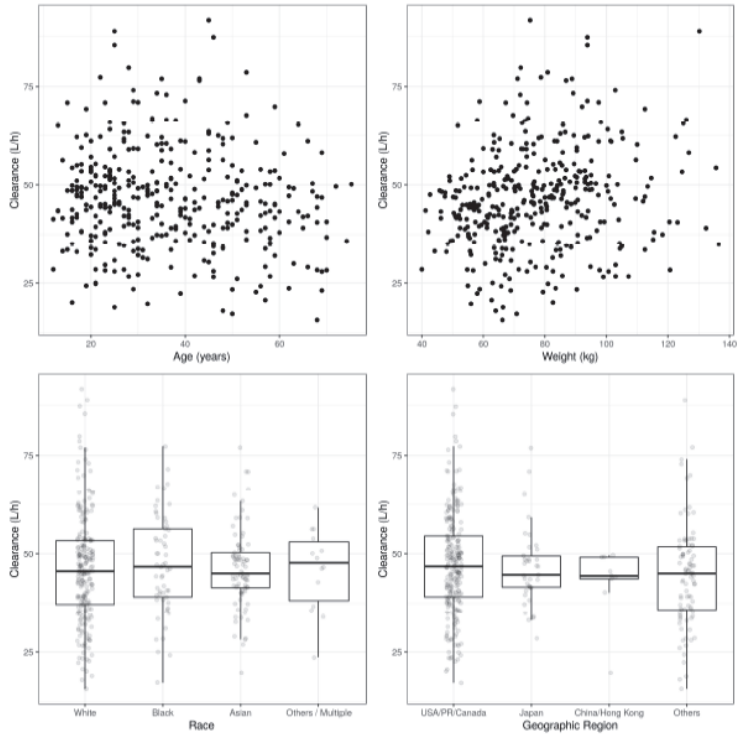


The shaded blue areas represent the 90% confidence interval of the 5th and 95th percentiles of simulated concentrations, the blue line represents median of the 5th and 95th percentiles of simulated concentrations; the shaded purple areas represent the 90% confidence interval of the 50th percentile of 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.

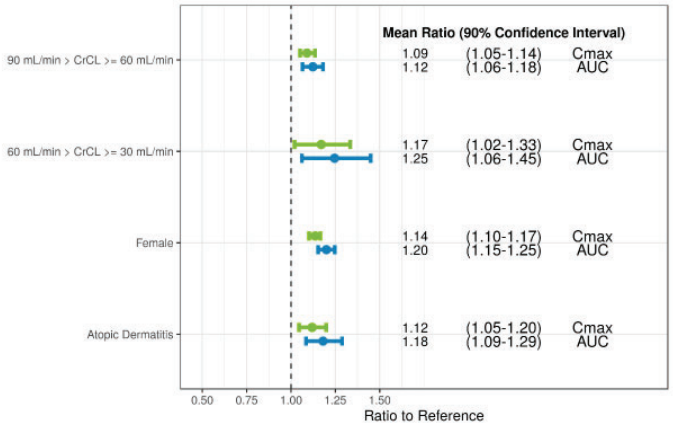
Figure 22. Effect of Intrinsic Factors on Upadacitinib CL/F.



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

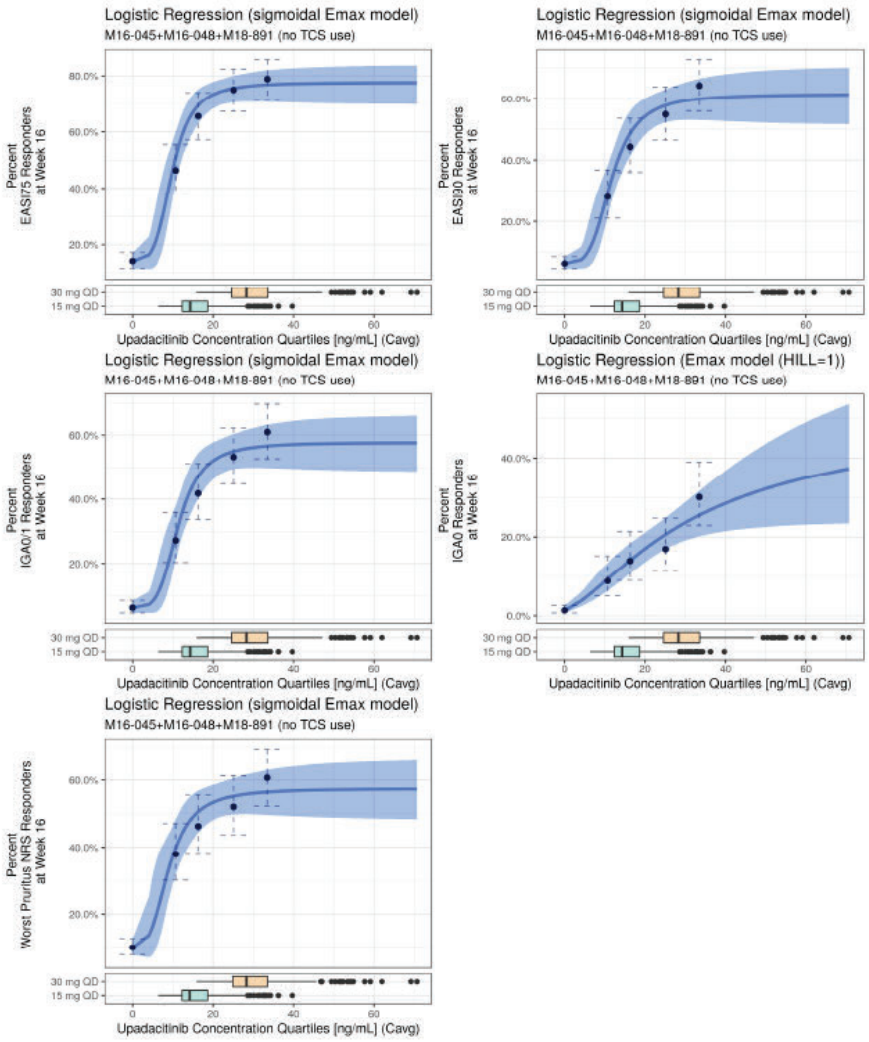
a. Disease duration was rounded to whole years.

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]



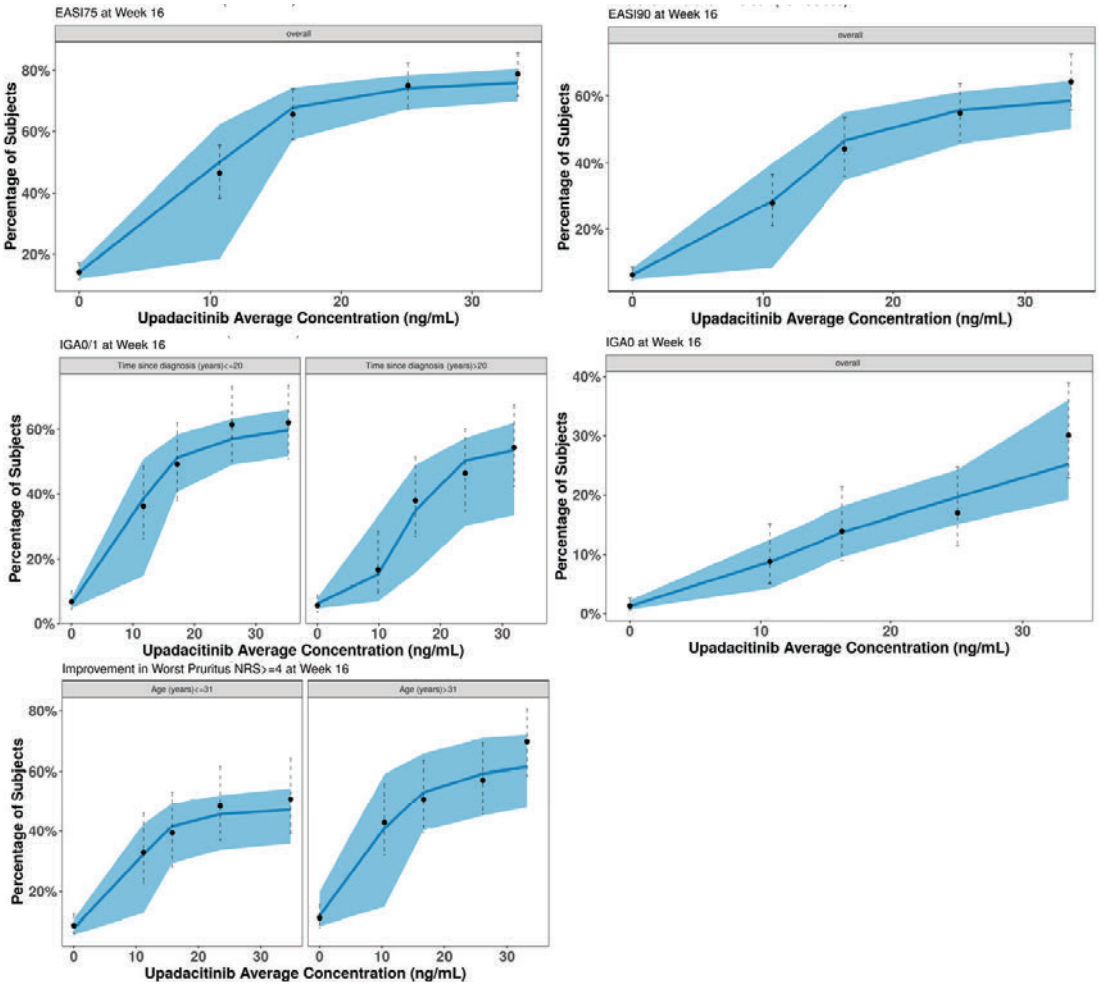
Source Exposure-Response Report R&D/20/0642, Page 33, Figure 6.

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.

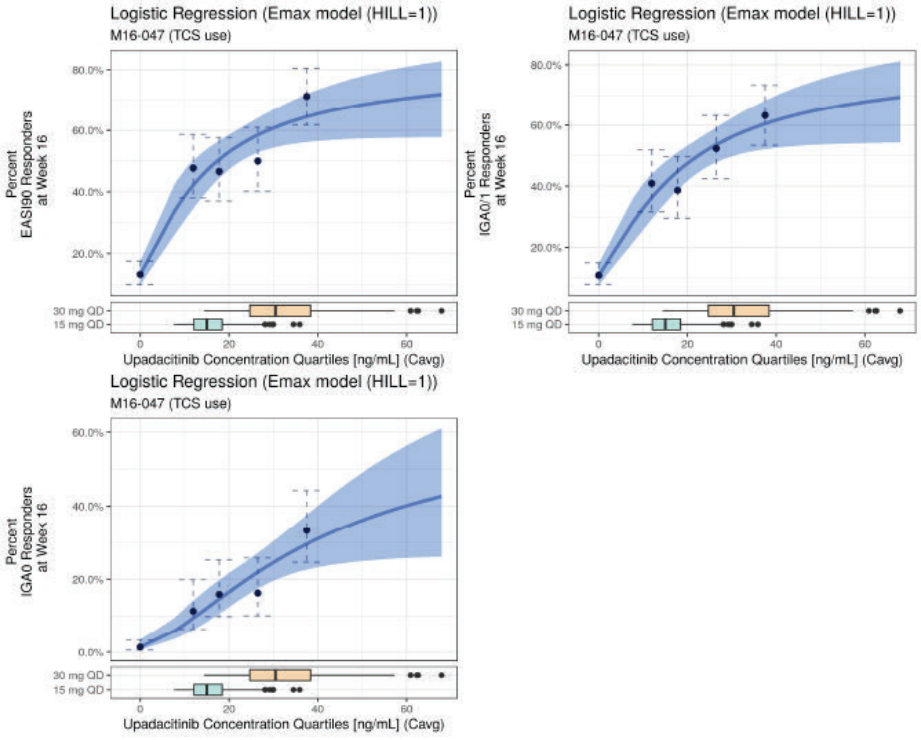
Clinical Efficacy Response Variable	Placebo	15 mg QD	30 mg QD
EASI 75	14% (11% – 18%)	63% (56% – 69%)	75% (67% – 81%)
EASI 90	6% (4% – 10%)	43% (34% – 50%)	57% (50% – 63%)
IGA 0/1	6% (4% – 9%)	41% (34% – 47%)	55% (46% – 62%)
IGA 0	1% (0% – 3%)	14% (10% – 18%)	23% (17% – 29%)
Improvement in Worst Pruritus 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.

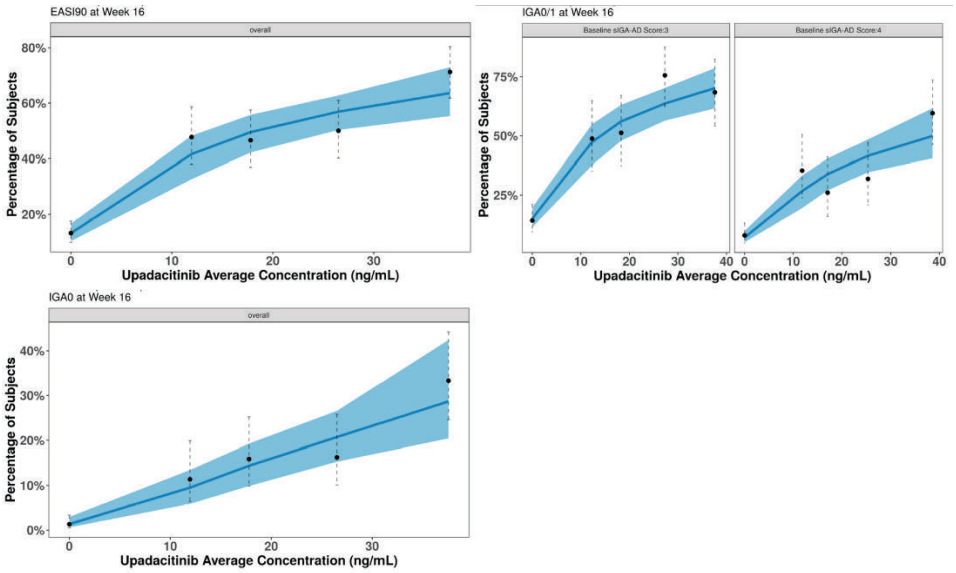
Table 98. Final Model Parameter Estimates for the Logistic Regression Exposure-Response Efficacy Models for Upadacitinib with TCS.

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.

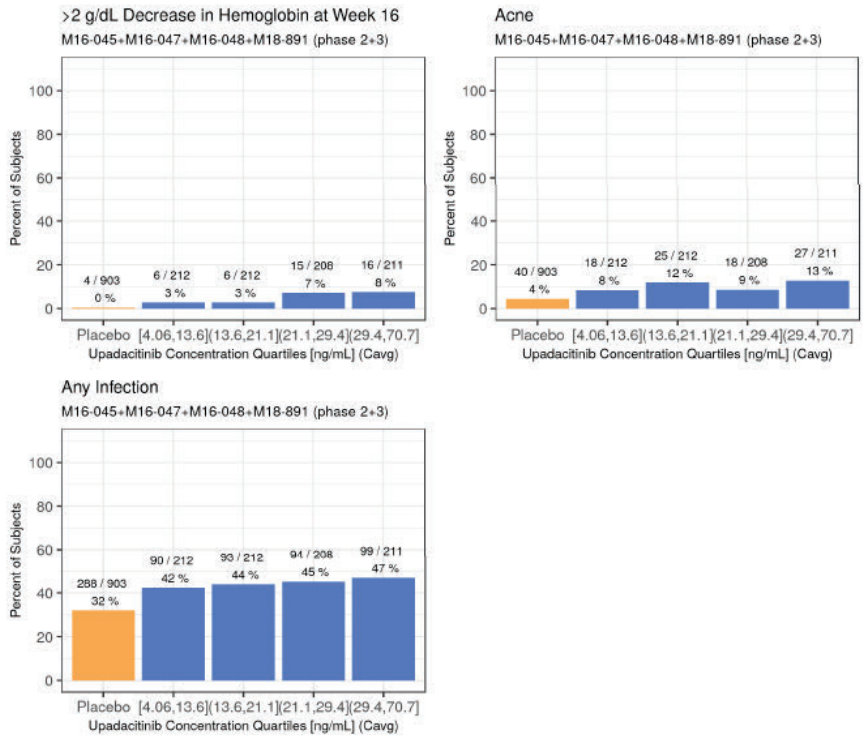
Study	Endpoint	Regimen	Clinical Response (%) per Overall Phase 3 Population	Clinical Response (%) per ER Analysis in Phase 3
M16-045	EASI75 at Week 16	Placebo	16.3	15.7
		15 mg QD	69.6	73.4
		30 mg QD	79.7	81.5
	EASI90 at Week 16	Placebo	8.1	7.8
		15 mg QD	53.1	58.5
		30 mg QD	65.8	61.7
	IGA0/1 at Week 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

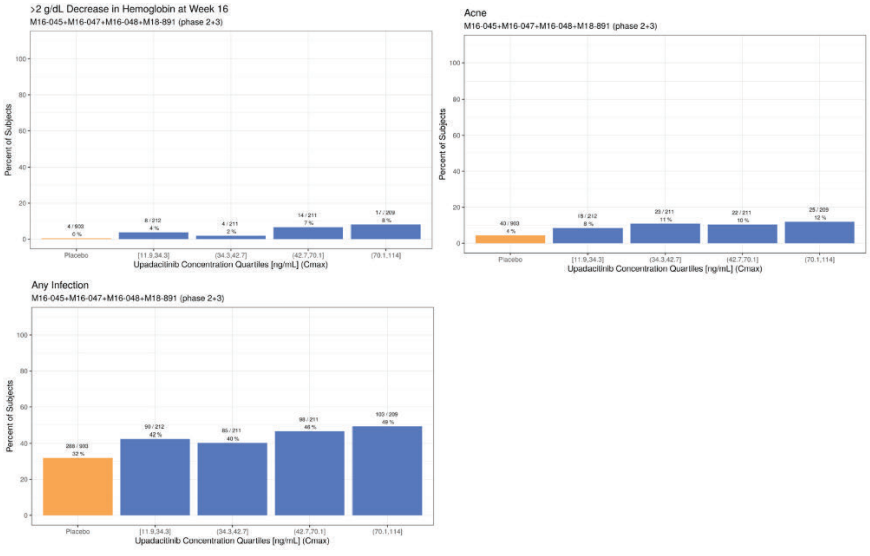
The relationship of selected safety endpoints (decrease in Hemoglobin > 2 g/dL from Baseline, any infection, and acne) and upadacitinib C_{avg} and C_{max} were shown in Figure 28 and Figure 29. No clear or marked trends for exposure-dependent relationships were observed between upadacitinib exposures 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

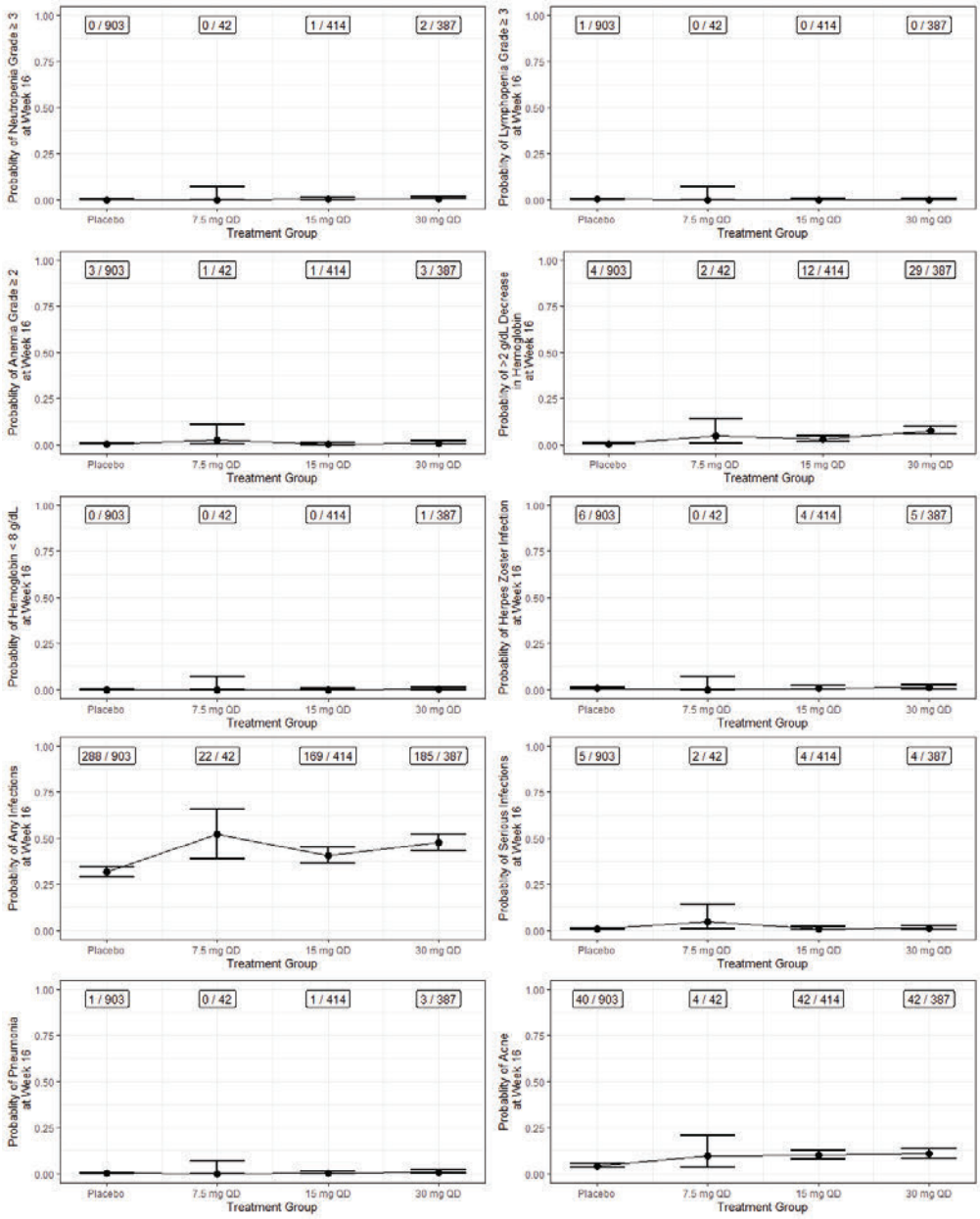


Source: Exposure-Response Report R&D/20/0642, Page 115-125, Figure 13.5_2.

Reviewer's comments:

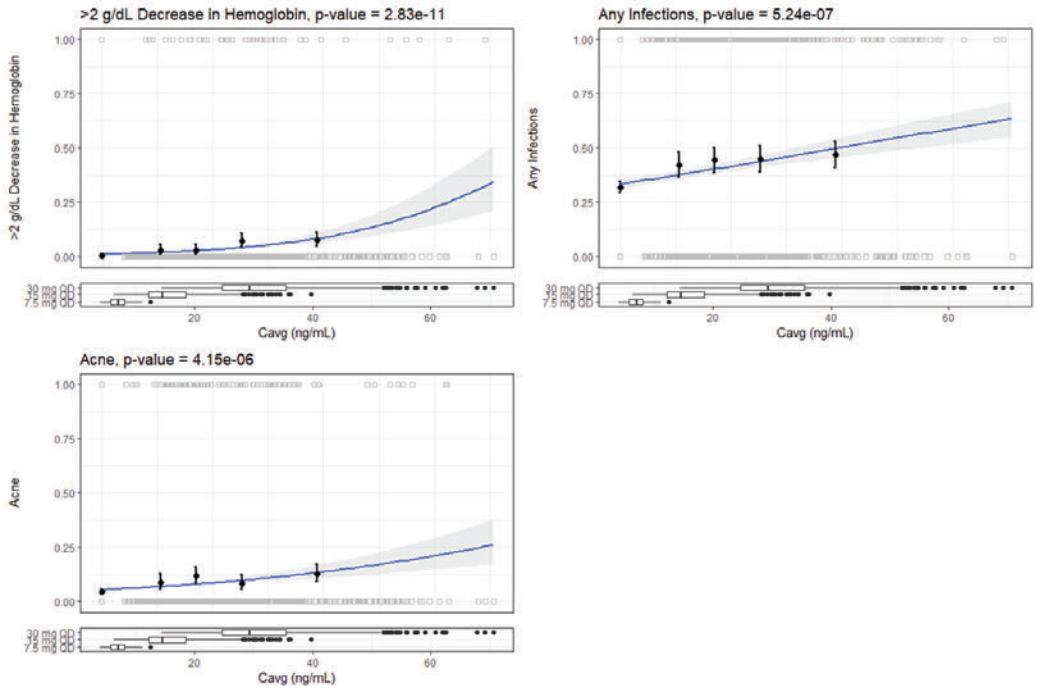
*As discussed in the exposure-responses efficacy analysis, the Demographic characteristics for subjects in exposure-response analysis were comparable with the overall study population. (*Table 100*) The results of Exposure-Response safety analysis for the selected safety endpoints were checked by the 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.



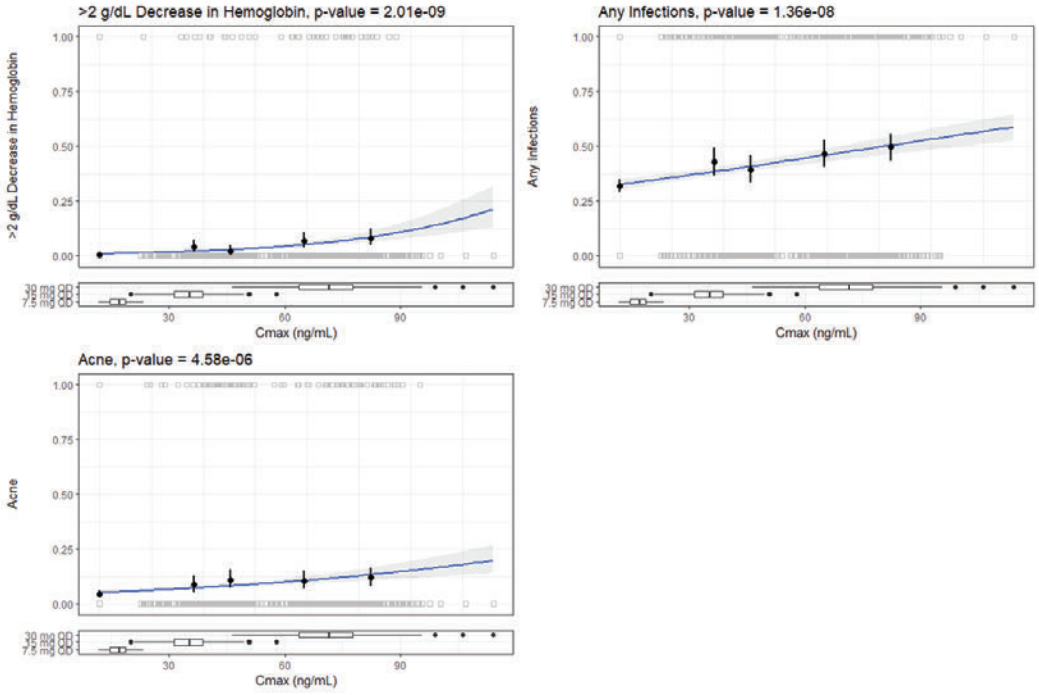
Source: Reviewer's analysis.

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	≤ 8.9%
Inter-assay for QCs	≤ 7.3%
Accuracy (% Mean Bias)	
Intra-assay for QCs	-4.4% to 8.7%
Inter-assay for QCs	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 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

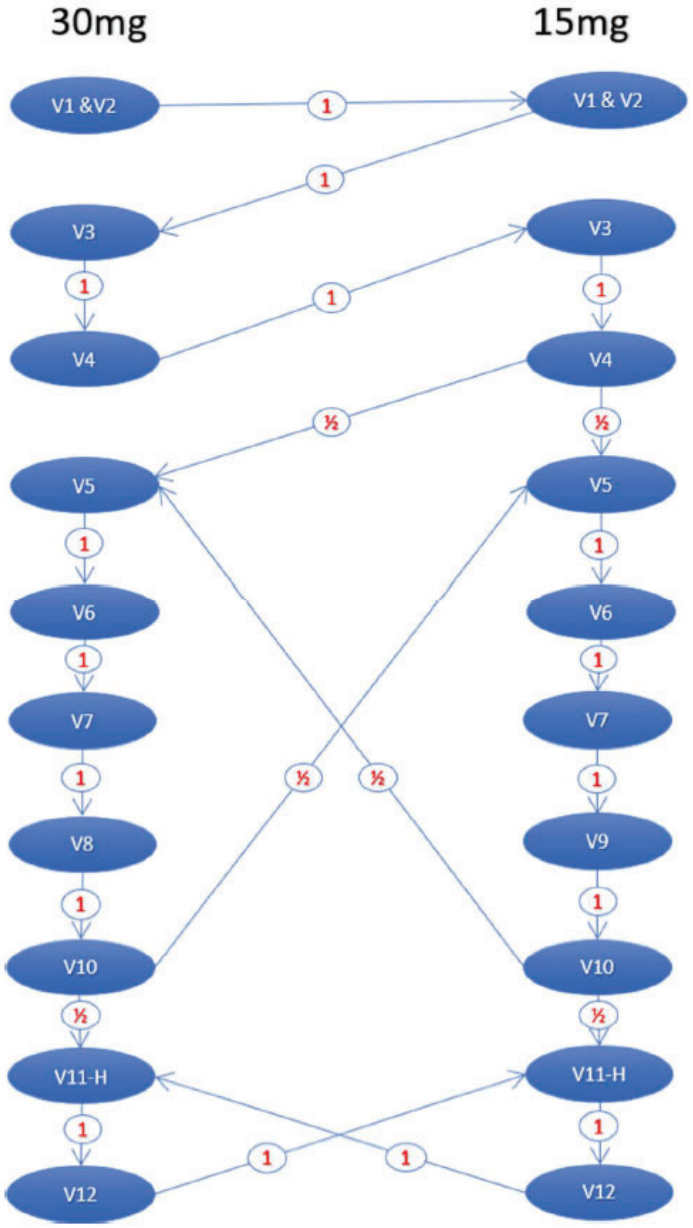
8. During the past 24 hours, how bad was your **worst rash (redness, blisters, bumpy skin)** due to AD?	No rash 0 1 2 3 4 5 6 7 8 9 10 Worst imaginable rash ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
9. During the past 24 hours, how bad was your **worst skin thickening** due to AD?	No skin thickening 0 1 2 3 4 5 6 7 8 9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



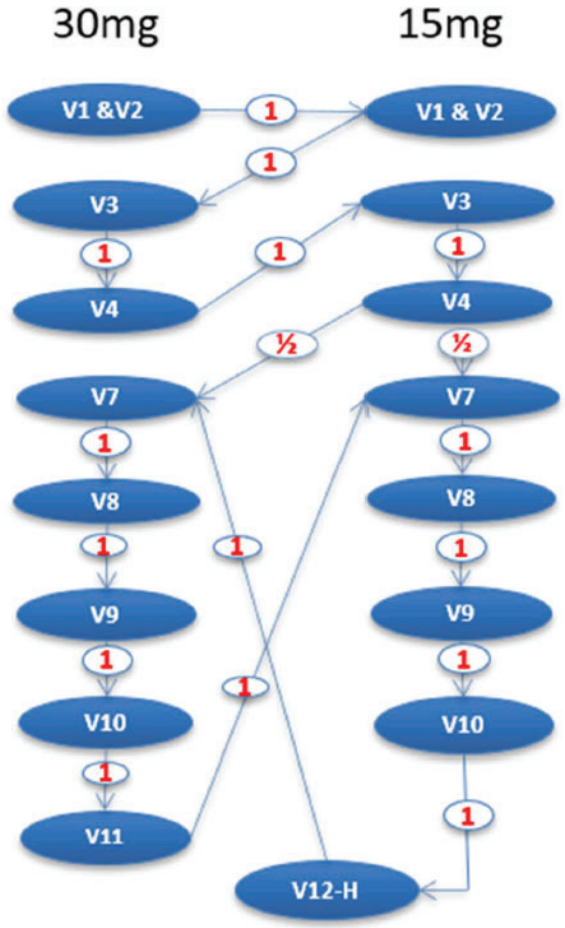
Source: page 19 of the SAP for Trial M16-045.

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%)

		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)
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])

		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)	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%)

		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)
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.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CRAIG H JOHNSON
01/13/2022 03:14:41 PM

SOO HYEON SHIN
01/13/2022 03:17:07 PM

YANGBING LI
01/13/2022 03:24:20 PM

JIANG LIU
01/13/2022 03:26:27 PM

CHINMAY SHUKLA
01/13/2022 03:28:16 PM

MATTHEW W GUERRA
01/13/2022 04:25:13 PM

MOHAMED A ALOSH
01/13/2022 04:56:01 PM

LAURA L JOHNSON
01/13/2022 04:58:35 PM

TONG LI-MASTERS
01/13/2022 05:00:36 PM

SNEZANA TRAJKOVIC
01/13/2022 05:13:39 PM

KENDALL A MARCUS
01/13/2022 05:19:29 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211675Orig1s004

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	November 29, 2021
To:	Craig Johnson, PharmD Regulatory Project Manager **Division of Dermatology and Dentistry (DDD)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Laurie Buonaccorsi, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	RINVOQ (upadacitinib)
Dosage Form and Route:	extended-release tablets, for oral use
Application Type/Number:	NDA 211675
Supplement Number:	S-004
Applicant:	AbbVie Inc.

1 INTRODUCTION

On October 15, 2020, AbbVie Inc. submitted for the Agency's review a Prior Approval Supplement (PAS) - Efficacy to their approved New Drug Application (NDA) 211675/S-004 for RINVOQ (upadacitinib) extended-release tablets. With this supplement, the Applicant proposes a new indication for RINVOQ (upadacitinib) for the treatment of (b) (4) (b) (4).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dentistry (DDD) on February 5, 2021, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for RINVOQ (upadacitinib) extended-release tablets.

2 MATERIAL REVIEWED

- Draft RINVOQ (upadacitinib) MG received on October 15, 2020, and received by DMPP and OPDP on November 16, 2021.
- Draft RINVOQ (upadacitinib) Prescribing Information (PI) received on October 15, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 16, 2021.
- Approved OLUMIANT (baricitinib) comparator labeling dated July 8, 2020.
- Approved XELJANZ (tofacitinib) comparator labeling dated September 25, 2020.
- Approved RINVOQ (upadacitinib) labeling dated July 10, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using font size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JESSICA M CHUNG
11/29/2021 09:56:04 AM

LAURIE J BUONACCORSI
11/29/2021 10:04:59 AM

BARBARA A FULLER
11/29/2021 10:26:09 AM

LASHAWN M GRIFFITHS
11/30/2021 06:57:12 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 29, 2021

To: Tong Li-Masters, MD, Clinical Reviewer,
Division of Dermatology and Dentistry (DDD)
Snezana Trajkovic, MD, Clinical Team Leader, DDD
Craig Johnson, Regulatory Project Manager, DDD

From: Laurie Buonaccorsi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments for RINVOQ™ (upadacitinib) extended-release tablets, for oral use (Rinvoq)

NDA: 211675/S-004

In response to DDD's consult request dated February 5, 2021, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the supplemental NDA submission for Rinvoq. This supplement expands the indication for Rinvoq to include 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 drug products, including biologics, or when use of those therapies are inadvisable.

Labeling

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DDD on November 16, 2021 and are provided below.

Medication Guide: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on October 15,2020 (container labeling), and June 30, 2021 (carton labeling), and we have no additional comments.

Thank you for your consult. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

49 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LAURIE J BUONACCORSI
11/29/2021 10:03:17 AM

Memorandum

To: NDA 211675/S-04
From: Renqin Duan, Ph.D., Pharmacology/Toxicology Reviewer
Through: Barbara Hill, Ph.D., Pharmacology/Toxicology Supervisor

Re:

SDN:	396 (S-04)
Submission date:	10/15/2020
Submission type:	Efficacy supplement
Drug:	Rinvoq (upadacitinib) tablet
Indication:	Atopic dermatitis
Route:	Oral
Applicant:	AbbVie Inc.

Introduction:

Rinvoq (upadacitinib, ABT-494, A-1293543) tablet, a Janus kinase (JAK) inhibitor, was approved for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate on August 16, 2019. The recommended dose of Rinvoq is 15 mg once daily.

With this submission, the applicant submits an efficacy supplemental New Drug Application (sNDA) for the treatment of (b) (4) (b) (4). The applicant proposes (b) (4) (b) (4).

No new nonclinical studies were submitted in this efficacy supplement. This nonclinical labeling review primarily focuses on the human exposure multiples of the nonclinical studies in the label using the higher dose of 30 mg QD proposed in this efficacy supplement. Calculations of the human exposure multiples are presented in the table below and the nonclinical sections of the Rinvoq label (Highlights {Pharmacologic Class}, Sections 5.6, 8.1, 8.2, 12.1 and 13.1) are evaluated in the following sections of this review.

Human Exposure Multiple Calculations

The human exposure multiples based on AUC comparison for the doses used in pivotal toxicology studies are provided in the following table.

Human Exposure Multiples for Doses used in Pivotal Toxicology Studies

Study	Route	Dose (mg/kg/day)	AUC (ng*hr/mL)	Multiples of human exposure[a] (on an AUC basis)	Multiples of human exposure[b] (on an AUC basis)
Rat embryofetal development study	Oral	5 75	680 33400	1.7 84	1.0 48
Rat embryofetal development study	Oral	1.5 4	115 629	0.3 1.6	0.2 0.9
Rabbit embryofetal development study	Oral	10 25	881 5950	2 15	1.3 8.5
Rat pre- and post-natal development study	Oral	10	1090	3	1.6
Rat fertility study	Oral	5 25 50 (M) 75 (F)	680[c] 8720[c] 16800[d] 33400[c]	2 22 42 84	1.0 13 24 48
Rat carcinogenicity	Oral	15 (M) 20 (F)	1670 4170	4 10	2.4 6.0

a Compared with the human AUC value at steady state at the maximum recommended human dose (MRHD) of 15 mg QD for rheumatoid arthritis: 396 ng·hr/ml (refer to clinical pharmacology review).
b Compared with the human AUC value at steady state at the MRHD of 30 mg QD for atopic dermatitis: 696 ng·hr/ml in adult AD patients (refer to clinical pharmacology review).
c estimated based on exposures in the rat embryofetal development study.
d estimated based on exposures in the four-week rat toxicity study.

Evaluation of the applicant's submitted labeling:

Revisions to the applicant's proposed wording for the nonclinical sections of the label are provided below. The underlined text is recommended for insertion into and the ~~strikethrough~~ text is recommended for deletion from the label.

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

RINVOQ is a Janus kinase (JAK) inhibitor indicated for the treatment of:

5 WARNINGS AND PRECAUTIONS

5.6 Embryo-Fetal Toxicity

Based on findings in animal studies, RINVOQ may cause fetal harm when administered to a pregnant woman. Administration of upadacitinib to rats and rabbits during organogenesis caused increases in fetal malformations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with RINVOQ and for 4 weeks following completion of therapy *[see Use in Specific Populations (8.1, 8.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from the pharmacovigilance safety database and postmarketing case reports ~~The limited human data~~ on use of RINVOQ in pregnant women are not sufficient to evaluate a drug-associated risk for major birth defects or miscarriage. Based on animal studies, ~~upadacitinib~~ RINVOQ has the potential to adversely affect a developing fetus.

In animal embryo-fetal development studies, oral upadacitinib administration to pregnant rats and rabbits at exposures equal to or greater than approximately ~~1.6 and 15 times the 15 mg dose and~~ (b) (4) 0.9 and 8.5 (b) (4) times the maximum recommended human dose (MRHD) of 30 mg ~~dose for rats and rabbits~~, respectively, resulted in dose-related increases in skeletal malformations (rats only), an increased incidence of cardiovascular malformations (rabbits only), increased post-implantation loss (rabbits only), and decreased fetal body weights in both rats and rabbits. No developmental toxicity was observed in pregnant rats and rabbits treated with oral upadacitinib during organogenesis at approximately ~~0.3 and 2 times the exposure at the 15 mg dose, respectively, and at~~ (b) (4) 0.2 ~~times (rat)~~ and 1.3 times ~~at a similar exposure in rabbits as the exposures at~~ the ~~maximum recommended human dose (~~MRHD~~)~~ of 30 mg. In a pre- and post-natal development study in pregnant female rats, oral upadacitinib administration at exposures approximately ~~3 times the~~ (b) (4) 1.6 times the MRHD of 30 mg resulted in no maternal or developmental toxicity *~~[(see Animal Data)]~~*.

The ~~estimated~~ background risks of major birth defects and miscarriage for the indicated population(s) are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriages are 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data suggest that increased disease activity is associated with the risk of developing adverse pregnancy outcomes in women with rheumatoid arthritis. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Data

Animal Data

In an oral embryo-fetal development study, pregnant rats received upadacitinib at doses of 5, 25, and 75 mg/kg/day during the period of organogenesis from gestation day 6 to 17. Upadacitinib was teratogenic (skeletal malformations that consisted of misshapen humerus and bent scapula) at exposures equal to or greater than approximately ~~1.7 times the 15 mg dose and~~ (b) (4) 1.0 times the MRHD of 30 mg (on an AUC basis at maternal oral doses of 5 mg/kg/day and higher). Additional skeletal malformations (bent forelimbs/hindlimbs and rib/vertebral defects) and decreased fetal body weights were observed in the absence of maternal toxicity at an exposure approximately ~~84 times the~~ (b) (4) ~~and~~ (b) (4) 48 times the MRHD of 30 mg (on an AUC basis at a maternal oral dose of 75 mg/kg/day).

In a second oral embryo-fetal development study, pregnant rats received upadacitinib at doses of 1.5 and 4 mg/kg/day during the period of organogenesis from gestation day 6 to 17. Upadacitinib was teratogenic (skeletal malformations that included bent humerus and scapula) at exposures approximately ~~1.6 times the~~ (b) (4) ~~mg dose and~~ (b) (4) 0.9 times the MRHD of 30 mg (on an AUC basis at maternal oral doses of 4 mg/kg/day). No developmental toxicity was observed in rats at an exposure approximately ~~0.3 times the 15 mg dose and 0.15~~ 0.2 times the MRHD of 30 mg (on an AUC basis at a maternal oral dose of 1.5 mg/kg/day).

In an oral embryo-fetal developmental study, pregnant rabbits received upadacitinib at doses of 2.5, 10, and 25 mg/kg/day during the period of organogenesis from gestation day 7 to 19. Embryolethality, decreased fetal body weights, and cardiovascular malformations were observed in the presence of maternal toxicity at an exposure approximately ~~15 times the~~ (b) (4) ~~dose and 7.6~~ 8.5 times the MRHD of 30 mg (on an AUC basis at a maternal oral dose of 25 mg/kg/day). Embryolethality consisted of increased post-implantation loss that was due to elevated incidences of both total and early resorptions. No developmental toxicity was observed in rabbits at an exposure approximately ~~2~~ (b) (4) times ~~the~~ (b) (4) ~~dose and at approximately the same exposure as~~ the MRHD of 30 mg (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

In an oral pre- and post-natal development study, pregnant female rats received upadacitinib at doses of 2.5, 5, and 10 mg/kg/day from gestation day 6 through lactation day 20. No maternal or developmental toxicity was observed in either mothers or offspring, respectively, at an exposure approximately ~~3 times the~~ (b) (4) 1.6 times the MRHD of 30 mg (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

8.2 Lactation

Risk Summary

There are no data on the presence of upadacitinib in human milk, the effects on the breastfed infant, or the effects on milk production. Available pharmacodynamic /toxicological data in animals have shown excretion of upadacitinib in milk *(see Data)*. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the potential for serious adverse reactions in the breastfed infant, advise patients that breastfeeding is not recommended during treatment with ~~upadacitinib~~ RINVOQ, and for 6 days (approximately 10 half-lives) after the last dose.

Data

~~*Animal Data*~~

A single oral dose of 10 mg/kg radiolabeled upadacitinib was administered to lactating female Sprague-Dawley rats on post-partum days 7-8. Drug exposure was approximately 30-fold greater in milk than in maternal plasma based on AUC_{0-t} values. Approximately 97% of drug-related material in milk was parent drug.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to starting treatment with RINVOQ *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Based on animal studies, upadacitinib may cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*. Advise female patients of reproductive potential to use effective contraception during treatment with RINVOQ and for 4 weeks after the final dose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Upadacitinib is 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. 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.

JAK enzymes transmit cytokine signaling through their pairing (e.g., JAK1/JAK2, JAK1/JAK3, JAK1/TYK2, JAK2/JAK2, JAK2/TYK2). 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. (b) (4) However, the relevance of inhibition of specific JAK enzymes to therapeutic effectiveness (b) (4) is not currently known.

Reviewer comment: The fourth and fifth sentences of the second paragraph under Section 12.1 were not included in the previous approved Rinvoq label and other same class product labels. The applicant refers those proposed edits to "Clinical Overview, Section 2.5.1.1. This reviewer recommends that these two sentences be deleted due to (b) (4) but defers to clinical/clinical pharmacology team to determine if those two sentences should be included in Section 12.1 of the Rinvoq label.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of upadacitinib was evaluated in Sprague-Dawley rats and Tg.rasH2 mice. No evidence of tumorigenicity was observed in male or female rats that received upadacitinib for up to 101 weeks at oral doses up to 15 or 20 mg/kg/day, respectively (approximately ~~4 and 10 times the~~ (b) (4) ~~and 2~~ 2.4 and 6.0 (b) (4) times the MRHD of 30 mg on an AUC basis, respectively). No evidence of tumorigenicity was observed in male or female Tg.rasH2 mice that received upadacitinib for 26 weeks at oral doses up to 20 mg/kg/day.

Mutagenesis

Upadacitinib tested negatively in the following genotoxicity assays: the *in vitro* bacterial mutagenicity assay (Ames assay), *in vitro* chromosome aberration assay in human peripheral blood lymphocytes, and *in vivo* rat bone marrow micronucleus assay.

Impairment of Fertility

Upadacitinib had no effect on fertility in male or female rats at oral doses up to 50 mg/kg/day in males and 75 mg/kg/day in females (approximately ~~42 and 84 times the~~ (b) (4)

[redacted] ~~and~~ [redacted] 24 and 48 [redacted] times the MRHD of 30 mg in males and females, respectively, on an AUC basis). However, maintenance of pregnancy was adversely affected at oral doses of 25 mg/kg/day and 75 mg/kg/day based upon dose-related findings of increased post-implantation losses (increased resorptions) and decreased numbers of mean viable embryos per litter (approximately ~~22 and 84 times the~~ [redacted] ~~and~~ [redacted] 13 and 48 [redacted] times the MRHD of 30 mg on an AUC basis, respectively). The number of viable embryos was unaffected in female rats that received upadacitinib at an oral dose of 5 mg/kg/day and were mated to males that received the same dose (~~approximately 2 times~~ [redacted] 1.0 times the MRHD of 30 mg on an AUC basis).

A clean version of the revised nonclinical portions of the label:

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

RINVOQ is a Janus kinase (JAK) inhibitor indicated for the treatment of:

5 WARNINGS AND PRECAUTIONS

[redacted] **Embryo-Fetal Toxicity**

Based on findings in animal studies, RINVOQ may cause fetal harm when administered to a pregnant woman. Administration of upadacitinib to rats and rabbits during organogenesis caused increases in fetal malformations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with RINVOQ and for 4 weeks following completion of therapy *[see Use in Specific Populations (8.1, 8.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from the pharmacovigilance safety database and postmarketing case reports on use of RINVOQ in pregnant women are not sufficient to evaluate a drug-associated risk for major birth defects or miscarriage. Based on animal studies, RINVOQ has the potential to adversely affect a developing fetus.

In animal embryo-fetal development studies, oral upadacitinib administration to pregnant rats and rabbits at exposures equal to or greater than approximately 0.9 and 8.5 times the maximum recommended human dose (MRHD) of 30 mg, respectively, resulted in dose-related increases in skeletal malformations (rats only), an increased

incidence of cardiovascular malformations (rabbits only), increased post-implantation loss (rabbits only), and decreased fetal body weights in both rats and rabbits. No developmental toxicity was observed in pregnant rats and rabbits treated with oral upadacitinib during organogenesis at approximately 0.2 and 1.3 times MRHD of 30 mg. In a pre- and post-natal development study in pregnant female rats, oral upadacitinib administration at exposures approximately 1.6 times the MRHD of 30 mg resulted in no maternal or developmental toxicity *(see Data)*.

The background risks of major birth defects and miscarriage for the indicated population(s) are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriages are 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data suggest that increased disease activity is associated with the risk of developing adverse pregnancy outcomes in women with rheumatoid arthritis. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Data

Animal Data

In an oral embryo-fetal development study, pregnant rats received upadacitinib at doses of 5, 25, and 75 mg/kg/day during the period of organogenesis from gestation day 6 to 17. Upadacitinib was teratogenic (skeletal malformations that consisted of misshapen humerus and bent scapula) at exposures equal to or greater than approximately 1.0 times the MRHD of 30 mg (on an AUC basis at maternal oral doses of 5 mg/kg/day and higher). Additional skeletal malformations (bent forelimbs/hindlimbs and rib/vertebral defects) and decreased fetal body weights were observed in the absence of maternal toxicity at an exposure approximately 48 times the MRHD of 30 mg (on an AUC basis at a maternal oral dose of 75 mg/kg/day).

In a second oral embryo-fetal development study, pregnant rats received upadacitinib at doses of 1.5 and 4 mg/kg/day during the period of organogenesis from gestation day 6 to 17. Upadacitinib was teratogenic (skeletal malformations that included bent humerus and scapula) at exposures approximately 0.9 times the MRHD of 30 mg (on an AUC basis at maternal oral doses of 4 mg/kg/day). No developmental toxicity was observed in rats at an exposure approximately 0.2 times the MRHD of 30 mg (on an AUC basis at a maternal oral dose of 1.5 mg/kg/day).

In an oral embryo-fetal developmental study, pregnant rabbits received upadacitinib at doses of 2.5, 10, and 25 mg/kg/day during the period of organogenesis from gestation day 7 to 19. Embryolethality, decreased fetal body weights, and cardiovascular malformations were observed in the presence of maternal toxicity at an exposure approximately 8.5 times the MRHD of 30 mg (on an AUC basis at a maternal oral dose of 25 mg/kg/day). Embryolethality consisted of increased post-implantation loss that was due to elevated incidences of both total and early resorptions. No developmental toxicity was observed in rabbits at an exposure approximately 1.3 times the MRHD of 30 mg (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

In an oral pre- and post-natal development study, pregnant female rats received upadacitinib at doses of 2.5, 5, and 10 mg/kg/day from gestation day 6 through lactation day 20. No maternal or developmental toxicity was observed in either mothers or offspring, respectively, at an exposure approximately 1.6 times the MRHD of 30 mg (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

8.2 Lactation

Risk Summary

There are no data on the presence of upadacitinib in human milk, the effects on the breastfed infant, or the effects on milk production. Available pharmacodynamic /toxicological data in animals have shown excretion of upadacitinib in milk *(see Data)*. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the potential for serious adverse reactions in the breastfed infant, advise patients that breastfeeding is not recommended during treatment with RINVOQ, and for 6 days (approximately 10 half-lives) after the last dose.

Data

A single oral dose of 10 mg/kg radiolabeled upadacitinib was administered to lactating female Sprague-Dawley rats on post-partum days 7-8. Drug exposure was approximately 30-fold greater in milk than in maternal plasma based on AUC_{0-t} values. Approximately 97% of drug-related material in milk was parent drug.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to starting treatment with RINVOQ *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Based on animal studies, upadacitinib may cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*. Advise female patients of reproductive potential to use effective contraception during treatment with RINVOQ and for 4 weeks after the final dose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Upadacitinib is 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. 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.

JAK enzymes transmit cytokine signaling through their pairing (e.g., JAK1/JAK2, JAK1/JAK3, JAK1/TYK2, JAK2/JAK2, JAK2/TYK2). 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. However, the relevance of inhibition of specific JAK enzymes to therapeutic effectiveness (b) (4) (b) (4) is not currently known.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of upadacitinib was evaluated in Sprague-Dawley rats and Tg.rasH2 mice. No evidence of tumorigenicity was observed in male or female rats that received upadacitinib for up to 101 weeks at oral doses up to 15 or 20 mg/kg/day, respectively (approximately 2.4 and 6.0 times the MRHD of 30 mg on an AUC basis, respectively). No evidence of tumorigenicity was observed in male or female Tg.rasH2 mice that received upadacitinib for 26 weeks at oral doses up to 20 mg/kg/day.

Mutagenesis

Upadacitinib tested negatively in the following genotoxicity assays: the *in vitro* bacterial mutagenicity assay (Ames assay), *in vitro* chromosome aberration assay in human peripheral blood lymphocytes, and *in vivo* rat bone marrow micronucleus assay.

Impairment of Fertility

Upadacitinib had no effect on fertility in male or female rats at oral doses up to 50 mg/kg/day in males and 75 mg/kg/day in females (approximately 24 and 48 times the MRHD of 30 mg in males and females, respectively, on an AUC basis). However, maintenance of pregnancy was adversely affected at oral doses of 25 mg/kg/day and 75 mg/kg/day based upon dose-related findings of increased post-implantation losses (increased resorptions) and decreased numbers of mean viable embryos per litter (approximately 13 and 48 times the MRHD of 30 mg on an AUC basis, respectively). The number of viable embryos was unaffected in female rats that received upadacitinib at an oral dose of 5 mg/kg/day and were mated to males that received the same dose (approximately 1.0 times the MRHD of 30 mg on an AUC basis).

Overall conclusions and recommendations:

The revised nonclinical portions of the Rinvoq label are approvable from a Pharmacology/Toxicology perspective. Refer to the approved labeling for any additional edits made during negotiation of labeling with the sponsor.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

Renqin DUAN
08/24/2021 10:50:21 AM

BARBARA A HILL
08/24/2021 11:13:40 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: April 27, 2021 **Date consulted:** February 24, 2021

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health, Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health, DPMH

Lynne Yao, MD, Director, DPMH

To: Division of Dermatology and Dentistry (DDD)

Drug: RINVOQ (upadacitinib) extended-release tablets, for oral use

NDA: 211675/ S-004

Applicant: AbbVie

Subject: Input for Postmarketing Requirements (PMRs)

Proposed Indication:

(b) (4)

Approved Indication:

Treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate.

Limitation of Use: Use of Rinvoq in combination with other JAK inhibitors, immunomodulating biologic (e.g., biologic DMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Materials Reviewed:

- DPMH consult request, dated February 24, 2021, DARRTS Reference ID 4752000.
- Applicant's submitted efficacy supplement and proposed labeling for NDA 211675, submitted October 15, 2020.
- DPMH review for abrocitinib, NDA 213871, by Jean Limpert, MD, dated February 16, 2021, DARRTS Reference ID: 4715000.[1]
- DPMH review for Olumiant (baricitinib), NDA 207924, by Jean Limpert, MD, dated February 8, 2021, DARRTS Reference ID: 4742935.[1]
- DPMH labeling review for Dupixent, BLA 761055, January 13, 2017, Christos Mastroyannis, MD, DARRTS reference ID: 4041992.[1,]

Consult Question: The Division of Dermatology and Dentistry (DDD) is in review of Rinvoq (upadacitinib) (JAK inhibitor) for the treatment of moderate to severe atopic dermatitis. DDD requests DPMH-MHT assistance in determining whether PMR studies on pregnancy and lactation would be appropriate for this product that is currently labeled for use with contraception during treatment, pregnancy testing prior to starting treatment and a recommendation not to breast feed during lactation.

INTRODUCTION AND BACKGROUND

On October 15, 2020, AbbVie. submitted an efficacy supplement to the new drug application (NDA) for Rinvoq (upadacitinib) extended release tablets. The proposed indication is the (b) (4) (b) (4)

On February 24, 2021, DDD consulted DPMH to provide input as to whether pregnancy and lactation postmarketing requirements (PMRs) are recommended.

State of Current Labeling

Based on animal studies, there is a Warning and Precautions subsection on Embryofetal Toxicity. In subsection 8.3 Females and Males of Reproductive Potential, there is a recommendation for pregnancy testing prior to initiating treatment and use of contraception during treatment.

[1] The abrocitinib, Olumiant (baricitinib) and Dupixent reviews were part of the materials reviewed but was not a source relied upon for the labeling recommendations and PMRs in this consult review.

Regulatory History

On July 10, 2020, Rinvoq, a Janus kinase (JAK) inhibitor, was approved for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. Rinvoq was initially reviewed by the Division of Rheumatology and Transplant Medicine (formerly the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)). Pregnancy- and lactation-related postmarketing requirements were not issued.

The JAK pathway is involved in cell adhesion and cell polarity which can affect early embryonic development. Animal data for the class of JAK inhibitors demonstrates varying degrees of embryofetal toxicity, including embryofetal toxicity warnings in labeling for some drugs in the class (e.g., upadacitinib).

There are currently no JAK inhibitors approved for the treatment of moderate-severe AD but there are multiple JAK inhibitors currently under review by DDD for this indication. DPMH is participating in those ongoing reviews. After assessment of the available human data and the conclusions from the Nonclinical review for each JAK inhibitor, DPMH has provided PMR recommendations for a pregnancy exposure registry, a complementary pregnancy study, and a milk only lactation study in women receiving a JAK inhibitor who are planning to discontinue breastfeeding or healthy volunteers.

Dupilumab is the only systemic biologic product currently approved for the treatment for moderate-severe AD. Dupilumab is a human monoclonal IgG4 antibody. In 2016, DDD (formerly the Division of Dermatology and Dental Products) consulted DPMH for pregnancy and lactation labeling.[1] DPMH recommended PMRs for a pregnancy exposure registry and complementary study and these PMRs were issued at the time of approval in March 2017.

Drug Characteristics[2]

Drug Class	JAK Inhibitor
Mechanism of Action	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.
Molecular Weight	389.38 Daltons
Protein Binding	52%
Terminal Half-Life	8-14 Hours

[2] Existing label as of July 10, 2020

Bioavailability	Not reported in humans. For monkeys: 59.3%, dogs: 76.8%
Adverse reactions	Based on adverse reactions observed in clinical trials, there is a potential risk of serious infections, malignancy, GI perforations, retinal detachment, and thrombosis

REVIEW

PREGNANCY

AD and Pregnancy

It is estimated up to 10% of adults in the United States are affected by AD though prevalence estimates are limited and vary based on case definitions.[3] For adults with AD, an estimated 44-57% have moderate disease and 12-21% have severe disease. Approximately half of the AD population are females and AD affects all age groups including women of reproductive potential.[4] AD does not have negative effects on fertility.[5]

Initial therapies include topical treatments and phototherapy. Systemic therapies are recommended when AD is not adequately controlled by these initial therapies and are typically needed for patients with moderate-severe AD. There are currently two approved systemic therapies for patients with moderate-severe AD: systemic corticosteroids and dupilumab. Systemic corticosteroids can be effective for severe acute exacerbations but are not recommended for long-term use. Use of systemic corticosteroids during pregnancy may result in adverse effects including elevated blood pressure, glucose intolerance, susceptibility to infection, and fetal growth restriction. Dupilumab is an injectable systemic IgG4 monoclonal antibody. Current data on dupilumab use in pregnancy are limited, but at this time, there are no known safety issues for use during pregnancy.[6,7,8] Drugs used off label include cyclosporin, methotrexate and azathioprine with major adverse reactions during pregnancy.

Review of Nonclinical Data[2]

In an embryo-fetal development study, pregnant rats received oral upadacitinib during the period of organogenesis from gestation day 6 to 17. Upadacitinib was teratogenic (skeletal malformations that consisted of misshapen humerus and bent scapula) at exposures equal to or greater than approximately 1.7 times the maximum recommended human dose (MRHD) (on an AUC basis at maternal oral doses of 5 mg/kg/day and higher). Additional skeletal malformations (bent forelimbs/hindlimbs and rib/vertebral defects) and decreased fetal body weights were observed in the absence of maternal toxicity at an exposure approximately 84 times the MRHD

---

[3] Chiesa Fuxench ZC, Block JK, Boguniewicz M, et al. Atopic Dermatitis in America Study: a cross-sectional study examining the prevalence and disease burden of atopic dermatitis in the US adult population. J Invest Dermatol. 2019;139(3):583-590.

[4] Heilskov, S., Deleuran, M.S. & Vestergaard, C. Immunosuppressive and Immunomodulating Therapy for Atopic Dermatitis in Pregnancy: An Appraisal of the Literature. Dermatol Ther (Heidelb) 10, 1215–1228 (2020).

[5] Langan, S.M.; Irvine, A.D.; Weidinger, S. Atopic dermatitis. Lancet 2020, 396, 345–360.

[6] Kage P, Simon JC, Treudler R. A case of atopic eczema treated safely with dupilumab during pregnancy and lactation. J Eur Acad Dermatol Venereol. 2020:34(6):e256–7.

[7] Heilskov, S., Deleuran, M.S. & Vestergaard, C. Immunosuppressive and Immunomodulating Therapy for Atopic Dermatitis in Pregnancy: An Appraisal of the Literature. Dermatol Ther (Heidelb) 10, 1215–1228 (2020).

[8] DPMH labeling review for Dupixent, BLA 761055, January 13, 2017, Christos Mastroyannis, MD, Medical Officer, DARRTs reference ID: 4041992

(on an AUC basis at a maternal oral dose of 75 mg/kg/day).

In an embryo-fetal developmental study, pregnant rabbits received oral upadacitinib during the period of organogenesis from gestation day 7 to 19. Embryolethality, decreased fetal body weights, and cardiovascular malformations were observed in the presence of maternal toxicity at an exposure approximately 15 times the MRHD (on an AUC basis at a maternal oral dose of 25 mg/kg/day). Embryolethality consisted of increased post-implantation loss that was due to elevated incidences of both total and early resorptions. No developmental toxicity was observed in rabbits at an exposure approximately 2 times the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

Reprotox[9] states that:

> The no effect levels were 0.3 (rat) and 2 (rabbit) times the human dose. The abnormalities in rat fetuses were misshapen humerus and bent scapula, which are a transient developmental delay attributable to under-mineralization of the bones. These findings do not constitute malformations. Administration during pregnancy and lactation to rats at 3 times the human dose produced no adverse effects on offspring development.

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 1 references the 87 pregnancies and outcomes from clinical trials (maternal age 18-45, exposure range 3-9 weeks from LMP to last dose)

[9] Truven Health Analytics LLC. Micromedex/ReproTox

Table 1: 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 2.

Table 2: Outcome of the 54 Pregnancies with Exposure to the Drug

Pregnancy Outcomes for Maternal Exposure Reports	Patients on Upadacitinib and Background Methotrexate 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 anomaly	8	9	17[a]
Live birth with congenital anomaly	-	-	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 pregnancies)	-	-	0

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

Table 3: 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.[10] 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. [11]

---

[10] Guidance for Industry: "Postapproval Pregnancy Safety Studies," Draft published May 2019. https://www.fda.gov/media/124746/download

[11] Industry Guidance (draft): "Clinical Lactation Studies: Considerations for Study Design" , Draft published May

DPMH RECOMMENDATIONS FOR POSTMARKETING REQUIREMENTS

1. Pregnancy PMR
   Conduct a worldwide descriptive study that collects prospective and retrospective data in women and their offspring who are 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 study will collect information for a minimum of 10 years. Use a structured approach to data collection and targeted questionnaires throughout pregnancy to obtain follow-up information on all exposed pregnancies of which you become aware. Results will be analyzed and reported descriptively. Data collected retrospectively will be analyzed separately and reported with the interim and final study reports.
2. Lactation PMR
   Perform a lactation study (milk only) in lactating women who have received therapeutic doses of Rinvoq (upadacitinib), using a validated assay to assess concentrations of upadacitinib in breast milk This study should be conducted in healthy lactating women who volunteer for clinical research and/or women prescribed upadacitinib who are willing to discontinue breastfeeding their infants.

DPMH LABELING RECOMMENDATIONS

Based on comments during the Rinvoq labeling meeting on March 9, 2021, and for DDD consideration, DPMH proposes the following labeling language consistent with the approach we recommend to other OND review divisions.

HIGHLIGHTS OF PRESCRIBING INFORMATION

WARNINGS AND PRECAUTIONS

• Embryo-Fetal Toxicity: RINVOQ may cause fetal harm based on animal studies. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (b) (4)

USE IN SPECIFIC POPULATIONS

• Lactation: Advise not to breastfeed. (8.2)

FULL PRESCRIBING INFORMATION

2.3 Important Administration Instructions

• (b) (4)

5 WARNINGS AND PRECAUTIONS

(b) (4) Embryo-Fetal Toxicity

2019

Based on findings in animal studies, RINVOQ may cause fetal harm when administered to a pregnant woman. Administration of upadacitinib to rats and rabbits during organogenesis (b) (4) caused increases in fetal malformations. Verify pregnancy status of females of reproductive potential prior to starting treatment. Advise females of reproductive potential to use effective contraception during treatment with RINVOQ and for 4 weeks following completion of therapy *[see Use in Specific Populations (8.1, 8.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from the pharmacovigilance safety database and postmarketing case reports on use of RINVOQ in pregnant women not sufficient to evaluate a drug-associated risk of major birth defects, miscarriage, (b) (4). Based on animal studies, upadacitinib has the potential to adversely affect a developing fetus.

In animal embryo-fetal development studies, oral upadacitinib administration to pregnant rats and rabbits at exposures equal to or greater than approximately 0.9 and 8.5 times the maximum recommended human dose (MRHD) of 30 mg, respectively, resulted in dose-related increases in skeletal malformations (rats only), an increased incidence of cardiovascular malformations (rabbits only), increased post-implantation loss (rabbits only), and decreased fetal body weights in both rats and rabbits. No developmental toxicity was observed in pregnant rats and rabbits treated with oral upadacitinib during organogenesis at approximately 0.2 and 1.3 times the MRHD of 30 mg. In a pre- and post-natal development study in pregnant female rats, oral upadacitinib administration at exposures approximately 1.6 times the MRHD of 30 mg resulted in no maternal or developmental toxicity (*see Data)*.

The estimated background risks of major birth defects and miscarriage for the indicated population(s) are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies are 2-4% and 15-20%, respectively.

Report pregnancies to the [applicant's] Adverse Event reporting line at 1-888-XXX-XXXX and [insert webpage].

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data suggest that increased disease activity is associated with the risk of developing adverse pregnancy outcomes in women with rheumatoid arthritis. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Data

Animal Data

In an oral embryo-fetal development study, pregnant rats received upadacitinib at doses of 5, 25, and 75 mg/kg/day during the period of organogenesis from gestation day 6 to 17.

Upadacitinib was teratogenic (skeletal malformations that consisted of misshapen humerus and bent scapula) at exposures equal to or greater than approximately 1.0 times the MRHD of 30 mg (on an AUC basis at maternal oral doses of 5 mg/kg/day and higher). Additional skeletal malformations (bent forelimbs/hindlimbs and rib/vertebral defects) and decreased fetal body weights were observed in the absence of maternal toxicity at an exposure approximately 48 times the MRHD of 30 mg (on an AUC basis at a maternal oral dose of 75 mg/kg/day).

In a second oral embryo-fetal development study, pregnant rats received upadacitinib at doses of 1.5 and 4 mg/kg/day during the period of organogenesis from gestation day 6 to 17. Upadacitinib was teratogenic (skeletal malformations that included bent humerus and scapula) at exposures approximately 0.9 times the MRHD of 30 mg (on an AUC basis at maternal oral doses of 4 mg/kg/day). No developmental toxicity was observed in rats at an exposure approximately 0.2 times the MRHD of 30 mg (on an AUC basis at a maternal oral dose of 1.5 mg/kg/day).

In an oral embryo-fetal developmental study, pregnant rabbits received upadacitinib at doses of 2.5, 10, and 25 mg/kg/day during the period of organogenesis from gestation day 7 to 19. Embryolethality, decreased fetal body weights, and cardiovascular malformations were observed in the presence of maternal toxicity at an exposure approximately 8.5 times the MRHD of 30 mg (on an AUC basis at a maternal oral dose of 25 mg/kg/day). Embryolethality consisted of increased post-implantation loss that was due to elevated incidences of both total and early resorptions. No developmental toxicity was observed in rabbits at an exposure approximately 1.3 times the MRHD of 30 mg (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

In an oral pre- and post-natal development study, pregnant female rats received upadacitinib at doses of 2.5, 5, and 10 mg/kg/day from gestation day 6 through lactation day 20. No maternal or developmental toxicity was observed in either mothers or offspring, respectively, at an exposure approximately 1.6 times the MRHD of 30 mg (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

8.2 Lactation

Risk Summary

There are no data on the presence of upadacitinib in human milk, the effects on the breastfed infant, or the effects on milk production. (b) (4)

When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the potential for serious adverse reactions in the breastfed infant, advise patients that breastfeeding is not recommended during treatment with RINVOQ, and for 6 days (approximately 10 half-lives) after the last dose.

Data

Animal Data

A single oral dose of 10 mg/kg radiolabeled upadacitinib was administered to lactating female Sprague-Dawley rats on post-partum days 7-8. Drug exposure was approximately 30-fold greater in milk than in maternal plasma based on AUC0-t values. Approximately 97% of drug-related material in milk was parent drug.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to starting treatment with RINVOQ *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Based on animal studies, upadacitinib may cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*. Advise female patients of reproductive potential to use effective contraception during treatment with RINVOQ and for 4 weeks after the final dose.

8.1

17 PATIENT COUNSELING INFORMATION

(b) (4)

Pregnancy

Advise pregnant women and females of reproductive potential that exposure to RINVOQ during pregnancy may result in fetal harm. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions* (b) (4) *) and Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment and for 4 weeks following the final dose of RINVOQ *[see Use in Specific Populations (8.3)]*.

Lactation

Advise women not to breastfeed during treatment with RINVOQ and for 6 days after the final dose *[see Use in Specific Populations (8.2)]*.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHRISTOS MASTROYANNIS
04/27/2021 04:35:51 PM

TAMARA N JOHNSON
04/27/2021 05:41:47 PM

LYNNE P YAO
05/03/2021 10:51:48 AM

Medical Officer's Review of NDA 211675/S-004
Ophthalmology Consultant

NDA 211675/S-004		Submission:	10/15/2020
IND 128180		Review completed:	1/22/2021

Name:	Rinvoq (upadacitinib) (UPA)
Sponsor:	AbbVie Inc
Pharmacologic Category:	Janus kinase (JAK) inhibitor
Indications:	Moderate to severe atopic dermatitis (AD)

Requested: The Applicant recently submitted NDA211675, efficacy supplement S-004, Rinvoq (upadacitinib) tablet for the treatment of (b) (4) There are reported cases of retinal detachment related to the study drug treatment, and there may be additional cases in data that will be submitted in the 120-day safety update report. We request your help in evaluating the relevant information on the risk of retinal detachment related to the study drug treatment.

Submitted: Supplement 4

2.5.5.2.5.3 Retinal Detachment
In the PBO-controlled AD Analysis Set, 1 event of retinal detachment was reported in the placebo group (rhegmatogenous retinal detachment) and 3 events (reported in 2 subjects) in the upadacitinib 15 mg group (2 events of retinal detachment and 1 event of retinal tear) (CSS Table 32).

In the Long-term Upadacitinib Phase 3 AD Analysis Set, there were 4 additional events reported: one event in the upadacitinib 15 mg group (retinal detachment) and 3 in the upadacitinib 30 mg group (1 event of retinal detachment and 2 events of rhegmatogenous retinal detachment; all 3 events were reported in the same subject).

2.7.4.2.1.8.2 Additional Safety Topics
Retinal Detachment
Atopic dermatitis of the face is associated with many ocular complications such as conjunctivitis, keratoconus, iritis, cataract, and retinal detachment (Rich 1985, Pietruszyńska 2020). Traumatic slapping or rubbing of the lids and/or head banging due to severe AD has been postulated to contribute to the formation of peripheral retinal tears (Takahashi 1996). Anterior vitreoretinal traction may play an important role in the pathogenesis of retinal breaks in eyes with atopic cataract and that the same pathological process may affect the formation of cataract and tractional retinal breaks in patients with AD (Sasoh 2015).

Cases of retinal detachment reported during the placebo-controlled period and through the data cutoff are presented in Table 32. Eight events were reported among 5 subjects (1 subject on upadacitinib 15 mg had 2 events [retinal detachment and retinal tear] and 1 subject on upadacitinib 30 mg had 3 events [retinal attachment and 2 events of rhegmatogenous retinal detachment]). All subjects were Asian, with 4 males and 1 female; ages of the subjects ranged from 25 to 45 years old. There were no cases in the Phase 2b study (Study M16-048) and the Japan regional study (Study M17-377).

All events of retinal detachment, retinal tear and rhegmatogenous retinal detachment were serious. One event (retinal detachment in the upadacitinib 15 mg group) was considered by the investigator to have a reasonable possibility of being drug related. None of the events led to discontinuation of study drug.

Table 32. Events of Retinal Detachment in the Global Phase 2 and 3 Studies

	PBO-Controlled Period			All Upadacitinib AD Analysis Set	
	Placebo	UPA 15 mg	UPA 30 mg	UPA 15 mg N=1371	UPA 30 mg N=1378
Serious	N=902 n (%)	N=899 n (%)	N=906 n (%)	PY = 955.0 Events	PY = 974.2 Events
Retinal detachment	0	2 (0.2)	0	3	1
Retinal tear	0	1 (0.1)	0	1	0
Rhegmatogenous retinal detachment	1 (0.1)	0	0	0	2

E/100PY = Events per 100 patient-years; PBO = placebo; PY = patient-years; QD = once daily; UPA = upadacitinib

Beyond the placebo-controlled period, there was 1 additional serious event of retinal detachment in the upadacitinib 15 mg group and 3 events reported in the same subject in upadacitinib 30 mg group. None of the events led to discontinuation of study drug.

Details of the events reported in the 5 subjects are presented below:

● Subject (b) (6)/Study M16-047 (placebo group): 45-year-old Asian male from Japan with a history of right retinal tear, vitreous surgery, and left rhegmatogenous retinal detachment who had a serious event of right rhegmatogenous retinal detachment on treatment Day 62. The event was successfully treated with vitreous surgery, retinal photocoagulation, and medications. The event was considered by the investigator as likely pre-existing as investigator reported that surgery for the right eye was needed 1 month prior to onset of study drug and therefore, it was considered to have no reasonable possibility of being related to study drug.

Reviewer's Comments: *Previous vitreous surgery is a significant risk factor for future retinal detachments.*

● Subject (b) (6)/Study M16-045 (upadacitinib 15 mg): 31-year-old male from Japan with a history of 2 prior retinal detachments, 2 vitreous surgeries, cataract, and allergic rhinitis, who noticed blurry vision of the left eye on Study Day 149. The subject was hospitalized, diagnosed with serious retinal detachment, and underwent successful vitreous surgery. The investigator reported this patient has severe AD, especially in his face and often rubs his eyes. Therefore, the investigator felt subject retinal detachment was possibly related to eye rubbing. The event was assessed as serious but having no reasonable possibility of relationship to study treatment.

Reviewer's Comments: *Previous vitreous surgery is a significant risk factor for future retinal detachments. AD of the face and eye rubbing are also risk factors for retinal detachments.*

● Subject (b) (6)/Study M16-047 (upadacitinib 15 mg): 27-year-old Asian male from Austria with a history of eye myopia and allergic conjunctivitis reported a serious event of retinal detachment of the left eye on treatment Day 43. The event resolved with treatment. The event was considered by the investigator to have a reasonable possibility of being related to study drug.

Reviewer's Comments: *High myopia (>6D), but not all myopia is a significant risk factor for a retinal detachment. The degree of myopia should be reported.*

● Subject (b) (6)/Study M18-891 (upadacitinib 15 mg): 35-year-old Asian female from Korea with a history of prior right retinal detachment, allergic rhinitis and bilateral cataract who presented with an episode of serious retinal detachment and one episode of serious right eye retinal tear on Study Day 31. She was successfully treated with vitrectomy. The event was considered by the investigator to have no reasonable possibility of being related to study drug.

Reviewer's Comments: *Previous vitreous surgery is a significant risk factor for future retinal detachments.*

● Subject (b) (6)/Study M16-047 (upadacitinib 30 mg): 25-year-old Asian male from China with a history of eye myopia and allergic rhinitis. He had one nonserious event of retinal detachment and one nonserious complicated cataract in the left eye on Study Day 124. Subject also had one serious event of rhegmatogenous retinal detachment in the right eye on Study Day 124 and one serious rhegmatogenous retinal detachment in the left eye on Study Day 201. Both events resolved without macular involvement. Study treatment was not interrupted. The investigator assessed the events as having a reasonable possibility of being related to study drug.

Reviewer's Comments: *High myopia (>6D), but not all myopia is a significant risk factor for a retinal detachment. The degree of myopia should be reported. All retinal detachments have to potential to lead to visual loss and all retinal detachments should be considered serious.*

TABLE 2.4__3.3.2

Treatment-Emergent Adverse Events by Primary MedDRA System Organ Class and Preferred Term (All Upadacitinib AD Analysis Set)

	UPA 15 mg QD	UPA 30 mg QD	All Doses	Total
	Phase 3 Global and Japan only	Phase 3 Global and Japan only	Phase 2	
	N=1371	N=1378	N=144	N=2893
Eye disorders	49	77	17	143
Conjunctivitis allergic	9	12	1	22
Dry eye	5	6	1	12
Vision blurred	4	4	2	10
Blepharitis	4	5		9
Lacrimation increased	4	1	2	7
Eye pruritus		5		5
Eye swelling		5		5
Cataract	1	3	1	5
Chalazion	1	3	1	5
Retinal detachment	3	1		4
Ulcerative keratitis	2	1	1	4
Eye irritation		1	2	3
Swelling of eyelid	1	1	1	3
Conjunctival haemorrhage		2		2
Rhegmatogenous retinal detachment		2		2
Conjunctival hyperaemia	1	1		2
Eye inflammation	1	1		2
Eye pain	1	1		2
Periorbital swelling	1	1		2
Glaucoma	2			2
Conjunctival deposit		1		1
Conjunctival irritation		1		1
Eczema eyelids		1		1
Eye allergy		1		1
Eye oedema		1		1
Eye paraesthesia		1		1
Eyelid disorder		1		1
Eyelid margin crusting		1		1
Eyelid oedema		1		1
Eyelid skin dryness		1		1
Eyelids pruritus		1		1
Keratitis		1		1
Macular hole		1		1
Maculopathy		1		1
Night blindness		1		1
Ocular hyperaemia		1		1
Papilloedema		1		1
Photophobia		1		1
Vernal keratoconjunctivitis		1		1
Vitreous detachment		1		1
Vitreous floaters		1		1
Atopic cataract	1			1

	UPA 15 mg QD	UPA 30 mg QD	All Doses	Total
	Phase 3 Global and Japan only	Phase 3 Global and Japan only	Phase 2	
	N=1371	N=1378	N=144	N=2893
Conjunctival lymphangiectasia			1	1
Episcleritis	1			1
Erythema of eyelid	1			1
Iridocyclitis			1	1
Macular degeneration	1			1
Meibomianitis			1	1
Periorbital oedema	1			1
Pterygium	1			1
Punctate keratitis			1	1
Retinal tear	1			1
Uveitis			1	1
Visual impairment	1			1
Xerophthalmia	1			1

Reviewer's Comments: *The most common ocular adverse events are related to dry eyes (dry eyes, blurred vision, and lacrimation increased).*

90 Day Safety Update: No additional events of retinal detachment were reported in the upadacitinib AD program since the initial submission.

Other Indications:
The safety databases for patients receiving upadacitinib for the treatment of rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis have been reviewed. There are no cases of retinal detachments in patients treated with upadacitinib for these other indications. With the exception of a few cases of uveitis, there were no significant ocular adverse events in these other indications.

Summary: 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.

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILEY A CHAMBERS
02/22/2021 07:44:33 AM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	February 18, 2021
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 211675/S-004
Product Name, Dosage Form, and Strength:	Rinvoq (upadacitinib) extended-release tablets, 15 mg and 30 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	AbbVie, Inc.
FDA Received Date:	October 15, 2020 and January 13, 2021
OSE RCM #:	2020-2194
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 REASON FOR REVIEW

AbbVie, Inc. submitted a Prior Approval Supplement (PAS) (NDA 211675/S-004) for Rinvoq (upadacitinib) extended-release tablets proposing a new 30 mg tablet strength presentation and indication, for the treatment of (b) (4) . The Division of Dermatology and Dentistry (DDD) requested that we review the proposed labels and labeling to determine if they are acceptable from a medication error perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

This Efficacy supplement provides revisions to the Prescribing Information (PI) and Medication Guide (MG) for the proposed indication of the treatment of (b) (4) and container labels and carton labeling for the new 30 mg strength presentation to support the dosing for the new indication. We note that the proposed dosing for proposed new indication for adult patients is (b) (4) (see Appendix A). Thus, we find the introduction of the 30 mg tablet strength presentation appropriate. We find the PI, MG, container labels, and carton labeling acceptable from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed Prescribing Information (PI) and Medication Guide (MG), container labels, and carton labeling are acceptable from a medication error perspective. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Rinvoq received on January 13, 2021 from AbbVie, Inc..

Table 2. Relevant Product Information for Rinvoq	
Initial Approval Date	August 16, 2019
Active Ingredient	upadacitinib
Indication	Current: treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate Proposed: (b) (4)
Route of Administration	oral
Dosage Form	extended-release tablets
Strength	Current: 15 mg Proposed: 15mg and 30 mg
Dose and Frequency	Current: Rheumatoid Arthritis – 15 mg once daily

<table>
<tr><td></td><td>Proposed:
<table>
<tr><td>Atopic Dermatitis</td><td>RINVOQ</td></tr>
<tr><td colspan="2">(b) (4)
[redacted]</td></tr>
<tr><td>Patients receiving:
Strong CYP3A4 inhibitors (e.g., ketoconazole) [see Drug Interactions (7)]</td><td>The recommended dose of RINVOQ is 15 mg once daily.</td></tr>
<tr><td>Patients with:
severe renal impairment [see Use in Specific Populations (8.7)]</td><td>The recommended dose of RINVOQ is 15 mg once daily.</td></tr>
</table></td></tr>
<tr><td>How Supplied</td><td>30 tablets in a bottle</td></tr>
<tr><td>Storage</td><td>Store at 2˚C to 25˚C (36˚F to 77˚F).
Store in the original bottle in order to protect from moisture.</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 14, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, rinvoq. Our search identified four relevant previous reviews[a,b,c,d], and we considered our previous recommendations to see if they are applicable for this current review.

[a] Purcell, J and McMillan T. Human Factors Study Report and Labels and Labeling Review for Rinvoq (NDA 211675). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUL 12. RCM No.: 2018-2751 and 2018-2752

[b] McMillan T. Label and Labeling Review for Rinvoq (NDA 211675). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUL 23. RCM No.: 2018-2751-1

[c] McMillan T. Label and Labeling Review for Rinvoq (NDA 211675). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 AUG 06. RCM No.: 2018-2751-2

[d] McMillan T. Label and Labeling Review for Rinvoq (NDA 211675/S-002) Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 DEC 21. RCM No.: 2020-1202

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following Rinvoq labels and labeling submitted by AbbVie, Inc..

- Container Label received on October 15, 2020
- Carton Labeling received on October 15, 2020
- Professional Sample Container Label received on October 15, 2020
- Professional Sample Carton Labeling received on October 15, 2020
- Prescribing Information and Medication Guide (Images not shown) received on January 13, 2021, available from \\CDSESUB1\evsprod\nda211675\0061\m1\us\114-labeling\draft\labeling\neg-lbl-6934.pdf

G.2 Label and Labeling Images

Container Labels

(b) (4)

[redacted]

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MADHURI R PATEL
02/18/2021 08:58:41 AM

SEVAN H KOLEJIAN
02/18/2021 09:28:34 AM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24

Date:	January 12, 2022
Reviewer:	Joel L. Wessfeld, MD MPH Division of Epidemiology I
Team Leader:	Catherine Lerro, PhD MPH Division of Epidemiology I
Deputy Director:	CAPT. Sukhminder K. Sandhu, PhD MPH MS Division of Epidemiology I
Subject:	Maternal and fetal outcomes
Drug Name:	upadacitinib (RINVOQ)
Application Type/Number:	NDA 211675 S-004
Submission Number:	eCTD 0054
Applicant/sponsor:	AbbVie
OSE RCM #:	2021-274

Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

Upadacitinib is a (small molecule, molecular weight 389.38) Janus kinase (JAK) inhibitor first approved in August 2019 for once daily oral administration (8- to 14-hour elimination half-life) in adults with moderately to severely active rheumatoid arthritis. Functioning as intracellular tyrosine kinases, the JAKs transmit cytokine signals by phosphorylating certain gene transcription factors. NDA 211675 S-004 seeks FDA approval for upadacitinib (b) (4) (b) (4).

1.2. Describe the Safety Concern

Atopic dermatitis (a chronic inflammatory skin disease) occurs in children and adults, including women in reproductive age groups. The use of upadacitinib by pregnant women might adversely affect pregnancy, fetal, or infant outcomes.

Citing animal studies, WARNINGS AND PRECAUTIONS in Prescribing Information (PI) for upadacitinib warns prescribers about Embryo-Fetal Toxicity.[a] The PI informs prescribers to "verify the pregnancy status of females of reproductive potential prior to starting treatment with RINVOQ." The PI also asks prescriber to "advise females of reproductive potential to use effective contraception during treatment with RINVOQ and for 4 weeks following completion of therapy."

The pregnancy section (Section 8.1; **APPENDIX 1**, as revised by the Division of Pediatrics and Maternal Health (DPMH)) presents data from pre-clinical studies in:[b]

- Pregnant rats that showed fetal skeletal malformations at maternal upadacitinib exposure equal to 0.9 to 1.0 times the maximum recommended human dose (MRHD).
- Pregnant rabbits that showed embryolethality, decreased fetal body weights, and cardiovascular malformations at maternal upadacitinib exposure equal to 8.5 times the MRHD.
- Rats that showed no maternal or developmental toxicity at maternal upadacitinib exposure (gestation day 6 through lactation day 20) equal to 1.6 times the MHRD.

Available data on use of upadacitinib in pregnant women are not sufficient to evaluate a drug-associated risk for major birth defects or miscarriage.[c] Clinical studies (all indications, as of

[a] Prescribing Information for RINVOQ™ (upadacitinib) extended-release tables, for oral use, revised 07/2020, accessed at Drugs@FDA on March 25, 2021.

[b] Mastroyannis C, T Johnson, and L Yao, Division of Pediatric and Maternal Health Review, filed under NDA 211675 on May 3, 2021 (DARRTS Reference ID: 4786528).

[c] *Ibid.*

February 15, 2021) have included 53 women and 54 pregnancies (one woman pregnant twice) with exposure to upadacitinib (any exposure in the one month before conception through end of first trimester).[d] No pregnancy ended in livebirth or stillbirth with congenital anomaly. Pregnancy outcomes included uncomplicated live birth (n=17), spontaneous abortion (n=14), elective termination (n=9), ectopic pregnancy (n=1), pregnancy ongoing (n=12), and outcome unknown (n=1).[e] Fourteen of these 54 upadacitinib-exposed pregnancies occurred in women with atopic dermatitis.

The sponsor searched its global safety database (through February 15, 2021) to identify 19 post-marketing reports of upadacitinib exposure during pregnancy. Pregnancy outcomes (known for three pregnancies) included full-term birth without congenital anomaly (n=1), spontaneous abortion (n=1), and ectopic pregnancy (n=1).[f]

Anticipating use in women of reproductive age and inadvertent exposure during unplanned pregnancy, the DPMH assessed the "limited information" available as a reason for additional post-market assessment in women exposed to upadacitinib during pregnancy.[g] Outcomes of interest include major congenital malformation, spontaneous abortion, stillbirth, pre-term birth, and small for gestational age. DPMH recommended that FDA require a single-arm pregnancy study that uses "targeted questionnaires" to collect follow-up information about pregnancies exposed to upadacitinib.[h,i]

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

☐ No approved indication, but practitioners may use product off-label in pregnant women

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy

[d] Agency Response, submitted to NDA 211675 (eCTD 0069) on March 24, 2021.

[e] *Ibid*.

[f] *Ibid.*

[g] Mastroyannis, *op cit*.

[h] *Ibid.*

[i] "Single-arm pregnancy study" is also known as a "pregnancy surveillance program (a structured approach for data collection with targeted questionnaires to obtain follow-up information on all exposed pregnancy of which sponsors become aware)." See, FDA Draft Guidance for Industry, Postapproval Pregnancy Safety Studies, accessed at https://www.fda.gov/media/124746/download on March 30, 2021, p 8.

is recognized

☒ No approved indication, but use in women of childbearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty

☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.

☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review).

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☐ Pregnancy registry with internal comparison group

☐ Pregnancy registry with external comparison group

☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)

☐ Electronic database study with chart review

☐ Electronic database study without chart review (*e.g.*, retrospective cohort study using claims or electronic medical record data or a case-control study nested in a pre-existing pregnancy or birth defect registry)

☒ Other, please specify: Single-arm pregnancy safety study, a protocol-driven observational cohort study that collects detailed data for descriptive analysis. DPMH might recommend a single-arm pregnancy safety study (also known as a pregnancy surveillance program) "when use of a product is not recommended during pregnancy."[j] This consideration applies to upadacitinib, as expressed in the upadacitinib label, which advises effective contraception in women with reproductive potential. Consequently, infrequent drug exposure anticipated in pregnant women precludes comparative analysis and negates any requirement for a preset sample size.

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population

☐ Exposures

☒ Outcomes

☐ Covariates

☒ Analytical Tools

For any checked boxes above, please describe briefly:

Outcomes: DPMH's PMR request for a single-arm pregnancy safety study requires "targeted questionnaires" for collection of detailed and specific information about the timing of upadacitinib use in relation to well-defined pregnancy outcomes. Data elements considered

[j] FDA Draft Guidance, *op. cit.*

appropriate for collection by targeted questionnaire (per FDA guidance) include drug or biological product exposures and results from neonatal physical examination. Data collection should occur at pre-determined intervals (e.g., at study enrollment, mid-point of pregnancy, estimated delivery date, 3-6 months postpartum, and 12 months postpartum.[k] A series of well-documented case narratives that present detailed clinical information acquired directly from primary sources (*e.g.*, medical records and providers) might permit credible assessment of the causal significance of an adverse event associated with upadacitinib exposure during pregnancy. The requirement for special questionnaires necessitates data collection not possible in the Sentinel Distributed Database (SDD).

Analytical tools: The requested PMR targets more than one outcome, including major congenital malformations (MCM), spontaneous abortions, stillbirths, small for gestational age, and preterm birth. Moreover, the MCM outcome covers several subclasses of potential interest (e.g., congenital malformation of the circulatory system, congenital malformation of the nervous system, or cleft lip and cleft palate). ARIA might address the complexity presented by multiple discrete outcomes by means of an appropriate data mining approach. However, a suitable data mining approach (e.g., TreeScan) is not yet available for signal detection of birth defects and other pregnancy outcomes in ARIA.

2.5. Please include the proposed PMR language in the approval letter.

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.

[k] Email communication from T Johnson (DPMH) to J Weissfeld (DEPI) on April 13, 2021.

APPENDIX 1: Section 8.1 text proposed by DPMH for RINVOQ (upadacitinib) tablets[1]

8.1 Pregnancy

Risk Summary

Available data from the pharmacovigilance safety database and postmarketing case reports on use of RINVOQ in pregnant women are not sufficient to evaluate a drug-associated risk for major birth defects, or miscarriage. Based on animal studies, RINVOQ has the potential to adversely affect a developing fetus. Advise patients of reproductive potential and pregnant patients of the potential risk to the fetus.

In animal embryo-fetal development studies, oral upadacitinib administration to pregnant rats and rabbits at exposures equal to or greater than approximately 2 and 17 times the 15 mg dose and 0.9 and 8.5 times the maximum recommended human dose (MRHD) of 30 mg, respectively, resulted in dose-related increases in skeletal malformations (rats only), an increased incidence of cardiovascular malformations (rabbits only), increased post-implantation loss (rabbits only), and decreased fetal body weights in both rats and rabbits. No developmental toxicity was observed in pregnant rats and rabbits treated with oral upadacitinib during organogenesis at approximately 0. 3 and 2.5 times the 15 mg dose and 0.2 and 1.3 times the MRHD of 30 mg, respectively. In a pre- and post-natal development study in pregnant female rats, oral upadacitinib administration at exposures approximately 1.6 times the MRHD of 30 mg resulted in no maternal or developmental toxicity (*see Data*).

The background risks of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriages are 2-4% and 15-20%, respectively.

Report pregnancies to the [applicant's] Adverse Event reporting line at 1-888-633-9110, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data suggest that increased disease activity is associated with the risk of developing adverse pregnancy outcomes in women with rheumatoid arthritis. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Data

Animal Data

In an oral embryo-fetal development study, pregnant rats received upadacitinib at doses of 5, 25, and 75 mg/kg/day during the period of organogenesis from gestation day 6 to 17. Upadacitinib was teratogenic (skeletal malformations that consisted of misshapen humerus and bent scapula) at exposures equal to or greater than approximately 1.0 times the MRHD of 30 mg (on an AUC basis at maternal oral doses of 5 mg/kg/day and higher). Additional skeletal malformations (bent forelimbs/hindlimbs and rib/vertebral defects) and decreased fetal body weights were observed in the absence of maternal toxicity at an exposure approximately 48 times the MRHD of 30 mg (on an

[1] Prescribing Information, submitted to NDA 211675 (eCTD 0061) on January 13, 2021.

AUC basis at a maternal oral dose of 75 mg/kg/day).

In a second oral embryo-fetal development study, pregnant rats received upadacitinib at doses of 1.5 and 4 mg/kg/day during the period of organogenesis from gestation day 6 to 17. Upadacitinib was teratogenic (skeletal malformations that included bent humerus and scapula) at exposures approximately 0.9 times the MRHD of 30 mg (on an AUC basis at maternal oral doses of 4 mg/kg/day). No developmental toxicity was observed in rats at an exposure approximately 0.2 times the MRHD of 30 mg (on an AUC basis at a maternal oral dose of 1.5 mg/kg/day).

In an oral embryo-fetal developmental study, pregnant rabbits received upadacitinib at doses of 2.5, 10, and 25 mg/kg/day during the period of organogenesis from gestation day 7 to 19. Embryolethality, decreased fetal body weights, and cardiovascular malformations were observed in the presence of maternal toxicity at an exposure approximately 8.5 times the MRHD of 30 mg (on an AUC basis at a maternal oral dose of 25 mg/kg/day). Embryolethality consisted of increased post-implantation loss that was due to elevated incidences of both total and early resorptions. No developmental toxicity was observed in rabbits at an exposure approximately 1.3 times the MRHD of 30 mg (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

In an oral pre- and post-natal development study, pregnant female rats received upadacitinib at doses of 2.5, 5, and 10 mg/kg/day from gestation day 6 through lactation day 20. No maternal or developmental toxicity was observed in either mothers or offspring, respectively, at an exposure approximately 1.6 times the MRHD of 30 mg (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOEL L WEISSFELD
01/12/2022 06:11:57 PM

CATHERINE C LERRO
01/12/2022 10:34:11 PM

SUKHMINDER K SANDHU
01/13/2022 09:56:13 AM

JUDITH W ZANDER
01/13/2022 10:16:03 AM

SARAH K DUTCHER
01/13/2022 10:22:47 AM

GERALD J DALPAN on behalf of ROBERT BALL
01/13/2022 12:13:54 PM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology ARIA Sufficiency Memorandum
Version: 2018-01-24

Date:	January 12, 2022
Reviewer:	Joel L. Weissfeld, MD MPH Division of Epidemiology I
Team Leader:	Mingfeng Zhang, MD PhD Division of Epidemiology I
Division Director:	CAPT. Sukhminder K. Sandhu, PhD MPH MS Division of Epidemiology I
Subject:	MACE, Malignancy, and Thrombosis
Drug Name:	upadacitinib (RINVOQ)
Application Type/Number:	NDA 211675 S-004
Submission Number:	0054
Applicant/sponsor:	AbbVie
OSE RCM #:	2021-276

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concerns?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
- Surveillance or Study Population	
- Exposure	
- Outcomes of Interest	X
- Covariates of Interest	
- Surveillance Design/Analytic Tools	

1. BACKGROUND INFORMATION

1.1. Medical Product

Upadacitinib is a Janus kinase (JAK) inhibitor first approved in August 2019 for once daily oral administration in adults with moderately to severely active rheumatoid arthritis.[a] NDA 211675 S-004 seeks FDA approval for treatment of (b) (4) (b) (4)

1.2. Describe the Safety Concern

During its review of NDA 211675 S-004, DDD used new information about the safety of tofacitinib (another JAK inhibitor) to inform its post-market safety requirements for upadacitinib.[b] As summarized below, the new information substantiated Major Adverse Cardiovascular Events (MACEs), malignancies, and thrombosis as safety risks due to treatment with tofacitinib.[c] Assessing these risks as effects plausibly produced by JAK inhibition in general, DDD categorized MACE, malignancy, and thrombosis as important potential post-market safety risks from upadacitinib treatment for atopic dermatitis.

This ARIA Sufficiency Memorandum presents OSE's ARIA Sufficiency Assessment for upadacitinib and the serious adverse events of MACE, malignancy, and thrombosis in adolescent and adult patients with atopic dermatitis.

Four sources of information support concerns about the post-market safety of upadacitinib: (1) randomized post-market study of the safety of another JAK inhibitor, (2) adverse events in clinical studies of upadacitinib, (3) class-wide biochemical toxicities from JAK inhibition, and (4) mechanism of therapeutic action (immunosuppression).

1. Study of another JAK inhibitor (*Phase 3b/4 Randomized Safety Endpoint Study of 2 Doses of a JAK inhibitor in Comparison to a Tumor Necrosis Factor (TNF) Inhibitor in Subjects with Rheumatoid Arthritis*)

   This study randomized ≥50-year-old patients with rheumatoid arthritis and ≥1 cardiovascular-disease risk factor to treatment with (a) a JAK inhibitor 10 mg daily (1456 patients with 3.64-year mean follow-up), (b) a JAK inhibitor 5 mg daily (1455 patients with 3.77-year mean follow-up), or (c) an inhibitor of tumor necrosis factor-alpha (TNF; 1451 patients with 3.77-year mean follow-up). MACE, malignancies, and thrombosis occurred more often in patients treated with a JAK inhibitor than patients treated by TNF inhibition (Table 1).

---

[a] Prescribing Information for RINVOQ (upadacitinib) extended-release tablets, for oral use, revised 07/2020, accessed at Drugs@FDA on March 24, 2021.

[b] Pfizer, Final Clinical Study Report (CSR), *Phase 3b/4 Randomized Safety Endpoint Study of 2 Doses of Tofacitinib in Comparison to a Tumor Necrosis Factor (TNF) Inhibitor in Subjects with Rheumatoid Arthritis* (A3921133), June 2, 2021, submitted to NDA 203214 (eCTD 1534) on July 1, 2021.

[c] Integrated Safety Review (ISR), Safety Labeling Changes for Janus Kinase Inhibitors for Inflammatory Conditions (Tofacitinib, Baricitinib, Upadacitinib), filed under NDA 203214 on August 17, 2021 (DARRTS Reference ID: 4842642).

Table 1: Adverse events in treatment groups from the *Phase 3b/4 Randomized Safety Endpoint Study of Two Doses of a JAK inhibitor in Comparison to a Tumor Necrosis Factor (TNF) Inhibitor in Subjects with Rheumatoid Arthritis)*

Comparing treatment with another JAK inhibitor (JAK) 10 mg daily vs. inhibition of tumor necrosis factor-alpha (TNF)				
	Number (%) of patients with event (On-Study)			
Endpoint	**TNF (N=1451)**	**JAK 10 mg (N=1456)**	**RR**	**95% CI**
MACE	43 (3.0)	59 (4.1)	1.37	0.93-2.01
Malignancy except NMSC	42 (2.9)	60 (4.1)	1.42	0.97-2.10
Lymphoma	1 (0.1)	6 (0.4)	5.98	0.72-49.6
Death	38 (2.6)	66 (4.5)	1.73	1.17-2.56
Thrombosis	56 (3.9)	86 (5.9)	1.53	1.10-2.13
Comparing treatment with another JAK inhibitor (JAK) 5 mg daily vs. inhibition of tumor necrosis factor-alpha (TNF)				
	Number (%) of patients with event (On-Study)			
Endpoint	**TNF (N=1451)**	**JAK 5 mg (N=1455)**	**RR**	**95% CI**
MACE	43 (3.0)	50 (3.4)	1.16	0.78-1.74
Malignancy except NMSC	42 (2.9)	62 (4.3)	1.47	1.00-2.16
Lymphoma	1 (0.1)	4 (0.3)	3.99	0.45-35.6
Death	38 (2.6)	49 (3.4)	1.29	0.85-1.95
Thrombosis	56 (3.9)	67 (4.6)	1.19	0.84-1.69

SOURCE: ISR Tables 14 and 16; CSR Table 14.2.2.1; RRs and 95% CIs calculated by DEPI
ABBREVIATIONS: RR – relative risk; CI – confidence interval; MACE – Major Adverse Cardiovascular Event; NMSC – non-melanoma skin cancer

2. Adverse events in clinical studies of upadacitinib

As shown in Table 2, MACE, malignancies, and venous thromboembolic events occurred in NDA study patients during treatment with upadacitinib for atopic dermatitis.

Table 2: Summary of patient demographics, drug exposure, and treatment-emergent adverse events of interest in ALL Upadacitinib AD Analysis Set for NDA 211675 S-004

Number of patients	2898
Patient age, years, median (IQR)	30 (22-46)
Cumulative drug exposure, patient-years	3256
Number of patients with drug exposure ≥48 weeks	2156
Deaths	2

Adverse Events of Special Interest, number of patients	
Serious infection	68
Herpes zoster (HZ) ≥2 dermatomes	37
Active tuberculosis (TB)	2
Opportunistic infection excluding TB and HZ	53
Malignancy excluding NMSC	9
Adjudicated Major Adverse Cardiovascular Event (MACE)	4
Adjudicated venous thromboembolism (VTE)	3
Other adverse events of interest, number of patients	
Lymphoma	3
Retinal detachment	4

SOURCE: Upadacitinib (ABT-494) Safety Update, submitted to NDA 211675, eCTD 0061, on January 13, 2021; Chambers WA, Medical Review by Ophthalmology Consultant, filed under 211675 on February 22, 2021 (DARRTS Reference ID: 4750274). Median and IQR for age determined by DEPI from ADLS analysis dataset submitted to NDA 211675 (eCTD 0061) on January 13, 2021.
ABBREVIATIONS: IQR – interquartile range; NMSC – non-melanoma skin cancer
FOOTNOTES:
1 Includes events occurring 30 days after treatment discontinuation.
2. For Malignancy excluding NMSC – Ten events in nine patients; two malignancy events (breast and colon cancer) occurred in one patient (USUBJID= M16-045 17021005) on separate dates.
3. Opportunistic infection excluding TB and HZ – The presentation in this table for this adverse-event category excludes oral candidiasis.

3. Class-wide biochemical toxicities from JAK inhibition

Laboratory assessments for NDA 211675 S-004 showed relationship between upadacitinib dose and LDL cholesterol (Table 3), a toxicity generally observed from JAK inhibition and a motivating rationale for the cardiovascular outcome trial (Study A3921133) conducted as a post-marketing requirement for tofacitinib (PMR 1934-3).

Table 3: Mean Baseline and Week-16 LDL cholesterol (mg/dL) for patients with non-missing values at both timepoints (Placebo-Controlled AD Analysis Set)

Group	N	Baseline	Week 16	Δ	95% CI
Placebo	764	99.1	100.8		
UPA 15 mg	842	99.4	107.5	6.5	4.3-8.7
UPA 30 mg	842	97.4	110.8	11.5	9.3-13.7

SOURCE: ISS Table 2.5.1.1
ABBREVIATIONS: LDL – low-density lipoprotein; Δ – mean change from ANCOVA model with terms for baseline value and clinical trial; CI – confidence interval

4. Mechanism of therapeutic action (immunosuppression)

As immunosuppressives, the JAK inhibitors present similar theoretical risks for opportunistic infection, serious infection, non-Hodgkin lymphoma, and possibly other types

of malignancy. Assessments conducted by the Office of Clinical Pharmacology found no compelling reason to attribute relative safety to JAK inhibitors with different target specificity.[d,e]

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Table 4: FDAAA Purpose

Assess a known serious risk	
Assess signals of serious risk	X
Identify unexpected serious risk	

1.4. Statement of Purpose

DDD characterized the regulatory purpose for a post-market assessment of upadacitinib and the serious adverse events of concern (MACE, malignancies, and thrombosis) as: signal refinement (evaluate the magnitude or clinical significance of a possible association between a drug treatment and a serious adverse event). As indicated by the study description in the following paragraph, OSE assessed sufficiency of ARIA for a study that compares adverse event incidence between atopic dermatitis patients treated with upadacitinib and atopic dermatitis patients not treated with upadacitinib (internal reference group).

Conduct an observational study to assess MACE, malignancy, and venous thromboembolism in adolescent and adult patients with atopic dermatitis during and after treatment with upadacitinib. For each adverse-event outcome separately, compare incidence in the target population against reference rates internally derived from analyses conducted in patients treated with dupilumab or other chronic systemic treatments for moderate-to-severe atopic dermatitis.

1.5. Effect Size of Interest or Estimated Sample Size Desired

The sample sizes for the desired post-market studies should target estimation of incidence rates for adverse events expected to occur with a frequency of ≈2 to 4 events per 1000 patient-years.[f]

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

For purposes of ARIA assessment, we defined the desired population as ≥12 year-old patients with atopic dermatitis treated with an agent usually reserved for moderate or severe disease.

Atopic dermatitis is a chronic pruritic inflammatory skin disease that occurs mostly in children, but also in adults. Associated features include personal or family history of atopy (asthma or hay fever) and dermatitis affecting skin creases (antecubital fossae, popliteal fossae, neck, areas around eyes, fronts of ankles). Appropriate modalities for chronic treatment of moderate or severe disease include (1) high- or ultra-high potency topical corticosteroids, (2)

---

[d] JAK inhibitors variably target four intracellular enzymes (JAK1, JAK2, JAK3, and TYK2).

[e] ISR, Non-Clinical Considerations, APPENDIX 1, pp 69-82.

[f] Pfizer, Final Study Report: External Controls for Risk Characterization in Support of the Abrocitinib Clinical Trial Program: A Population-Based External Cohort Study using The Kaiser Permanente Northern California Members (B7451044), submitted to NDA 213871 (eCTD 0001) on June 29, 2020, Table 1, pp 23-25.

phototherapy, (3) immunosuppression (with methotrexate, azathioprine, mycophenolic acid, or cyclosporine), and (4) dupilumab.

2.2 Is ARIA sufficient to assess the intended population?

YES. ARIA reliably captures patient age. The Sentinel Distributed Database (SDD) permits identification of patients encountering medical care with a presumptive diagnosis of atopic dermatitis (ICD-10-CM L20). National Drug Classification (NDC) and Current Procedural Terminology (CPT) codes in SDD permit identification of patients with healthcare claims for medical treatments typically considered appropriate for moderate or severe atopic dermatitis. (See Section 3.)

The objectives for the requested post-market evaluation require a real-world sample of patients who receive upadacitinib (or other appropriate medical treatment) for no apparent reason other than atopic dermatitis. ARIA can reasonably satisfy this regulatory requirement, for example, by using diagnosis and procedure codes in SDD to define an exposed cohort of ≥12-year-old patients with (1) a new (index) pharmacy dispensing for upadacitinib (an inappropriate treatment for mild atopic dermatitis) occurring within 90 days of a previous medical encounter ostensibly for atopic dermatitis (ICD-10-CM L20) and (2) no pre-index medical encounters (within 365 days) ostensibly for any other upadacitinib treatment indication (currently only rheumatoid arthritis, ICD-10-CM M05-M06).

3 EXPOSURES

3.1 Treatment Exposure

For purposes of ARIA assessment, we defined the exposure of interest as treatment with upadacitinib. For certain endpoints (*e.g.*, malignancy), treatment-related events might increase in frequency after a post-initiation latent period or persist after discontinuation of treatment.

3.2 Comparator Exposure

For purposes of ARIA assessment, we considered two reference (comparator) exposures, a broad reference defined by several treatment approaches and a narrow reference defined by one treatment (dupilumab, an interleukin-4 receptor alpha antagonist).

A broad reference might define exposure by any treatment selected from a class (other than JAK inhibitors) typically reserved for moderate or severe atopic dermatitis. Candidate treatment classes include (1) high- or ultra-high potency topical corticosteroids, (2) phototherapy, (3) cyclosporine, and (4) dupilumab. Post-market assessments in SDD might use a broadly defined reference to obtain precise estimates of adverse event incidence in adults and adolescents with moderate or severe atopic dermatitis. A narrow reference might define exposure by treatment with dupilumab, a modern biologic approved in 2017 for moderate-to-severe atopic dermatitis. (During post-SAM discussions, DDD introduced a requirement for a comparator restricted to "dupilumab or other chronic systemic treatments for moderate-to-severe atopic dermatitis." This definition covers dupilumab and cyclosporine and excludes topical steroids and phototherapy.)

3.3 Is ARIA sufficient to identify the exposures of interest?

YES. NDCs (*e.g.*, 0074-2306) in SDD permit identification of patients with pharmacy dispensings for upadacitinib (an orally administered drug).

NDCs in SDD permit identification of patients with pharmacy dispensings for non-upadacitinib

treatments, including, for example, (1) cyclosporine (*e.g.*, Neoral® oral liquid-filled capsule, NDCs 0078-0246 and 0078-0248) and (2) dupilumab (*i.e.*, Dupixent®, a biologic formulated for self-administration by subcutaneous injection, NDCs 0024-5914, 0024-5915, 0024-5916, and 0024-5918).

ARIA tools generate longitudinal records of outpatient pharmacy dispensings, which permit construction of patient-specific episodes of treatment with upadacitinib or other topical, oral, or self-injectable agents used in patients with moderate or severe atopic dermatitis.

CPTs in SDD also permit identification of medical encounters for phototherapy procedures used to treat moderate or severe atopic dermatitis (Table 4). Individual phototherapy sessions for atopic dermatitis typically occur frequently (*e.g.*, twice weekly) over a period of time defined by clinical response.[g]

Table 4: Current Procedural Terminology for phototherapy and photo-chemotherapy.

CPT	PROCEDURE – LONG DESCRIPTION
96900	ACTINOTHERAPY ULTRAVIOLET LIGHT
96910	PHOTOCHEMOTX TAR&UVB/PETROLATUM/UVB
96912	PHOTOCHEMOTX PSORALENS&ULTRAVIOLET PUVA
96913	PHOTOCHEMOTHERAPY DERMATOSES 4-8 HRS SUPERVISION

DDD presented upadacitinib as a long-term treatment for a chronic condition. As of November 24, 2020 (data cutoff date), 1920 (66.3%) of 2898 patients in the ALL Upadacitinib AD Safety Population had continued upadacitinib treatment for at least 52 weeks.[h] Therefore, ARIA might reasonably use an intention-to-treat risk window, defined as the 3-year period after an index exposure to upadacitinib (or reference treatment), with follow-up terminating on death, disenrollment, end of study period, Sentinel Data Partner data cutoff date, or (depending on the safety outcome) discontinuation of the cohort-defining treatment.

Upadacitinib and dupilumab present distinct differences for prescribers and patients.

- Upadacitinib is a tablet taken orally once daily and dupilumab a subcutaneous injection self-administered every other week.
- Labeling for dupilumab carries Warnings and Precautions for (1) hypersensitivity, (2) conjunctivitis and keratitis, (3) eosinophilic conditions, and (4) parasitic infections.[i] Updated labeling for upadacitinib will present Boxed Warnings for (1) serious bacterial, fungal, viral, and opportunistic infection (including tuberculosis), (2) all-cause mortality

[g] Sidbury R, *et al*. Guidelines of care for the management of atopic dermatitis. Part 3: Management and treatment with phototherapy and systemic agents. J Am Acad Dermatol. 2014;71(2):327-349.

[h] Upadacitinib (ABT-494) Safety Update, submitted to NDA 211675 (eCTD 0061) on January 13, 2021.

[i] Prescribing Information for DUPIXENT® (dupilumab) injection, for subcutaneous use, 10/2021 (Revised), accessed at Drugs@FDA on October 25, 2021.

(including sudden cardiovascular death), (3) malignancies (including lymphoma and lung cancer), (4) MACE, and (5) pulmonary embolism and venous thrombosis.[j]

- FDA labeling indicates dupilumab for "the treatment of patients aged 6 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable."[k] Updated FDA labeling will restrict upadacitinib to "adult and pediatric patients 12 years of age and older with *refractory* [*emphasis added*], moderate to severe atopic dermatitis whose disease is not adequately controlled with *other systemic drugs, including biologics* [*emphasis added*], or when use of those therapies are inadvisable."[l]

These differences introduce strong potential for patient channeling that might severely challenge or possibly invalidate (non-randomized) observational studies seeking causal estimates of upadacitinib treatment effects. Despite these limitations, we assessed dupilumab (and the other comparator treatments considered) as **ARIA Sufficient** for signal refinement (the regulatory purpose for the post-market safety assessment required by DDD).

4 OUTCOMES

4.1 Outcomes of Interest

The motivating outcomes behind a possible post-market requirement include MACE, malignancies, and thrombosis. Other outcomes of concern include serious infections, opportunistic infections (including herpes zoster), hepatoxicity (including drug induced liver injury), and retinal detachment.

DDD defined MACE to include myocardial infarction (MI), stroke, cardiovascular death, and sudden cardiovascular death. FDA defines (1) myocardial infarction as "myocardial necrosis in a clinical setting consistent with myocardial ischemia," (2) stroke as an "acute episode of [typically persistent] focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction," (3) cardiovascular death as "death resulting from an acute myocardial infarction (MI), sudden cardiac death, death due to heart failure (HF), death due to stroke, death due to cardiovascular (CV) procedures, death due to CV hemorrhage, and death due to other CV causes," and (4) sudden cardiac death as "death that occurs unexpectedly and not within 30 days of an acute MI."[m,n]

The National Cancer Institute (NCI) defines malignancy as a disease "in which abnormal cells divide without control and can invade nearby tissues."[o] The NCI Surveillance, Epidemiology,

---

[j] Safety Labeling Change Notification (SLC), filed under NDA 211675 on August 23, 2021 (DARRTS Reference ID: 4845606).

[k] Prescribing Information for DUPIXENT® (dupilumab) injection, *op. cit.*

[l] Prescribing Information for RINVOQ™ (upadacitinib) extended-release tablets, for oral use, accessed as [NDA 211675 S004 Prescribing Information w edits 080321 v3.docx] on DDD SharePoint site (link) on October 26, 2021.

[m] Hicks KA, *et al*. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. Circulation. 2018;137:961-972.

[n] With sudden cardiac death further defined by reference to seven clinical scenarios.

[o] National Cancer Institute, Dictionary of Cancer Terms, accessed at Definition of malignancy - NCI Dictionary of Cancer Terms - National Cancer Institute on October 27, 2021.

and End Results (SEER) Program identifies primary-site tumors with malignant (invasive) potential by behavior code (NAACCR Item #523).[p]

Venous thromboembolism (VTE) includes deep vein thrombosis (DVT) and pulmonary embolism (PE). Criteria for definite DVT typically require confirmation by venography, duplex ultrasound, imaging (computerized tomography or magnetic resonance imaging), or autopsy.[q] Criteria for definite PE typically require confirmation by angiography, imaging, or pathology.[r]

4.2 Is ARIA sufficient to assess the outcomes of interest?

NO. The particular regulatory purpose for post-market assessment of upadacitinib safety requires accurate estimates of adverse event incidence. For study outcomes with low incidence (such as, MACE, malignancies, and VTE in the atopic dermatitis patient population), recent FDA Guidance for Real-World Data (*e.g.*, SDD) stresses the importance of identifying outcomes with both high specificity and high sensitivity.[s] Post-market studies using electronic healthcare data (such as, SDD) might accurately identify the outcomes of interest by complete verification of possible events initially ascertained by sensitive code search. Adequate verification typically requires standardized clinical review of primary patient records stored in paper or electronic medical record systems. An electronic healthcare data source linked to a suitable cancer registry might accurately identify patients with a newly recognized malignancy. However, ARIA capabilities currently exclude (1) clinical review of primary patient records for outcome verification and (2) SDD linkage to population-based cancer registries. In the particular regulatory context presented by upadacitinib NDA 211675 S-004, sufficient post-market assessment of ultra-rare and heterogenous outcomes (such as lymphoma) requires access to primary patient records for detailed characterization and accurate classification.

Complete capture of MACE requires a method for identifying sudden cardiac deaths that occur in settings outside the healthcare system. Post-market studies might accurately ascertain sudden cardiac deaths in an electronic healthcare data source if linked to a population-based mortality register (*e.g.*, U.S. National Death Index). However, ARIA capabilities currently exclude SDD linkage to the National Death Index.[t] In certain settings, OSE might accept one approach for assessing sudden cardiac death and entirely different approaches for assessing other MACE components. In the current regulatory context, sufficient assessment of MACE as a composite requires a uniform approach that assesses each of the MACE components with comparable rigor.

---

[p] Adamo M, Groves C, Dickie L, Ruhl J. (September 2021). SEER Program Coding and Staging Manual 2022. National Cancer Institute, Bethesda, MD 20892, accessed at SEER Program Coding and Staging Manual 2022 (cancer.gov) on October 27, 2021, pp 106-108.

[q] Spencer FA, *et al*. The Worcester Venous Thromboembolism Study: a population-based study of the clinical epidemiology of venous thromboembolism. J Gen Intern Med. 2006;21:722-727.

[r] *Ibid*.

[s] Food and Drug Administration, September 2021, Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products, Draft Guidance for Industry, accessed at https://www.fda.gov/media/152503/download on October 27, 2021, , p19.

[t] OSE often cites incomplete capture of sudden cardiac death as a reason for determining ARIA Not Sufficient for MACE. For precedent, see, Liu W, *et al*., ARIA Sufficiency Memo for romosozumab (Evenity®), filed under BLA 761062 on March 18, 2019 (DARRTS Reference ID: 4405363).

ARIA might identify VTE with sufficient specificity for some regulatory purposes.[u] In some clinical settings (*e.g.*, after orthopedic surgery), events operationally defined by coded information in an electronic healthcare data source might identify VTE with near perfect specificity (*i.e.*, positive predictive value approaching 100%).[v] However, OSE finds no evidence to support a determination that a highly specific operational definition might achieve the sensitivity required for accurate estimation of VTE incidence in the atopic dermatitis patient population.

Finally, poor patient retention in SDD limits the usefulness of ARIA for long latency outcomes (such as, malignancy).[w]

To address the regulatory purpose presented by upadacitinib treatment for atopic dermatitis, OSE finds **ARIA Not Sufficient** in the Outcomes domain. Sufficiency requires particularly rigorous methods for ascertaining and characterizing the motivating outcomes of concern (MACE, malignancies, and thrombosis) and any other serious adverse event regarded as appropriate for post-market assessment.

In summary, the particular regulatory purpose presented for post-market assessment of upadacitinib safety requires accurate estimates of adverse event incidence. Accurate estimation requires methods that identify outcomes with both high specificity and high sensitivity. ARIA algorithms for identifying the outcomes of concern generally have poor or unknown sensitivity and minimally acceptable category-wide specificity (e.g., lymphoma as a broad outcome class) but poor or unknown specificity for possibly important outcomes within a class (e.g., peripheral T-cell lymphoma).

A quantitative assessment conducted for this ARIA Sufficiency Memorandum indicated that ARIA using a highly specific and moderately sensitive method (75% sensitivity) might estimate incidence with accuracy sufficient for signal refinement. This quantitative assessment also indicated that ARIA with insensitive methods (<50% sensitivity) would underestimate incidence with a magnitude of error large enough to defeat the regulatory purpose for the post-market study required by DDD. Meaningful quantitative bias analysis (QBA) of ARIA results would require information currently unavailable about the sensitivity of ARIA methods for ascertaining MACE, malignancy, and thrombosis.

5 COVARIATES

5.1 Covariates of Interest

Table 5 lists covariates possibly important to data analysis and study interpretation. ARIA might use information about these covariates to conduct analyses in patient subgroups defined by sex, age, treatment history, and disease severity.

---

[u] For precedent, see, Ajao A, *et al.*, ARIA Sufficiency Memo for Levonorgestrel and Ethinyl Estradiol Transdermal System, filed under NDA 204017 on January 25, 2020 (DARRTS Reference ID: 4565904).

[v] Tamariz L, et al. A systematic review of validated methods for identifying venous thromboembolism using administrative and claims data. Pharmacoepidemiol Drug Saf. 2012;21 Suppl 1:154-162.

[w] OSE often cites poor long-term follow as a reason for determining ARIA Not Sufficient for malignancy. For precedent, see, Callahan C, *et al.*, ARIA Sufficiency Memo for mavenclad (Cladribine®), filed under NDA 022561 on March 20, 2020 (DARRTS Reference ID: 4406278).

Table 5: Covariates of Interest

Safety Endpoint	Possibly Important Covariates
MACE	age, sex, history of hypertension, history of diabetes, history of myocardial infarction or stroke (possible criterion for cohort exclusion), history of other cardiovascular disease, AD disease severity, and tobacco use history
Malignancy	age, sex, history of HIV/AIDS, organ transplantation, or autoimmune disease (possible criteria for cohort exclusion), AD disease severity, history of malignancy (possible criterion for cohort exclusion), and tobacco use history
Venous thrombo-embolism	age, sex, concomitant use of oral contraceptives (women only), AD disease severity, and history of thrombosis (possible criterion for cohort exclusion)

ABBREVIATION: AD – atopic dermatitis

5.2 Is ARIA sufficient to assess the covariates of interest?

YES. ARIA reliably captures patient sex and age. ARIA might credibly use diagnosis, procedure, and pharmacy codes in SDD to exclude patients with organ transplantation, autoimmune disease, HIV infection, or malignancy history.

Within limits imposed by the time-restricted historical patient record available in SDD, ARIA might credibly use diagnosis, procedure, and pharmacy codes in SDD to classify patients into subgroups defined by medical history. Cohort eligibility requiring 12-month pre-index enrollment in SDD should provide sufficient data capture for signal refinement.

ARIA offers no method for direct assessment of AD severity, a factor expected to determine exposure (upadacitinib or reference exposure) and possibly associated with one or more of the outcomes of interest. However, ARIA might use pre-index AD-specific treatments as a crude proxy for AD severity.[x] ARIA offers incomplete methods for assessing lifestyle risk factors (*e.g.*, tobacco use history). Despite these limitations, we assessed covariate capture as ARIA Sufficient for signal refinement.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

ARIA might address the objectives for post-market assessment by conducting analyses in patient cohorts defined by age, index AD treatment, and pre-index medical history.

Applicable ARIA analytic tools permit descriptive (Level 1) and comparative (Level 2) analysis, as indicated below.

- Level 1 (Descriptive) Analysis
  - To determine exposure (number of exposed patients and patient-years at risk).

[x] Cho Y-T, *et al*. Prevalence of baseline comorbidities in patients with atopic dermatitis: A population-based cohort study in Taiwan. JAAD Int. 2020;1(1):50-58 (https://doi.org/10.1016/j.jdin.2020.05.002).

  - To calculate (background) incidence rates for the adverse events of interest in ≥12-year-old patients with moderate or severe atopic dermatitis.

- Level 2 (Comparative) Analysis
  - Covariate Stratification – to calculate incidence rates for the adverse events of interest in patient cohorts defined by exposure (upadacitinib, broad reference, or narrow reference) and other covariates (age, sex, index year, and pre-index medical history).
  - Propensity Score Analysis – to estimate an effect size with additional control for pre-index AD-specific treatments (as a proxy for AD severity).[y]

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

YES. ARIA offers tools suited to the objectives for this post-market assessment. Post-market assessment in ARIA might proceed with a preliminary series of feasibility analyses (using Level 1 tools), followed later by a comparative analysis using the appropriate Level 2 tool (as determined by results from feasibility analysis) – Covariate Stratification or Propensity Score Analysis.

In a favorable setting, ARIA Propensity Score Analysis in SDD might produce a credible quantitative estimate for causal effect. Regardless of the analytic tool, however, conditions necessary for credible causal analysis in ARIA might not apply to post-market assessment of upadacitinib and the outcomes of interest. As discussed above, factors that limit ARIA include (1) concern about the suitability of dupilumab as an active comparator, (2) validity of algorithms available for identifying the outcomes of interest, and (3) absence of a direct method for assessing AD severity. Although these factors preclude ARIA from signal evaluation (to inform causality), we considered Propensity Score Analysis as a possibly useful tool for signal refinement, which is the regulatory purpose for this PMR.

7 NEXT STEPS

On October 5, 2021, OSE closed a series of Signal Assessment Meetings (SAMs conducted on March 22, September 10, and September 23, 2021) and confirmed its determination of **ARIA Not Sufficient** by email exchanges with representatives from the OSE Sentinel Core Team, OSE Division of Epidemiology I (DEPI), OSE Division of Pharmacovigilance I, and OND Division of Dermatology and Dentistry (DDD).[z]

Upon approval of NDA 211675 S-004, DDD will issue a FDAAA Post-Marketing Requirement (PMR) for a study fitting the following description.

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

[y] Methods available in ARIA for Propensity Score Analysis include matching, stratification, inverse probability of treatment weighting (IPTW), and stratum weighting.

[z] Bui Nguyen T, October 5, 2021 (email), RE: INPUT NEEDED - VIRTUAL SIGNAL SAFETY ASSESSMENT, NDA 211675/S-004 UPADACITINIB, filed in ECMS Documentum as [RE_ INPUT NEEDED - VIRTUAL SIGNAL SAFETY ASSESSMENT.....NDA 211675_S-004 UPADACITINIB.pdf] on October 27, 2021 (Object ID: 090026fc803780a3).

(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.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOEL L WEISSFELD
01/12/2022 11:21:12 AM

MINGFENG ZHANG
01/12/2022 05:08:30 PM

SUKHMINDER K SANDHU
01/13/2022 09:55:47 AM

JUDITH W ZANDER
01/13/2022 10:15:31 AM

SARAH K DUTCHER
01/13/2022 10:22:34 AM

GERALD J DALPAN on behalf of ROBERT BALL
01/13/2022 12:14:42 PM