# NDA/BLA Multi-Disciplinary Review and Evaluation

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| **Application Type** | Prior approval supplements, new Type 3 NDA |
| **Application Number(s)** | NDA 211675/S-021<br>NDA 211675/S-022<br>NDA 218347 |
| **Priority or Standard** | Standard |
| **Submit Date(s)** | June 28, 2023 (211675/S-021 and 218347) and June 30, 2023 (211675/S-022) |
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| **PDUFA Goal Date** | April 28, 2024 (211675/S-021 and 218347) and April 30, 2024 (211675/S-022) |
| **Division/Office** | Division of Rheumatology and Transplant Medicine (DRTM)/ Office of Immunology and Inflammation (OII) |
| **Review Completion Date** | See electronic stamp date |
| **Established/Proper Name** | Upadacitinib |
| **(Proposed) Trade Name** | Rinvoq, Rinvoq LQ |
| **Pharmacologic Class** | Janus kinase (JAK) inhibitor |
| **Code name** | N/A |
| **Applicant** | AbbVie, Inc. |
| **Dosage form** | Extended-release tablet, oral immediate-release solution |
| **Applicant Proposed Dosing Regimen** | 10 to <20 kg: 3 mg (3 mL oral solution) twice daily<br>20 to <30 kg: 4 mg (4 mL oral solution) twice daily<br>≥ 30 kg: 6 mg (6 mL oral solution) twice daily or 15 mg (one 15 mg tablet) once daily |
| **Applicant Proposed Indication(s)/Population(s)** | Treatment of pediatric patients 2 years of age and older with active polyarticular (b) (4) juvenile idiopathic arthritis (b) (4) who have had an inadequate response or intolerance to one or more TNF blockers<br><br>Treatment of pediatric patients 2 years of age and older with active (b) (4) psoriatic arthritis (b) (4) |
| **Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication** | None |
| **Recommendation on Regulatory Action** | Approval |

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| **Recommended Indication(s)/Population(s)** (if applicable) | Treatment of pediatric patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis who have had an inadequate response or intolerance to one or more TNF blockers<br><br>Treatment of patients 2 years of age and older with active psoriatic arthritis who have had an inadequate response or intolerance to one or more TNF blockers |
| **Recommended SNOMED CT Indication Disease Term for each Indication** (if applicable) | Not applicable |
| **Recommended Dosing Regimen** | 10 to <20 kg: 3 mg (3 mL oral solution) twice daily<br>20 to <30 kg: 4 mg (4 mL oral solution) twice daily<br>≥30 kg: 6 mg (6 mL oral solution) twice daily or 15 mg (one 15 mg tablet) once daily |

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OPQA I =Office of Product Quality Assessment I
OPDP=Office of Prescription Drug Promotion
OSIS= Office of Study Integrity and Surveillance
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis I
DRISK=Division of Risk Management

## Signatures

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# Glossary

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| AC | advisory committee |
| AD | atopic dermatitis |
| ADME | absorption, distribution, metabolism, excretion |
| AE | adverse event |
| AR | adverse reaction |
| BID | twice daily |
| BLA | biologics license application |
| BPCA | Best Pharmaceuticals for Children Act |
| BRF | Benefit Risk Framework |
| CBER | Center for Biologics Evaluation and Research |
| CDER | Center for Drug Evaluation and Research |
| CDRH | Center for Devices and Radiological Health |
| CDTL | Cross-Discipline Team Leader |
| CFR | Code of Federal Regulations |
| CMC | chemistry, manufacturing, and controls |
| COSTART | Coding Symbols for Thesaurus of Adverse Reaction Terms |
| CRF | case report form |
| CRO | contract research organization |
| CRT | clinical review template |
| CSR | clinical study report |
| CSS | Controlled Substance Staff |
| DHOT | Division of Hematology Oncology Toxicology |
| DMC | data monitoring committee |
| ECG | electrocardiogram |
| eCTD | electronic common technical document |
| ER | extended-release |
| ETASU | elements to assure safe use |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FDASIA | Food and Drug Administration Safety and Innovation Act |
| GCP | good clinical practice |
| GRMP | good review management practice |
| ICH | International Conference on Harmonisation |
| IND | Investigational New Drug |
| IR | immediate-release |
| ISE | integrated summary of effectiveness |
| ISS | integrated summary of safety |
| ITT | intent to treat |

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|---|---|
| JIA | juvenile idiopathic arthritis |
| JPsA | juvenile psoriatic arthritis |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | modified intent to treat |
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for Adverse Event |
| NDA | new drug application |
| NME | new molecular entity |
| OCS | Office of Computational Science |
| QD | daily |
| OPQA I | Office of Product Quality Assessment I |
| OSE | Office of Surveillance and Epidemiology |
| OSI | Office of Scientific Investigation |
| PBRER | Periodic Benefit-Risk Evaluation Report |
| pcJIA | polyarticular course juvenile idiopathic arthritis |
| PD | pharmacodynamics |
| PI | prescribing information |
| pJIA | polyarticular juvenile idiopathic arthritis |
| PK | pharmacokinetics |
| PMC | postmarketing commitment |
| PMR | postmarketing requirement |
| PP | per protocol |
| PPI | patient package insert (also known as Patient Information) |
| PREA | Pediatric Research Equity Act |
| PRO | patient reported outcome |
| PsA | psoriatic arthritis |
| PSUR | Periodic Safety Update report |
| RA | rheumatoid arthritis |
| REMS | risk evaluation and mitigation strategy |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SGE | special government employee |
| SOC | standard of care |
| SUR | safety update report |
| TEAE | treatment emergent adverse event |

# 1 Executive Summary

## 1.1. Product Introduction

Upadacitinib (Rinvoq) is an oral, small molecule Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes that 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 transcriptions (STAT) which modulate intracellular activity including gene expression. Upadacitinib modulates the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs.

Upadacitinib is approved in the United States (U.S.) for the treatment of adults with moderate to severe rheumatoid arthritis (RA), adults with psoriatic arthritis (PsA), adults with ankylosing spondylitis (AS), adults with non-radiographic axial spondyloarthritis (nr-axSpA), adults with ulcerative colitis (UC), and for adults and pediatric patients ≥ 12 years of age with refractory, moderate to severe atopic dermatitis (AD). Upadacitinib is available as 15 mg, 30 mg, and 45 mg extended-release tablets.

AbbVie Inc. (Applicant) submitted Supplements 21 (S-021) and 22 (S-022) to New Drug Application (NDA) 211675 for upadacitinib for the following indications, respectively:

- Treatment of pediatric patients 2 years of age and older with active polyarticular (b) (4) juvenile idiopathic arthritis (b) (4) who have had an inadequate response or intolerance to one or more TNF blockers (NDA 211675/S-021)
- Treatment of patients 2 years of age and older with active (b) (4) psoriatic arthritis (JPsA) (NDA 211675/S-022)

The Applicant also submitted NDA 218347 as a Type 3 NDA for a new formulation to allow for pediatric dosing of patients receiving upadacitinib:

- Upadacitinib 1 mg/mL Oral Solution to allow for administration to patients weighing less than 30 kg or unable to swallow solid dosage forms

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action is approval of Rinvoq/Rinvoq LQ (also referred to as upadacitinib , the naming convention used in this review) for the following indications:

- Treatment of pediatric patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis (pJIA) who have had an inadequate response or intolerance one of more TNF blockers (NDA 211675/S-021, NDA 218347)

- Treatment of patients 2 years of age and older with active psoriatic arthritis who have had an inadequate response or intolerance to one or more TNF blockers (NDA 211675/S-022, NDA 218347)

Juvenile Idiopathic Arthritis (JIA) is the term used to refer to multiple subtypes of inflammatory arthritis of one or more joints occurring for at least 6 weeks in a child younger than 16 years of age. Polyarticular JIA (pJIA) is one form of JIA and is defined by the presence of ≥ 5 inflammatory joints with onset prior to age 16 years and a minimum duration of 6 weeks and is the form of JIA most similar to adult RA. Other forms of JIA may also have polyarticular joint involvement but are defined based on other clinical characteristics, such as psoriatic skin disease in juvenile psoriatic arthritis (JPsA), also referred to as pediatric PsA. JPsA or pediatric PsA is the form of JIA most similar to adult PsA. The clinical manifestations of pJIA and pediatric PsA are discussed further in Section 2.1.

The recommendation of approval for the treatment of active pJIA is based on an extrapolation of efficacy of upadacitinib established in adults with RA, based on a PK-matching approach and supportive descriptive efficacy assessments from Study M15-340. Study M15-340 enrolled patients with JIA with polyarticular involvement of multiple subtypes, not specifically limited to ILAR classification criteria for pJIA. Therefore, in this review, this study population of patients with polyarticular course JIA will be referred to as JIA with active polyarthritis.

The following aspects were considered for the extrapolation of efficacy approach for pediatric patients with pJIA from adults with RA:

1. Disease similarity between adult patients with RA and pediatric patients with pJIA
2. Similar PK exposure-response in adult patients with RA and pediatric patients with pJIA
3. Extrapolation of efficacy in pediatric pJIA patients from adult RA patients

Study M15-340 was a 156-week, open-label, multiple-dose, multicenter, multipart, PK, safety, and tolerability in pediatric subjects ages 2 to less than 18 years old with JIA with active polyarthritis. PK data from Study M15-340 were included in the population PK analysis. The Clinical Pharmacology review team has determined that the proposed weight-tiered dosing strategy provides comparable upadacitinib exposure in pediatric patients 2 to less than 18 years of age with JIA with active polyarthritis to that with the currently approved dosing regimen in adult RA patients, supporting the extrapolation of efficacy from adult RA patients. In addition, supportive numerical trends of improvement from baseline were observed for the descriptive efficacy endpoints in Study M15-340. No new safety signals were identified, and the observed safety of upadacitinib in patients with JIA with active polyarthritis was consistent with the known safety profile of upadacitinib in RA and other approved indications.

The recommendation of approval for the treatment of pediatric patients 2 years of age and older with active PsA is not based on additional clinical data; rather it is based on a PK-matching extrapolation approach using data from patients with JIA with active polyarthritis in Study M15-340. The following aspects were considered for the extrapolation of efficacy:

1. Disease similarity between adult and pediatric patients with PsA
2. PK bridge between adult and pediatric patients
3. Rationale for the expectation of similar PK in JIA with active polyarthritis and in the JIA subgroup of pediatric PsA
4. Extrapolation of efficacy in pediatric patients from adult PsA patients

The Clinical Pharmacology review team has determined that the Applicant has established an adequate PK bridge to support an extrapolation of the efficacy established in adults with PsA to pediatric patients 2 years and older with active PsA at the proposed upadacitinib dose. Following the proposed weight-tiered upadacitinib dosing regimen, upadacitinib exposures are predicted to be generally comparable between adults with RA and PsA and pediatric patients with JIA with active polyarthritis. Based on (1) the disease similarity of pediatric and adult PsA, (2) the similarity in PK of upadacitinib across pediatric and across adult indications, as well as (3) the similarity in PK of upadacitinib between adults with PsA and children with JIA with active polyarthritis, the upadacitinib systemic exposure in pediatric patients 2 to 17 years of age with active PsA is expected to be comparable to the systemic exposure in adult subjects with active PsA. The PK bridge thus supports the extrapolation of established efficacy of upadacitinib in the adult PsA population to the pediatric PsA population. The safety of upadacitinib in pediatric patients with PsA is established by leveraging the safety in pediatric patients with JIA with active polyarthritis treated with upadacitinib in Study M15-340 and by additional supporting data from clinical studies in pediatric and adolescent patients treated with upadacitinib in the atopic dermatitis (AD) development program.

## 1.3. Benefit-Risk Assessment

**Benefit-Risk Summary and Assessment**

Polyarticular juvenile idiopathic arthritis (pJIA)
Polyarticular juvenile idiopathic arthritis (pJIA) is a childhood-onset inflammatory arthritis affecting ≥ 5 joints during the first 6 months of disease and encompasses the RF+ polyarthritis and RF- polyarthritis subtypes of the International League of Associations for Rheumatology (ILAR) classification for Juvenile Idiopathic Arthritis (JIA). Polyarticular JIA is the form of JIA most similar to adult RA, with articular manifestations being predominant. Without appropriate treatment, pJIA can lead to significant life-long disability that starts in childhood. Although there are 6 recently FDA-approved therapies for pJIA and polyarticular-course JIA (pcJIA or JIA with active polyarthritis) in the United States (abatacept, adalimumab, etanercept, golimumab, tocilizumab, and tofacitinib), there still remains an unmet need for additional therapeutic options in this population since not all patients respond to the approved treatments.

Upadacitinib is an oral, small molecule Janus kinase (JAK) inhibitor. It was first approved for the treatment of the treatment of adults with moderately to severely active RA who have had an inadequate response or intolerance to methotrexate on August 16, 2019. At the time of approval, post-marketing requirements (PMR) under Pediatric Research Equity Act (PREA) were issued to conduct a multiple-dose pharmacokinetic study in children from 2 to less than 18 years of age with JIA (PMR 3680-1) and to conduct a randomized withdrawal, double-blind, placebo-controlled study to evaluate the efficacy and safety of upadacitinib in children from 2 to less than 18 years of age with pcJIA (PMR 3680-2). The Applicant submitted Study M15-340 in NDA 211675/S-021 to address PMR 3680-1 and to support a request for release from PMR 3680-2.

Study M15-340 is a 156-week, open-label, multiple-dose, multicenter, multipart, PK, safety, and tolerability study in pediatric subjects ages 2 to less than 18 years old with JIA with active polyarthritis. The efficacy of upadacitinib in pJIA is based on exposure and extrapolation of established efficacy of upadacitinib in RA. The similarities between the clinical presentation, disease progression, and responsiveness to therapies, including TNFα-inhibitors, of pJIA and RA support the extrapolation of efficacy based on PK-matching. The exposures observed in JIA patients with active polyarthritis treated with upadacitinib in Study M15-340 were within the range of exposures seen in RA patients treated with upadacitinib in the adequate and well-designed studies previously submitted to support the approval of upadacitinib in moderately to severely active RA: Studies M13-549, M13-542, M14-465, M13-545, and M15-555. The proposed weight-tiered dosing strategy in pediatric

patients with either upadacitinib oral extended-release tablets or oral immediate-release solution provides steady state trough concentrations across age groups in pediatric patients (2-17 years old) comparable to that of the currently approved dosing regimen in adult RA patients. In addition, supportive numerical trends of improvement from baseline were observed for the descriptive efficacy endpoints in the open-label uncontrolled Study M15-340 in JIA with active polyarthritis.

The safety assessment of upadacitinib for pJIA is based primarily on the safety data from 83 subjects with active JIA with polyarthritis in Study M15-340. Additional supportive safety data for upadacitinib in pediatric subjects were provided the Applicant's development program for atopic dermatitis in pediatric patients. The overall safety profile was generally consistent with the safety observed with treatment with upadacitinib in adult RA patients and the known safety profile of another JAK inhibitor in pJIA/JIA with active polyarthritis. No new safety signals were identified.

The Applicant has provided adequate data to inform the benefit-risk assessment of upadacitinib for the treatment of active pJIA in patients 2 to less than 18 years of age. Overall, the efficacy and safety evidence provided in NDA 211675/S-021 supports a favorable benefit-risk profile of upadacitinib for the treatment of pJIA patients at ages of 2 to less than 18 years at the proposed dosing. The safety of upadacitinib in JIA with active polyarthritis was consistent with the known safety of upadacitinib and offers an acceptable risk for the therapeutic benefits. Approval of upadacitinib will provide an additional treatment option in the United States and the second approval for pJIA/JIA with active polyarthritis in this drug class. Therefore, we recommend approval of upadacitinib for pediatric patients 2 years of age and older with active pJIA.

Study M15-340 was designed and conducted consistent with the post-marketing requirement under PMR 3680-1. Therefore, we recommend the PMR be considered fulfilled based on the results of Study M15-340. Additionally, given the adequacy of the information in NDA 211675/S-021 to inform the efficacy and safety of upadacitinib in children from 2 to less than 18 years of age with JIA with active polyarthritis, we recommend releasing the Applicant from the post-marketing requirement under PMR 3680-2.

<u>Pediatric psoriatic arthritis (PsA)</u>

Psoriatic arthritis (PsA) is a chronic progressive inflammatory arthritis associated with psoriasis that may result in permanent joint damage and disability. Pediatric psoriatic arthritis (pediatric PsA), also referred to as psoriatic juvenile idiopathic arthritis or juvenile psoriatic arthritis (JPsA), is a subtype of the broader group of childhood inflammatory arthritides that comprise JIA. Clinical manifestations of pediatric PsA are similar to adult PsA with peripheral and axial arthritis, enthesitis, dactylitis, and cutaneous and nail changes. Juvenile psoriatic arthritis comprises between 2 to 11% of children with JIA, and it has a calculated annual incidence of ~3 per million children. Without appropriate treatment, JIA,

including pediatric PsA, can lead to significant disability. Although there are 5 recently FDA-approved treatments for pediatric PsA (golimumab, secukinumab, ustekinumab, etanercept, and abatacept), there remains an unmet need for therapeutic options in this population since not all patients respond to the approved treatments.

Upadacitinib was approved for the treatment of adults with active PsA who have had an inadequate response or intolerance to one or more TNF blockers on December 14, 2021. At the time of approval, the Agency issued a PMR under PREA (PMR-4201) to provide PK and safety information to support the pediatric assessment of upadacitinib for the treatment of juvenile psoriatic arthritis (JPsA or pediatric patients with PsA) in children 5 to 17 years of age. The Applicant has submitted NDA 211675/S-022 to address the PMR.

No clinical trials or dedicated pharmacokinetic studies were conducted in pediatric patients with PsA in support of NDA 211675/S-022. The efficacy of upadacitinib in pediatric patients ages 2 and older with active PsA was extrapolated from adults with PsA where efficacy has been demonstrated previously in adequate and well-designed clinical trials: Studies M15-554 and M15-572. To support the PK bridge between adults and children with PsA, PK data for upadacitinib were compared in JIA with active polyarthritis from Study M15-340 and in adults with PsA and RA. The exposures observed in JIA patients with active polyarthritis were comparable to the exposures in adults with PsA and RA. Therefore, the exposure in pediatric PsA would be expected to be comparable to the exposure in adult PsA patients. With the establishment of this scientific bridge and given the significant disease similarity between pediatric and adult patients with PsA, it is scientifically justified to extrapolate the efficacy established in adults with PsA to pediatric patients with PsA.

The safety of upadacitinib in pediatric patients with PsA is supported by the safety in pediatric patients with pJIA observed in Study M15-340. The PK exposure of upadacitinib is expected to be similar between pJIA and pediatric PsA patients with the same weight-tiered dosing regimen, either with upadacitinib oral extended-release tablets or upadacitinib 1 mg/mL oral immediate-release solution. In addition, there are no significant disease-specific factors that would be expected to impact safety differently as pJIA and pediatric PsA are both subtypes of JIA. These considerations support the relevance of safety data from JIA with active polyarthritis population to the pediatric PsA population. The overall safety profile of upadacitinib in JIA with active polyarthritis was generally consistent with the safety observed with upadacitinib in adult RA and PsA patients. No new safety signals were identified.

The Applicant has provided adequate information to inform the benefit-risk assessment of upadacitinib for the treatment of pediatric patients with PsA and support the expansion of the indication for upadacitinib for the treatment patients 2 years of age and older with active PsA. Approval of upadacitinib will provide an additional treatment option in the United States for pediatric patients with PsA and will be the first

approval for pediatric PsA for this drug class. Therefore, we recommend approval of upadacitinib for pediatric patients 2 years of age and older with active PsA.

We also recommend that PMR 4201-1 be considered fulfilled based on the information submitted in NDA211675/S-022.

Conclusion

The benefit-risk profile for upadacitinib is favorable for the treatment of pediatric patients 2 years of age and older with active pJIA who have had an inadequate response or intolerance to one or more TNF blockers pediatric patients with PsA, and for the treatment of pediatric patients 2 years of age and older with active PsA. However, additional characterization of the long-term safety profile of upadacitinib, is required in postmarketing studies. Specifically:

- The Applicant provided limited data on the long-term safety of upadacitinib in patients with JIA with active polyarthritis.
- There are a number of effective therapeutic options for this patient population that have physiological functions in immune system development.
- Recent evidence from non-clinical studies with other JAK inhibitors suggests effects on skeletal system and bone ossification.

Therefore, to ensure the long-term benefit-risk profile of upadacitinib in pJIA and pediatric patients with PsA remains favorable, the review team concluded that safety should be further assessed by a long-term safety study in pJIA and pediatric PsA with inclusion of control groups for each disease population, to evaluate for malignancies, serious and opportunistic infections, thromboses, and effects on growth.

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| **Analysis of Condition** | Polyarticular Juvenile Idiopathic Arthritis<br>• Juvenile Idiopathic Arthritis (JIA) refers to multiple subtypes of inflammatory arthritis of one or more joints occurring for at least 6 weeks in a child younger than 16 years of age.<br>• Polyarticular juvenile idiopathic arthritis (pJIA), one form of JIA, is a | Polyarticular Juvenile Idiopathic Arthritis<br>• PJIA is a serious, disabling form of juvenile inflammatory arthritis with significant impact on quality of life for patients and families. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | serious inflammatory arthritis in children, defined by the presence of ≥5 inflammatory joints with onset prior to age 16 years and a minimum duration of 6 weeks.<br>• The prevalence of JIA in developed countries has been reported to be between 16 and 150/100,000 children, and pJIA accounts for approximately 13-35% children with JIA.<br>• PJIA is the form of JIA most similar to adult rheumatoid arthritis (RA) in clinical manifestations as well as response to therapy.<br><br>Pediatric Psoriatic Arthritis<br>• Psoriatic JIA, also referred to as pediatric psoriatic arthritis (pediatric PsA) and juvenile psoriatic arthritis (JPsA), is a subtype of JIA and comprises between 2 to 11% of children with JIA.<br>• Clinical manifestations of pediatric PsA are similar to adult PsA with peripheral and axial arthritis, enthesitis, dactylitis, and cutaneous and nail changes. | Pediatric Psoriatic Arthritis<br>• Pediatric PsA is a serious disabling form of juvenile inflammatory arthritis with significant impact on quality of life for patients and families.<br>• Pediatric PsA and adult PsA share similar disease manifestations, disease progression, and similar response to treatment, supporting the similarity of the diseases to support the extrapolation of efficacy from adult PsA to pediatric PsA based on exposure matching. |
| **Current Treatment Options** | Polyarticular Juvenile Idiopathic Arthritis<br>• Recommendations for treatment are based on Expert Consensus Treatment Guidelines, and treatment is determined based on active disease manifestations. | Polyarticular Juvenile Idiopathic Arthritis<br>• There are several approved therapies for pJIA. However, there remains a population of patients with uncontrolled |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | • Approved treatments include some NSAIDs, corticosteroids (oral, parenteral, and intra-articular), conventional DMARDs such as sulfasalazine and methotrexate, tofacitinib, and biologic DMARDs such as tumor necrosis factor (TNF) inhibitors, tocilizumab, and abatacept.<br><br>Pediatric Psoriatic Arthritis<br>• Recommendations for treatment are based on Expert Consensus Treatment Guidelines, and treatment is determined based on active disease manifestations.<br>• Standard-of-care treatments for pediatric patients with pediatric patients with PsA is similar to treatment in adult patients and includes initial treatment with NSAIDs, followed by the addition of non-biologic DMARDs, and/or TNF-inhibitors in patients with persistent disease activity. | disease despite currently available treatments.<br><br>Pediatric Psoriatic Arthritis<br>• There is an unmet need for safe and effective therapies for pediatric patients with PsA since not all patients respond to currently approved treatments. |
| **Benefit** | Polyarticular Juvenile Idiopathic Arthritis<br>• In Study M15-340, 83 pediatric subjects ages 2 to less than 18 years with JIA with active polyarthritis received weight-tiered dosing either upadacitinib oral extended-release tablets or upadacitinib 1 mg/mL oral immediate-release solution.<br>• The exposures observed in subjects with JIA with active polyarthritis treated with upadacitinib in Study M15-340 were within the range of exposures seen in adult RA subjects in the adequate, well-controlled studies (Studies M13-549, M13-542, M14-465, M13-545, and M15-555) previously submitted to support the approval of upadacitinib for moderately to | Polyarticular Juvenile Idiopathic Arthritis<br>• Efficacy of upadacitinib in pediatric patients ages 2 to less than 18 years of age with active pJIA is based on PK-exposure matching and extrapolation of established efficacy of upadacitinib in adults with RA.<br>• Descriptive efficacy assessments in Study M15-340 were consistent with improvement with treatment with upadacitinib in patients with JIA with |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | severely active RA.<br>• Numerical trends in improvement from baseline were observed for the descriptive efficacy endpoints in Study M15-340, providing additional supportive evidence of efficacy.<br><br><u>Pediatric Psoriatic Arthritis</u><br>• No clinical studies of upadacitinib in pediatric patients with PsA were submitted. The efficacy of upadacitinib in pediatric patients ages 2 to less than 18 years old with active PsA was assessed via a full efficacy extrapolation approach from existing efficacy and PK/PD data in adults with PsA and pediatric patients with JIA with active polyarthritis treated with upadacitinib.<br>• The efficacy of upadacitinib in adults with PsA was demonstrated previously in adequate and well controlled studies (Studies M15-554 and M15-572) that supported the approval of upadacitinib for adults with active PsA.<br>• To support a PK bridge between adults and children with PsA, PK data from adults with RA and PsA were compared, and cross-referenced PK data from S-021 for pediatric subjects with JIA with active polyarthritis in Study M15-340 were compared with PK data from adults with PsA.<br>• Systemic exposures were matched between adults with PsA, adults with RA, and pediatric subjects with JIA with active polyarthritis, supporting the similarity of exposures in adults and pediatric patients with PsA. | active polyarthritis.<br><br><u>Pediatric Psoriatic Arthritis</u><br>• Efficacy of upadacitinib in pediatric patients ages 2 to less than 18 years of age with active PsA is based on PK-exposure matching in pediatric subjects with JIA with active polyarthritis and extrapolation of established efficacy of upadacitinib in adults with PsA.<br>• This approach is justified based on disease similarities between pediatric and adult PsA, as well as the consistent exposure-response in adults with RA and pediatric patients with pJIA. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| **Risk and Risk Management** | Polyarticular Juvenile Idiopathic Arthritis<br>• The safety database (N=83) from Study M15-340 is sufficient to provide a risk assessment for upadacitinib in the pediatric population of pJIA and is further supported by additional safety data from the Applicant's development program for atopic dermatitis in pediatric patients.<br>• In Study M15-340, there were no deaths.<br>• Treatment-emergent serious adverse events and adverse events (TE-SAEs and TEAEs, respectively) leading to discontinuation occurred in 4 subjects. The events were singular by preferred term, expect for 2 TEAEs of JIA (worsening of) leading to discontinuation of 2 subjects.<br>• TE-SAEs and TEAEs were most frequently reported within the system organ classes of Infections and Infestations and Gastrointestinal Disorders, consistent with the known safety profile of upadacitinib.<br>• Adverse Events of Special Interest (AESI) included:<br>  ○ 2 subjects (2.4%) with serious infections<br>  ○ 2 subjects (2.4%) with opportunistic infections<br>  ○ 6 subjects (7.2%) with hepatic disorder<br>  ○ 4 subjects (4.8%) with anemia<br>  ○ 3 subjects (3.6%) with neutropenia<br>  ○ 2 subjects (2.4%) with lymphopenia<br>  ○ 6 subjects (6.2%) with creatine phosphokinase elevation<br>• There were no new safety signals. | Polyarticular Juvenile Idiopathic Arthritis<br>• The overall safety profile of upadacitinib in the pJIA population was generally consistent with the safety observed in adult RA and other approved indications for upadacitinib. There were no new safety signals. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | Pediatric Psoriatic Arthritis<br>• The PK exposure with weight-tiered dosing either with upadacitinib oral extended-release tablets or upadacitinib 1 mg/mL oral immediate-release solution is expected to be similar in patients with JIA with active polyarthritis and pediatric PsA, supporting the relevance of safety data from JIA patients with active polyarthritis to the expected safety in the pediatric PsA population.<br>• The safety database from Study M15-340 is sufficient to provide a risk assessment for upadacitinib in the pediatric population of PsA and is further supported by additional safety data from the Applicant's development program for atopic dermatitis in pediatric patients. | Pediatric Psoriatic Arthritis<br>• Polyarticular JIA and pediatric PsA are both forms of JIA. It is reasonable to leverage the safety data from Study M15-340 in pediatric subjects with JIA with polyarthritis.<br>• The overall safety profile of upadacitinib in pediatric patients with active pJIA 2 to less than 17 years was generally consistent with the safety observed in adult RA and PsA patients. There were no new safety signals.<br>• The safety of upadacitinib in pediatric PsA is expected to be similar to that of patient with pJIA.<br><br>Long-Term Safety<br>• Long-term safety data in pJIA and pediatric PsA are limited. Therefore, based on the known safety risks of upadacitinib and JAK inhibitors, a PMR will be conducted to evaluate malignancies, serious and opportunistic infections, thromboses, and effects on growth. |

## 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 | | |
| | | X | Patient reported outcome (PRO) | Section 8.1.2 |
| | | ☐ | Observer reported outcome (ObsRO) | |
| | | X | Clinician reported outcome (ClinRO) | Section 8.1.2 |
| | | ☐ | 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

The ILAR classification system is the currently accepted classification system used to characterize arthritis in children and adolescents (Petty 2004). In this system, JIA is broadly defined as arthritis of one or more joints occurring for at least 6 weeks in a child younger than 16 years of age, where other diagnoses have been excluded. In the United States, JIA affects an estimated 294,000 children between the ages of 0 and 17 years of age (Espinoza 2012). As summarized in Table 1, the ILAR classification system divides JIA into 7 different clinical subtypes based on the presence of clinical features in the first 6 months of disease.

**Table 1. ILAR Classification of JIA Subtypes**

| Category | Diagnostic Criteria |
|---|---|
| **Systemic Arthritis** | Fever of at least 2 weeks duration (daily for at least 3 days) and arthritis in ≥1 joint, plus one or more of the following:<br>1. Erythematous rash<br>2. Generalized lymphadenopathy<br>3. Hepatomegaly and/or splenomegaly<br>4. Serositis<br>Exclusions: a, b, c, d |
| **Oligoarthritis (persistent or extended)** | Arthritis affecting ≤4 joints during the first 6 months of disease<br>There are 2 subcategories:<br>1. Persistent: affecting no more than 4 joints throughout the disease course<br>2. Extended: affecting more than 4 joints after the first 6 months of disease<br>Exclusions: a, b, c, d, e |
| **Polyarthritis, Rheumatoid Factor (-)** | Arthritis affecting ≥5 joints during the first 6 months of disease; test for RF is negative Exclusions: a, b, c, d, e |
| **Polyarthritis, Rheumatoid Factor (+)** | Arthritis affecting ≥5 joints during the first 6 months of disease; ≥ 2 tests for RF at least 3 months apart during the first 6 months of disease is positive<br>Exclusions: a, b, c, e |
| **Psoriatic arthritis** | Arthritis and psoriasis, or arthritis and at least 2 of the following:<br>1. Dactylitis<br>2. Nail pitting or onycholysis<br>3. Psoriasis in a first-degree relative<br>Exclusions: b, c, d, e |

| | |
|---|---|
| **Enthesitis related arthritis (ERA)** | Arthritis and enthesitis, or arthritis or enthesitis with at least 2 of the following:<br>1. The presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain**<br>2. The presence of HLA-B27 antigen<br>3. Onset of arthritis in a male over 6 years of age<br>4. Acute (symptomatic) anterior uveitis<br>5. History of ankylosing spondylitis, enthesitis related arthritis, sacroiliiitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative<br>Exclusions: a, d, e |
| **Unclassified arthritis** | Arthritis that fulfills criteria in no category or in 2 or more of the above categories |

Exclusions: a) Psoriasis or a history of psoriasis in the patient or first-degree relative; b) Arthritis in an HLA-B27 positive male beginning after the sixth birthday; c) Ankylosing spondylitis, enthesitis-related arthritis, sacroiliiitis with inflammatory bowel disease or acute anterior uveitis or a history of one of these disorders in a first-degree relative; d) the presence of IgM rheumatoid factor on at least 2 occasions at least 3 months apart; and e) the presence of systemic JIA in the patient.
*JIA is arthritis of unknown etiology that begins before the 16th birthday and persists for at least 6 weeks.
**Inflammatory lumbosacral pain is defined as lumbosacral pain at rest with morning stiffness that improves with movement. Abbreviation: RF=rheumatoid factor
Petty RE, Southwood TR, Manners P, et al., 2004, International League of Associations for Rheumatology classification of juvenile idiopathic arthritis, second revision, Edmonton, 2001, *J Rheumatol*, 31:390-2.

The populations of patients with pJIA and pediatric patients with PsA for which the Applicant is seeking licensure for upadacitinib in in S-021 and S-022, respectively, are discussed in detail below in the context of the ILAR classification system.

### 2.1.1. Polyarticular Juvenile Idiopathic Arthritis (pJIA)

Polyarticular Juvenile Idiopathic Arthritis (pJIA) is a childhood-onset inflammatory arthritis affecting ≥5 joints during the first 6 months of disease and encompasses the RF+ polyarthritis and RF- polyarthritis subtypes of the ILAR classification for JIA described in Table 1 (Petty 2001; Oberle 2014; Feger 2019). Differences in classification criteria complicate epidemiologic studies. However, the prevalence of JIA in developed countries has been reported to be between 16 and 150/100,000 children, corresponding to an estimated prevalence in the United States of approximately 300,000 children (Ravelli 2007; Espinosa 2012). Among patients with JIA, pJIA accounts for approximately 13-35% of cases (Ravelli 2007; Oberle 2014).

PJIA occurs more frequently in females than males (Ravelli 2007; Oberle 2014). There is a bimodal distribution in the age of onset with a peak between ages 2 and 5 years and a second peak between 10 and 14 years. In children under 10 years of age, the disease often begins with an oligoarthritis course, affecting one or two joints, and then progresses to involve five or more

joints. Older children may have a more rapid onset. The laboratory findings are notable for the presence of antinuclear antibodies typically in younger children, whereas a rheumatoid factor is more often present in older children, particularly females. Extraarticular manifestations, such as uveitis, can also be present. Without appropriate treatment, pJIA can lead to significant life-long disability starting in childhood.

The upadacitinib clinical development program evaluated upadacitinib in a JIA patient population with active polyarthritis encompassing the following ILAR subgroups: rheumatoid factor (RF) positive polyarticular JIA, RF negative polyarticular JIA, extended oligoarticular JIA, and systemic JIA (sJIA) without systemic manifestations. Because the program included JIA patients with active polyarticular involvement not limited to the polyarticular subgroup by the ILAR classification (i.e., sJIA without systemic manifestations) for this program and in this review, the term "JIA with active polyarthritis" is used to refer to the study population evaluated.

### 2.1.2. Pediatric Psoriatic Arthritis

Psoriatic arthritis in children can also be referred to as pediatric PsA, psoriatic JIA, or juvenile psoriatic arthritis (JPsA). For this review, psoriatic arthritis in children will be referred to as pediatric PsA. The ILAR criteria classify pediatric PsA as subtype of JIA characterized by arthritis and psoriasis or arthritis and at least 2 of the following: dactylitis, nail pitting or onycholysis, psoriasis in a first-degree relative (Petty 2004). Exclusions to a classification of PsA include arthritis in an HLA-B27 positive male after age 6; ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome (reactive arthritis), acute anterior uveitis, or a history of one of these in a first degree relative; presence of IgM rheumatoid factor on at least 2 occasions at least 3 months apart; and presence of systemic JIA (Petty 2004). The Vancouver Criteria for juvenile psoriatic arthritis define definite juvenile psoriatic arthritis by the presence of 2 major criteria (arthritis and psoriasis) or arthritis plus 3-4 minor criteria (dactylitis, nail pitting, family history of psoriasis in first or second degree relative, psoriasis-like lesion) (Southwood 1989). Notably, the presence of skin rash is not required for classification based on either criteria. Psoriatic JIA or juvenile psoriatic arthritis comprises between 2 to 11% of children with JIA (Stoll 2011; Ravelli 2007).

Aside from a difference in the timing of psoriasis and arthritis onset, pediatric PsA and adult PsA share many of the same disease characteristics and clinical manifestations, suggesting that they may be a spectrum of the same disease (Brunello 2022). Table 2 presents a detailed comparison of the clinical manifestations of PsA in children and adults. There are also data suggesting that the pathogenesis of pediatric and adult PsA are similar based on elevated levels of the pro-inflammatory cytokines IL-17, IL-23, and tumor necrosis factor observed in patients with these diseases (Carvalho 2021).

In children, the age of onset of PsA has a biphasic distribution with a peak between ages 2 to 4 years and a second peak at 9 to 11 years of age. Younger patients are more commonly female with a positive ANA, while older children are more likely to have axial disease and enthesitis (Stoll 2006; Zisman 2017). In general, the initial presentation is a monoarthritis or oligoarthritis, and the most commonly involved joints are knee and ankle with hip joint disease in up to 20% to 30% of patients (Nigrovic 2024). In the absence of effective therapy, the arthritis will often progress to polyarticular disease. Pediatric psoriatic arthritis can affect the axial skeleton in 10% to 30% of patients (Stoll2006). Sacroiliitis is more frequent in patients with older age at onset, who are often positive for the HLA-B27 antigen. Approximately 60% of children in the older subgroup of pediatric PsA have enthesitis, as compared to 22% of younger patients (Southwood 1989). Dactylitis is observed in 20 to 40% of patients (Southwood 1989). Chronic painless uveitis occurs in 10 to 15% of children with pediatric PsA and more commonly in younger patients with a positive ANA (Stoll 2006). Psoriasis occurs in 40 to 60% of patients with pediatric psoriatic arthritis, and nail changes are observed in 50 to 80%.

**Table 2. Similarities and Differences Between PsA in Adults and in Children**

| Clinical Feature | Adults | Children |
|---|---|---|
| **Timing of psoriasis and arthritis onset** | Psoriasis prior to arthritis | Arthritis prior to psoriasis |
| **Peripheral arthritis**<br>**Oligoarticular**<br>**Polyarticular**<br>**Oligo-extended** | <br>20-55%<br>20-60%<br>7-40% | <br>45-55%<br>35-55%<br>15-38% |
| **Axial arthritis** | 7-40% | 10-30% |
| **Radiological damage** | 47% | 25% |
| **Enthesitis** | 30-50% | 12-45% |
| **Dactylitis** | 40-50% | 17-37% |
| **Nail involvement** | 41-93% | 37-57% |
| **Uveitis** | 8% | 8-13% |
| **HLA-B27 positive** | 40-50% | 10-25% |
| **ANA positive** | 16% | 40-46% |

Adapted from Brunello F, Tirelli F, Pegoraro L, Dell'Apa F, et al., 2022, New insights on juvenile psoriatic arthritis. *Front Pediatr*, 10:884727.

## 2.2. Analysis of Current Treatment Options

### 2.2.1. Treatments for Polyarticular Juvenile Idiopathic Arthritis

Table 3 lists the approved biological DMARDs for pJIA/JIA with active polyarthritis. Five (5) therapies are currently approved. Abatacept was approved April 8, 2008, for age 2 years and older; adalimumab was approved February 22, 2008, for age 2 years and older; etanercept was approved May 27, 1999, for age 2 years and older; intravenously administered was approved September 30, 2020, for age 2 years and older; and tocilizumab was approved April 30, 2013, for age 2 years and older. The approvals for intravenously administered abatacept, adalimumab, etanercept, and intravenously administered tocilizumab were based on randomized withdrawal studies. The approvals for subcutaneously abatacept and tocilizumab were based on PK matching and efficacy extrapolation from intravenously administered abatacept and tocilizumab, respectively.

In addition, tofacitinib was approved on September 28, 2020, for the treatment of pediatric patients age 2 years and older with polyarticular course juvenile idiopathic arthritis, also referred to in this review as JIA with active polyarthritis. As discussed in Section 2.1.1, JIA with active polyarthritis includes the pJIA subgroup of JIA. The approval of tofacitinib was based on the results of a randomized withdrawal study in pediatric patients with JIA with active polyarthritis.

Several NSAIDs (celecoxib, naproxen, ibuprofen, rofecoxib, meloxicam, and tolectin), as well as glucocorticoids, are also approved for the treatment of JIA and juvenile rheumatoid arthritis (JRA) and are used as off-label treatments for pJIA.

**Table 3. FDA-Approved Treatments for pJIA/JIA With Active Polyarthritis**

| Product Name | Relevant Indication | Year of Approval | Dosing/ Administration | Efficacy Information | Important Safety and Tolerability Issues |
|---|---|---|---|---|---|
| Abatacept | pJIA | 2005/2008 | Children ≥ 2 years: IV formulation<br><75 kg 10 mg/kg at wks 0, 2, and 4, then q4w<br>≥75 kg 750 mg at wks 0, 2, and 4, then q 4w<br><br>Children ≥2 years: SC formulation<br>10 kg to <25 kg: 50 mg qw<br>25 kg to <50 kg: 87.5 mg qw<br>≥50 kg: 125 mg qw | RW study with fewer flares (IV); OL PK-extrapolation (SC) | Similar to safety profile in adults |

| | | | | | |
|---|---|---|---|---|---|
| Adalimumab | pJIA | 2002/2008 | Children ≥2years: 10 to <15 kg: 10 mg SC q2w<br><br>15 to <30 kg:20 mg SC q2w<br><br>≥30 kg: 40 mg SC q2w | RW study with fewer flares vs PBO | Infections, hypersensitivity, and ↑CPK |
| Etanercept | pJIA | 1998/1999 | Children ≥2 years:<br><63 kg: 0.8 mg/kg SC qw<br><br>≥63 kg: 50 mg SC qw | RW study with fewer flares vs PBO | Similar to safety profile in adults |
| Golimumab | pJIA | 2009/2020 | Children ≥2 years: IV formulation 80mg/$m^2$ at wks 0, 2, and 4, then q8w | OL, single-arm PK, safety, and exploratory efficacy study; PK extrapolation | Similar to safety profile in adults |
| Tocilizumab | pJIA | 2010/2013 | Children ≥2 years:<br>IV formulation<br>≥2 years of age:<br><30 kg: 10mg/kg q2w<br>≥30 kg: 8 mg/kg q2w<br><br>SC formulation<br><30kg: 162 mg q3w<br>≥30kg: 162 mg q2w | IV: RW study with fewer flares compared to PBO<br><br>SC: PK extrapolation | Similar to safety profile in adults |
| Tofacitinib | Polyarticular Course JIA* | 2012/2020 | Children ≥2 years:<br>10 to <20 kg: 3.2 mg (3.2 mL oral solution) BID;<br>20 to <40 kg: 4 mg (4 mL oral solution) BID<br><br>≥40 kg: 5 mg (one 5 mg tablet or 5 mL oral solution) BID | RW study with fewer flares vs PBO | Similar to safety profile in adults |

Abbreviations: CPK=phosphokinase; DB=double-blind; IV=intravenous; JRA=Juvenile Rheumatoid Arthritis; PBO=placebo; PC=placebo-controlled; PhGA=Physician Global Assessment; pJIA=polyarticular juvenile idiopathic arthritis; PK=pharmacokinetic; Q2W=every other week; QW=every week; Q4W=every four weeks; Q8W=every eight weeks; R=randomized; RW=randomized withdrawal; SC=subcutaneous; WKs= weeks
*The efficacy information that supported approval of tofacitinib came from a RWD study in 225 JIA patients with active polyarthritis. 143 of these patients had a diagnosis in an ILAR subgroup of pJIA (i.e., rheumatoid factor (RF) positive polyarticular JIA or RF negative polyarticular JIA). The study also included patients with extended oligoarticular JIA, juvenile psoriatic arthritis, enthesitis-related arthritis of patients, and systemic JIA without systemic manifestations.

Patients with pJIA are generally managed via expert, consensus-driven, treatment regimens recommended for JIA that were updated in 2019 by the American College of Rheumatology/ Arthritis Foundation (Ringold 2019). Initial treatment regimens are based on a patient's level of disease activity (amount of peripheral joint involvement and/or systemic manifestations). The treatment regimens are similar to those used to treat adults with RA. Patients who have low disease activity are typically treated with a nonbiologic DMARD (preferably methotrexate with leflunomide and sulfasalazine as alternatives) as first-line treatment. NSAIDs and intra-articular glucocorticoid injections are also recommended as adjunct therapies. Initiation of treatment with a biological DMARD is generally reserved for patients who are intolerant or who are considered conventional DMARD failures as a result of persistent or progressing underlying disease activity. Short courses of oral glucocorticoids may be used in such cases as bridging therapy until non-biologic or biologic DMARD therapy becomes effective. Physical therapy to maintain range of motion, to prevent deformities, and to minimize loss of function of affected joints is an integral component of the treatment and management of children with pJIA.

Although these guidelines included anti-TNF biologics, tocilizumab, abatacept, and rituximab, they did not include therapies with JAK inhibition as a mechanism of action because of a lack of published studies in pediatrics at the time. Notably, the most recent treatment guidelines were published in 2019, prior to the approval date of tofacitinib for pediatric patients with JIA with active polyarthritis.

### 2.2.2. Treatments for Pediatric Psoriatic Arthritis

Table 4 lists the therapies currently approved for pediatric patients with PsA, or JPsA. Five (5) therapies are currently approved. Intravenous golimumab was approved September 29, 2020, for age 2 years and older; secukinumab was approved December 22, 2021, for age 2 years and older; ustekinumab was approved July 29, 2022, for age 2 years and older; etanercept was approved October 19, 2023, for age 2 years and older; and subcutaneous abatacept was approved October 31, 2023, for age 2 years and older. All of these approvals were based on a PK matching and efficacy extrapolation methodology except for secukinumab, which was approved based on a randomized withdrawal study.

In additional, similar to pJIA, NSAIDs (celecoxib, naproxen, ibuprofen, rofecoxib, meloxicam, and tolectin) and glucocorticoids approved for the treatment of JIA and JRA are used as off-label treatments for pediatric PsA.

**Table 4. FDA-Approved Treatments for Pediatric Psoriatic Arthritis**

| Product Name | Relevant Indication | Year of Approval | Dosing/ Administration | Efficacy Information | Important Safety and Tolerability Issues |
|---|---|---|---|---|---|
| Abatacept | Pediatric patients with PsA | 2005/2003 | SC formulation:<br>10 to <25 kg dose is 50 mg qw<br><br>25 to <50 kg dose is 87.5 mg qw<br><br>≥50 kg dose is 125 mg qw | PK extrapolation using data from adult PsA | Similar to safety profile in adults |
| Etanercept | Pediatric patients with JPsA | 1998/2003 | SC formulation:<br>0.8 mg/kg qw (maximum 50 mg qw) | PK extrapolation using data from adult PsA | Similar to safety profile in adults |
| Golimumab | Pediatric patients with PsA | 2009/2020 | Children ≥2 years: IV formulation: 80mg/$m^2$ IV over 30 minutes at Wks 0 and 4, and then q8w thereafter | PK extrapolation using data from pJIA study | Similar to safety profile in adults |
| Ustekinumab | Pediatric patients with PsA | 2009/2022 | SC formulation:<br><60 kg dose is 0.75 mg at Wks 0 and 4 and then q12w thereafter<br><br>≥60 mg dose is 45 mg at Wks 0 and 4 and then q12w thereafter<br><br>>100 kg with co-existent moderate-to-severe plaque psoriasis 90 mg at Wks 0 and 4 and then q12w thereafter | PK extrapolation using data from adult PsA | Similar to safety profile in adults |

| | | | | | |
|---|---|---|---|---|---|
| Secukinumab | Pediatric patients with PsA | 2016/2021 | Children ≥2 years:<br>≥15 kg to <50 kg dose is 75 mg SC at Wks 0, 1, 2, 3, and 4 and then q4w thereafter<br>≥50 kg dose is 150 mg SC at Wks 0, 1, 2, 3, and 4 and then q4w thereafter | RW study with fewer flares vs PBO | Similar to safety profile in adults |

Abbreviations: CPK=phosphokinase; DB=double-blind; IV=intravenous; JRA=Juvenile Rheumatoid Arthritis; PBO=placebo; PC=placebo-controlled; PhGA=Physician Global Assessment; PK=pharmacokinetic; Q2W=every other week; QW=every week; Q4W=every four weeks; Q8W=every eight weeks; R=randomized; RW=randomized withdrawal; SC=subcutaneous; WKs= weeks

Similar to other ILAR subgroups of JIA including pJIA, pediatric PsA patients also are generally managed via expert, consensus-driven, treatment regimens recommended for JIA that were updated in 2019 by the American College of Rheumatology/Arthritis Foundation (Ringold 2019). Initial treatment regimens are based on a patient's level of disease activity (amount of peripheral joint involvement and the presence/absence of axial skeletal involvement and/or systemic manifestations). The treatment regimens are also similar to those used to treat pediatric patients with other subtypes of JIA and adults with PsA. Pediatric PsA patients with oligoarthritis without axial or systemic involvement or who have low disease activity are typically treated with NSAIDs and intra-articular injections of glucocorticoids that can be escalated to include a nonbiologic DMARD (methotrexate, sulfasalazine) as second-line treatment for persistent disease activity. Initiation of treatment with a biological DMARD is generally reserved for patients who are intolerant or who are considered conventional DMARD failures as a result of persistent or progressing underlying disease activity. Short courses of oral glucocorticoids may be used in such cases as bridging therapy until non-biologic or biologic DMARD therapy becomes effective. Pediatric PsA patients who have dactylitis that fails to respond to local glucocorticoid injection or who have sacroiliac and/or axial involvement are typically treated with a biologic DMARD along with an NSAID for symptomatic relief. Physical therapy to maintain range of motion, to prevent deformities, and to minimize loss of function of affected joints is an integral component of the treatment and management of children with PsA.

Although these guidelines included anti-TNF biologics, tocilizumab, abatacept, and rituximab, they did not include biologics with other mechanisms of action (e.g., anti-IL-17 and anti-IL-12/23 inhibition) due to a lack of published studies in pediatrics at the time. Notably, these most recent treatment guidelines were published in 2019, prior to the approval dates of golimumab, secukinumab, ustekinumab, etanercept, and abatacept for pediatric patients with PsA.

# 3 Regulatory Background

## 3.1. U.S. Regulatory Actions and Marketing History

Upadacitinib was first approved in the United States on August 16, 2019, for the treatment of adults with moderately to severely active RA who have had an inadequate response or intolerance to methotrexate. The following postmarketing studies were required at the time of the original approval of upadacitinib for the treatment of RA:

**PMR 3680-1**: Conduct a multiple-dose pharmacokinetic study in children from 2 to less than 18 years of age with juvenile idiopathic arthritis (JIA).

- Final Report: February 2021

**PMR 3680-2**: Conduct a randomized withdrawal, double-blind, placebo-controlled study to evaluate the efficacy and safety of upadacitinib in children from 2 to less than 18 years of age with polyarticular-course JIA (pcJIA).

- Final Report: October 2026

On September 10, 2021, a deferral extension of the final report due date for PMR 3680-1 was granted until March 2023.

On December 2, 2021, the indication for RA was updated to treatment of adults with moderately to severely active RA who have had an inadequate response or intolerance to one or more TNF blockers. A Safety Labeling Change (SLC) to reflect JAK-inhibitor class risks in inflammatory conditions including increased risks of major adverse cardiovascular events, malignancy, thrombosis, and mortality was implemented after the assessment of a postmarketing safety study from another JAKi product. As part of the SLC, the indication for RA was revised to reflect that population for which the benefit-risk could be better justified.

Upadacitinib was also approved on December 14, 2021, for the treatment of adults with active PsA who have had an inadequate response or intolerance to one or more TNF blockers. The following postmarketing study was required with the approval of upadacitinib for the treatment of PsA:

**PMR 4201-1**: Provide PK and safety information to support the pediatric assessment of upadacitinib for the treatment of juvenile psoriatic arthritis (JPsA) in children 5 to 17 years of age.

- Final Report: October 2026

Upadacitinib was subsequently approved for the following additional indications:

- 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 (January 14, 2022)
- Adults with moderately to severely active ulcerative colitis who have had an inadequate response or intolerance to one or more TNF blockers (March 16, 2022)
- Adults with active ankylosing spondylitis who have had an inadequate response or intolerance to one or more TNF blockers (April 29, 2022)
- Treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation who have had an inadequate response or intolerance to TNF blocker therapy (October 21, 2022)
- Treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response or intolerance to one or more TNF blockers (May 18, 2023)

## 3.2. Summary of Presubmission/Submission Regulatory Activity

The Agency had several regulatory interactions with the Applicant regarding the clinical development of upadacitinib for the treatment of pJIA and pediatric PsA under IND 114717.

On March 18, 2015, the Agency granted upadacitinib an orphan-drug designation (#15-4854) for treatment of pediatric (aged 0 through 16 years) JIA International League of Associations for Rheumatology (ILAR) categories excluding systemic JIA.

On May 30, 2017, the Agency agreed with a full waiver for upadacitinib for JPsA, or pediatric PsA, as proposed in the agreed initial pediatric study plan (iPSP) for the PsA development program. Agreement with the planned waiver request was based on a justification relying on the assumption that adequate and well-controlled studies were needed to address PREA requirements for PsA. The number of patients with pediatric psoriasis was considered small such that studies would be impossible or highly impractical.

On March 23, 2018, AbbVie submitted the clinical study protocol to address PMR 3680-01, study M15-340 "An Open-Label Multiple-Dose Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Upadacitinib in Pediatric Subjects with Polyarticular Course Juvenile Idiopathic Arthritis."

On January 14, 2020, at the pre-sNDA meeting for the adult PsA clinical development program, the Agency communicated reconsideration of the approach to PREA requirements for PsA and recommended that the requirements be addressed via a PK study in pediatric PsA patients to support the extrapolation of efficacy from the adult PsA indication. Based on an evolving understanding of the high degree of similarity of the disease between adults and

pediatric patients with PsA and the considerations of a PK-matching and extrapolation of efficacy from adults to pediatric patients discussed at the FDA/MCERSI (University of Maryland Center of Excellence in Regulatory Science and Innovation) public workshop on October 2, 2019, titled "Accelerating Drug Development for Polyarticular Juvenile Idiopathic Arthritis (pJIA)," the Agency now considered studies in pediatric PsA patients possible.

In Type C Meeting Final Written Responses provided on August 7, 2020, the Agency also communicated that a PK-based extrapolation approach from RA for pJIA could be reasonable with appropriate justification, also based on discussions from the FDA/MCERSI public workshop on October 2, 2019. As long as upadacitinib is not the first-in-class with established efficacy for pJIA, an extrapolation approach could be considered. Exposure matching for pediatric formulations should be bridged to the approved commercial drug product under fasted and fed conditions. The advice regarding a PK-based extrapolation of efficacy reflected a change in Agency thinking since the approval of upadacitinib for RA at which time the efficacy in pJIA would need to be supported by data from a controlled study like the randomized withdrawal study required under PMR 3680-2. The Agency also provided comments on a proposed safety database consisting of 54 subjects with JIA with active polyarthritis and supported by safety data from AbbVie's pediatric AD development program, including 40 pediatric subjects 2 to less than 12 years of age and 540 adolescent subjects. AbbVie would need to ensure that there was adequate long-term exposure, particularly in pediatric subjects 2 to less than 12 years, to inform the risk-benefit assessment of upadacitinib for pJIA. AbbVie would also need to justify the relevance of safety in patients with AD to the safety in patients with pJIA, including a comparison of upadacitinib systemic exposure between the JIA with active polyarthritis and AD pediatric populations.

In subsequent Type C Meeting Final Written Responses provided on April 14, 2021, the Agency noted that a long-term safety study for another JAK inhibitor, tofacitinib, showed an increased risks of major adverse cardiovascular events (MACE) and malignancies compared to TNF inhibitors and informed AbbVie that this safety information from tofacitinib, as discussed in a Drug Safety Communication dated February 4, 2021, would be considered in the benefit-risk assessment of upadacitinib for pJIA. Otherwise, the Agency reiterated openness to a PK extrapolation approach from RA to support efficacy in pJIA, predicated on a justification that pediatric pJIA and adult RA are sufficiently similar diseases and data supporting dosing in pediatric patients matching the effective PK exposures in adult RA patients. To support the safety of upadacitinib for pJIA, the Agency reiterated the need for adequate long-term exposure in pediatric patients and a sufficient distribution of subjects across all age and weight ranges for the proposed pediatric dosing. AbbVie should also provide an adequate justification of the relevance of justify the relevance of safety in patients with AD to the safety in patients with pJIA. The Agency disagreed with the Applicant's proposed exposure matching and formulation bridging approach and provided the following advice:

- The efficacy extrapolation should be based on comparable upadacitinib exposure in

children and adults with dosing within each body weight category for JIA patients with active polyarthritis providing similar exposure to adults with RA.

- The Agency noted that administration of upadacitinib extended-release tablets with food may result in considerable increases in AUC and Cmax and asked the Applicant to clarify how these potential increases would be addressed in Study M15-340.
- Before continuing Study M15-340, the Agency asked the Applicant to provide adequate bridging between the multiple oral immediate-release solution pediatric formulations proposed at the time for dosing subjects less than 30 kg or unable to tolerate oral administration of the approved upadacitinib extended-release (ER) tablets before continuing Study M15-340. The Applicant's proposed approach based on the high solubility and high permeability of upadacitinib appeared reasonable.
- The Applicant's formulation bridging should also adequately support the relative bioavailability estimation between pediatric solution formulation and the approved ER tablets.
- The Applicant was asked to submit information for a Biopharmaceutics Classification System (BCS) designation for the drug product and was advised that a request for BCS Class I classification could be submitted as an amendment to IND 114717.

On March 24, 2022, the Agency denied requested milestone extensions for PMR 3680-1 and PMR 3680-2, the PREA PMRs issued with approval of upadacitinib for RA. AbbVie requested an extension of the final report deadline (b) (4) However, after discussing with the Pediatric Review Committee (PeRC), the Division determined no extensions were needed. Even though the long-term safety cohorts would not be complete by the March 2023 deadline, the PK part of the study to fulfill PMR 3680-1 was expected to be complete before the March 2023 deadline. For PMR 3680-2, an extension request was considered premature since the final report deadline was not due until 2026.

In the Type C Meeting Final Written Responses provided on July 21, 2022, the Agency agreed a PK-based extrapolation of efficacy of pediatric PsA from adult PsA using PK data from Study M15-340 and leveraging safety information from JIA with active polyarthritis together with additional support from pediatric and adolescent AD may be reasonable to support upadacitinib in pediatric PsA. An adequate justification for the proposed extrapolation should include information to support the similarity of the two diseases, similar expected PK between pJIA and pediatric PsA, a rationale for PK bridging (i.e., comparable exposure) between adult PsA and pediatric PsA, appropriate justification and information to support extrapolating efficacy in pediatric PsA from adult PsA, and a justification of the relevance of safety data from JIA with active polyarthritis. For both pJIA and pediatric PsA, the justifications of extrapolation

from their respective adult indications should also include adequate support for extrapolating from once daily dosing with the approved oral extended- release tablets in adults to the proposed twice daily dosing with the oral immediate-release solution in pediatric patients weighing less than 30 kg or unable to tolerate oral administration of the approved upadacitinib ER tablets. The Agency reiterated concerns about the proposed safety database, particularly for ages 2 to less than 12, noting that the planned numbers of subjects in that age group were small for reliable assessment of rare or latent events and that additional safety information may be needed post-marketing.

On March 22, 2023, a Type B Meeting took place that served as the pre-supplementary NDA (sNDA) meeting for S-021 and S-022 as well as the pre-NDA meeting for NDA 218347. The Agency indicated that the Applicant should submit separate sNDAs for pJIA and pediatric PsA. A Type 3 NDA could be concurrently submitted for the new pediatric formation, an immediate-release oral solution. The planned justification of relevance of proposed supporting safety data from the Applicant's pediatric AD program appeared generally reasonable, though the final determination would be an sNDA review matter. The Agency agreed that the Applicant could submit subject-level data from pediatric AD patients 2 to less 12 years and a summary of pooled long-term adolescent data from the studies that previously supported approval for AD 12 years and older. Agreement was also reached that Applicant could submit the 4-month Safety Update Report (SUR) for Study M15-340 by October 30, 2023.

On March 24, 2024, the Applicant submitted PK information from Part 1 of Study M15-340 under NDA 211675 in accordance with the agreed final report date of March 2023 for PMR 3680-1. This PK information was also included in the submission of NDA 211671/S-021 on June 28, 2024.

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

## 4.1. Office of Scientific Investigations (OSI)

Review of the data did not identify any data integrity issues. No OSI inspections were deemed necessary.

The Office of Study Integrity and Surveillance (OSIS) conducted a remote regulatory assessment of the bioanalytical portion of Study M15-340 and concluded that the data from the audited study is reliable. Refer to the OSIS review by Dr. Makini Cobourne-Duval dated March 8, 2024, for more details.

## 4.2. Product Quality

The Applicant introduced a new formulation of upadacitinib, a 1 mg/mL oral solution, in NDA 218347. The data submitted under NDA 218347 support the conclusion that the proposed control strategy for the new presentation combined with in-process release, and stability testing ensure process consistency and drug substance, formulated drug substance, and drug product with appropriate quality attributes. The manufacturing facilities are in acceptable current good manufacturing practice compliance to manufacture the proposed drug product. The Office of Product Quality Assessment I (OPQA I) recommends approval of NDA 218347 based on the Integrated Quality Assessment finalized on March 5, 2024.

## 4.3. Clinical Microbiology

Not applicable

## 4.4. Devices and Companion Diagnostic Issues

Not applicable.

# 5 Nonclinical Pharmacology/Toxicology

## 5.1. Executive Summary

The Applicant submitted efficacy supplements NDA 211675/S-021 and NDA 211675/S-022 for Rinvoq (upadacitinib) for the treatment of pediatric patients 2 years of age and older with active pJIA and pediatric patients 2 years of age and older with active PsA, respectively. The Applicant, Abbvie, also submitted a Type 3 NDA 218347, Rinvoq LQ, proposing an immediate-release (IR) upadacitinib oral solution (1 mg/mL) for the treatment of pJIA (≥2 years) and PsA (≥2 years) for administration to patients unable to swallow solid dosage forms. The proposed oral liquid formulation doses for pediatric patients weighing 10 to <20 kg, 20 to <30 kg, and ≥30 kg are 3 mg (3 mL oral solution) twice daily, 4 mg (4 mL oral solution) twice daily, 6 mg (6 mL oral solution) twice daily, respectively. No new nonclinical studies were submitted. The Applicant has cross-referenced NDA 211675 Rinvoq (upadacitinib) extended-release tablets. Nonclinical pharmacology and toxicology studies conducted with Rinvoq (upadacitinib) were reviewed with the original NDA 211675 submission.

All excipients contained in the IR upadacitinib oral solution (1 mg/ml) are below those listed in the FDA Inactive Ingredient Database (IID) for approved oral drug products (refer to F2 formulation in Table 15). A nonclinical safety evaluation of the extractables and leachables for the Rinvoq LQ primary container closure system was conducted under NDA 218347 (dated March 19, 2024). From the nonclinical perspective, there are no safety concerns based on the results of the extractable and leachable studies.

# 6 Clinical Pharmacology

## 6.1. Executive Summary

Upadacitinib is a Janus kinase (JAK) inhibitor. Rinvoq (upadacitinib, extended-release (ER) tablets, 15 mg, 30 mg, and 45 mg) has been approved for the treatment of adults with moderately to severely active rheumatoid arthritis (RA), adults with active psoriatic arthritis (PsA), adults and pediatric patients 12 years of age and older with refractory, moderate to severe atopic dermatitis (AD), adults with moderately to severely active ulcerative colitis (UC), adults with moderately to severely active Crohn's disease (CD), adults with active ankylosing spondylitis (AS), and adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation with the approved dosage of:

- RA, PsA, AS, non-radiographic axial spondyloarthritis: 15 mg once daily (QD)
- AD: 15 mg or 30 mg QD for patients 12 years of age and older weighing at least 40 kg and adults less than 65 years of age; 15 mg QD for adults 65 years of age and older
- UC: 45 mg QD for 8 weeks, then 15 mg or 30 mg QD
- CD: 45 mg QD for 12 weeks, then 15 mg or 30 mg QD

The Applicant submitted NDA 211675/S-021 on June 28, 2023, and NDA 211675/S-022 on June 30, 2023, respectively, for the marketing approval for upadacitinib for the treatment of pediatric patients 2 years of age and older with active pJIA and for the treatment of pediatric patients 2 years of age and older with active PsA. On June 28, 2023, the Applicant also submitted NDA 218374 proposing an immediate-release (IR) upadacitinib oral solution (1 mg/mL) for the treatment of pediatric patients 2 years of age and older. The proposed dosing regimen for both pJIA and pediatric PsA is:

- 10 to <20 kg: 3 mg (3 mL oral solution) twice daily (BID)
- 20 to <30 kg: 4 mg (4 mL oral solution) BID
- ≥30 kg: 6 mg (6 mL oral solution) BID or 15 mg (one 15 mg ER tablet) QD

Upadacitinib oral solution (1 mg/mL) is proposed to be given with or without food.

NDA 211675 S-021 and S-022 and NDA 218347 consist of one phase 1 PK study evaluating the PK, safety, and tolerability of upadacitinib in pediatric subjects with JIA with active polyarthritis (Study M15-340, n=57), two population PK and simulation analysis reports for upadacitinib efficacy in JIA with polyarthritis (Reports R&D/22/1451 and R&D/22/1711), and one simulation analysis report for upadacitinib efficacy in pediatric PsA (Report R&D/22/1712).

**Summary of Clinical Pharmacology Assessment**
The Office of Clinical Pharmacology, Division of Inflammation and Immune Pharmacology (DIIP), and Division of Pharmacometrics (DPM) have reviewed the clinical pharmacology data

submitted under NDA211675/S-021, NDA211675/S-022, and NDA 218347. The submissions are recommended for approval from a clinical pharmacology perspective.

## 6.2. Summary of Clinical Pharmacology Assessment

### 6.2.1. Pharmacology and Clinical Pharmacokinetics

Rinvoq (upadacitinib) is a JAK inhibitor and has been approved for the treatment of adult patients with RA, PsA, UC, CD, AS, active non-radiographic axial spondyloarthritis, and adults and pediatric patients 12 years of age and older with AD. Refer to the approved labeling of Rinvoq regarding upadacitinib PK characteristics in subjects with the approved indications. The major findings for this Clinical Pharmacology review are as follows:

- RINVOQ® LQ (upadacitinib) oral solution
    - Rinvoq tablets and Rinvoq LQ are not bioequivalent; therefore, the 2 dosage forms are not interchangeable on a milligram-per-milligram basis. The 15 mg QD ER formulation (Rinvoq tablets) and 6 mg BID IR oral solution (RINVOQ® LQ) provide similar upadacitinib daily plasma exposures (Cmax,ss, AUC0-24,ss, Ctrough,ss).

- Pediatric subjects with JIA with active polyarthritis
    - In phase 1 PK study in pediatric subjects with JIA with active polyarthritis (Study M15-340), the median Tmax of upadacitinib is 3 hours and 1 hour following the administration of ER tablet and IR oral solution, respectively. Upadacitinib apparent oral clearance increased with increasing body weight in subjects with JIA with active polyarthritis.
    - In population PK analysis, body weight has been identified a significant covariate on upadacitinib apparent clearance and volume of distribution in pediatric patients, supporting the proposed weight-tiered dosing regimen of upadacitinib in pediatric patients. Population PK analysis suggested that exposure parameters (such as AUC and Cmax) were comparable across age groups (≥2 years) following the proposed dosing regimen.
    - The proposed upadacitinib pediatric dosing regimen, including BID regimen with IR oral solution and QD regimen with ER tablet, is predicted to provide comparable PK exposure (Cmax and AUC) in pediatric subjects with JIA with active polyarthritis as compared to the approved 15 mg ER tablet QD regimen in adults with RA, supporting the efficacy extrapolation from adults with RA to pediatric subjects with pJIA.
    - Simulations showed that the efficacy in pediatric subjects with JIA with active polyarthritis with the proposed dosing regimen is predicted to be comparable to

adults with RA with the approved 15 mg QD regimen and also similar across all age groups in pediatrics (2 to <6 years, 6 to <12 years, and 12 to <18 years).

- Pediatric subjects with PsA
    - Upadacitinib PK has not been studied in pediatric patients with PsA. As upadacitinib PK is comparable between adults with RA and PsA, it is expected that upadacitinib PK is also comparable between pediatric subjects with pJIA and pediatric subjects with PsA.
    - The proposed upadacitinib pediatric dosing regimen, including BID regimen with IR oral solution and QD regimen with ER tablet, is predicted to provide comparable PK exposure in pediatric subjects with PsA as compared to the approved 15 mg ER tablet QD regimen in adults with PsA, supporting the efficacy extrapolation from adults with PsA to pediatric subjects with PsA.
    - Simulations showed that the efficacy in pediatric subjects with PsA with the proposed dosing regimen is comparable to adults with PsA with the approved 15 mg QD regimen and is also similar across all age groups in pediatrics (2 to <6 years, 6 to <12 years, and 12 to <18 years).
    - In addition, safety information from relevant pediatric populations like pJIA can be leveraged. For disease similarity and justification of the relevance of safety data from pJIA, refer to Section 8.

### 6.2.2. General Dosing and Therapeutic Individualization

**General Dosing**

The proposed dosing regimen for pJIA (≥2 years) and pediatric PsA (≥2 years) is

- 10 to <20 kg: 3 mg (3 mL oral solution) BID
- 20 to <30 kg: 4 mg (4 mL oral solution) BID
- ≥30 kg: 6 mg (6 mL oral solution) BID or 15 mg (one 15 mg ER tablet) QD

Upadacitinib oral solution (1 mg/mL) is proposed to be given with or without food.

**Therapeutic Individualization**

The proposed dosing adjustments for pediatric patients 2 years of age and older with pJIA and pediatric PsA regarding intrinsic and extrinsic factors are consistent with the approved recommendations for RA and PsA.

**Outstanding Issues**

None

## 6.3. Comprehensive Clinical Pharmacology Review

### 6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Rinvoq (upadacitinib) is a JAK inhibitor and has been approved for the treatment of adult patients with RA, PsA, UC, CD, AS, nr-axSpA, and adults and pediatric patients 12 years of age and older with AD. Refer to the approved labeling of Rinvoq regarding upadacitinib PK characteristics in subjects with the approved indications.

RINVOQ® LQ (upadacitinib) oral solution
Rinvoq tablets and Rinvoq LQ are not bioequivalent; therefore, the 2 dosage forms are not interchangeable on a milligram-per-milligram basis.

The relative bioavailability of another upadacitinib IR oral solution (1 mg/mL) (F0) has been characterized in Study M16-552 (Table 17). Results of Study M16-552 indicated that under fasted condition, administration of two 6 mg doses of upadacitinib oral solution (Formulation F0; 1 mg/mL) 12 hours apart resulted in 30% higher Cmax and 17% higher AUC as compared to administration of a single dose of the 15 mg upadacitinib ER tablet (ER7).

In addition, the population PK model in pediatrics was used to simulate the plasma concentration-time profiles with the QD and BID regimens in pediatric subjects weighing ≥30 kg, who are eligible for receiving either 6 mg BID oral solution or 15 mg QD ER tablets. Simulation results indicate that 15 mg QD using the ER formulation and 6 mg BID using the IR oral solution provide similar upadacitinib daily plasma exposures (Cmax,ss, $AUC_{0-24}$,ss, Ctrough,ss) (Figure 4, Table 15).

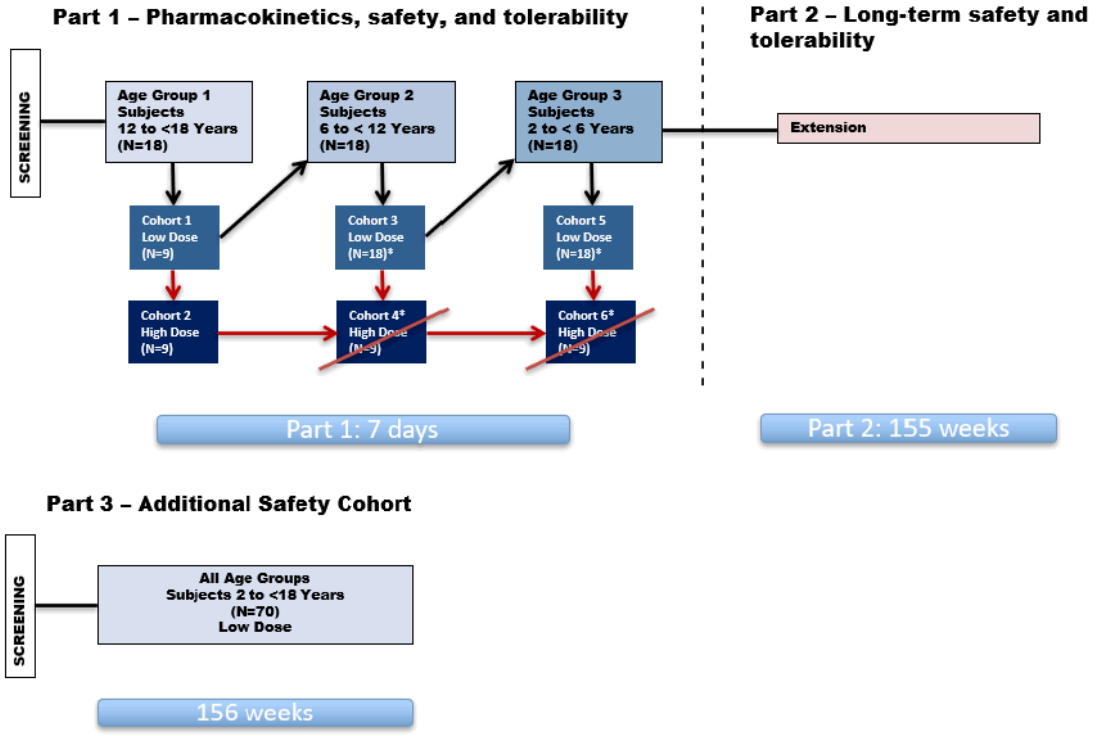
Upadacitinib PK in pediatric patients 2 years and older with pJIA in phase 1 Study M15-340
Upadacitinib PK in pediatric patients with pJIA has been characterized in a phase 1 PK study (Study M15-340). Study M15-340 is a phase 1, multiple-dose, open-label study consisting of three parts in pediatric subjects ages 2 to less than 18 years with JIA with active polyarthritis (Figure 1). As of September 22, 2022, 57 subjects with JIA with active polyarthritis were enrolled in this study and received study drug, including 51 subjects who completed Part 1.

In Part 1, subjects received upadacitinib for 7 days at two dose levels, Low Dose and High Dose levels, to provide comparable plasma exposures within each body weight category to 15 mg QD and 30 mg QD of the upadacitinib ER tablet in adults with RA, respectively. On Day 7, subjects were administered upadacitinib approximately 30 minutes after a meal and blood samples were collected for PK assessment. Upadacitinib dose was administered based on body weight. A dosing scheme with four body weight categories (Table 5) was initially proposed, which was then revised (Table 6) to match PK exposure in adults with RA based on preliminary PK analysis of the data from 23 subjects who completed Part 1.

PK results indicated that the median Tmax of upadacitinib in JIA with active polyarthritis is 3 hours and 1 hour following the administration of the ER tablet formulation and the IR oral solution, respectively (Table 7) . As upadacitinib is a medication for chronic use, the slight Tmax difference is not expected to be clinically significant for efficacy or safety. Upadacitinib apparent oral clearance increased with increasing body weight in subjects with JIA with active polyarthritis.

As the Applicant's PK exposure summary (Table 7) includes data from patients administered with doses other than the proposed dosing regimen, FDA conducted independent analysis. With the proposed dosing regimen in pediatric JIA patients, the PK exposure is generally comparable across age groups, with a mean $AUC_{0\text{-}24h}$ of 318, 394, and 480 ng·h/mL in pediatric pJIA patients 12-<18 years old, 6-<12 years old, and 2-<6 years old, respectively (Table 9). The PK exposure is also generally comparable across different weight groups with the proposed weight-tiered dosing regimen (Table 8). In addition, the PK exposure is generally comparable with the PK exposure in adult patients with RA ($AUC_{0\text{-}24h}$ of 376 ng·h/mL, Table 11). Note that the PK exposure seems high ($AUC_{0\text{-}24h}$ of 552 ng·h/mL ) in the two pediatric patients who took the 6 mg BID solution dose compared to patients who took 15 mg QD ER tablet. This could be explained by the low bodyweight which were just above the 30 kg cutoff, and the small sample size. The PK data with 4 mg BID were also only available in 3 pJIA patients. To utilize all available pediatric PK data with upadacitinib, a population PK analysis was conducted.

**Figure 1. Study Design Schematic (Study M15-340)**




* As of Protocol Version 9.0, High Dose Cohorts 4 and 6 were removed and Low Dose Cohorts 3 and 5 were to enroll approximately 18 subjects each, instead of the initially planned 9 subjects each.

Note: As of Protocol Version 10.0, Part 3, an additional safety cohort was added, to assess long-term safety and tolerability of the Low Dose of upadacitinib, without intensive pharmacokinetic sample collection. As of Protocol Version 11.0, at the end of study (Week 156), if the investigator believes the subject would benefit from treatment with upadacitinib, the subject had an option to receive this treatment through Post-Trial Access.

Source: Figure 1, CSR for Study M15-340

**Table 5. Initial Upadacitinib Dosing by Body Weight Category and Dose Level in Study M15-340**

| | Body Weight Category[a] | | | |
|---|---|---|---|---|
| **Dose Level** | **10 to < 15 kg** | **15 to < 25 kg** | **25 to < 40 kg** | **≥ 40 kg** |
| Low Dose | 1.6 mg BID Oral Solution | 2 mg BID Oral Solution | 7.5 mg QD Tablet or 3 mg BID Oral Solution (according to ability to swallow tablet) | 15 mg QD Tablet |
| High Dose | 3.2 mg BID Oral Solution | 4 mg BID Oral Solution | 15 mg QD Tablet or 6 mg BID Oral Solution (according to ability to swallow tablet) | 30 mg QD Tablet |

a. These body weight categories were used in Protocol Version 1.0 to Protocol Version 7.0. As of Protocol Version 8.0, the body weight categories were updated as detailed in Table 3.

Source: Table 2, CSR for Study M15-340 CSR

**Table 6. Revised Upadacitinib Dosing by Body Weight Category and Dose Level in Study M15-340**

| | Body Weight Category[a] | | |
|---|---|---|---|
| **Dose Level** | **10 to < 20 kg** | **20 to < 30 kg** | **≥ 30 kg** |
| Low Dose | 3 mg BID oral solution | 4 mg BID oral solution | 15 mg QD tablet (or 6 mg BID oral solution if unable to swallow tablet) |
| High Dose[b] | 6 mg BID oral solution | 8 mg BID oral solution | 30 mg QD tablet (or 12 mg BID oral solution in unable to swallow tablet) |

a. These body weight categories were used starting in Protocol Version 8.0.

b. As of Protocol Version 9.0, High Dose dosing regimen for the younger age groups (Age Group 2:6 to < 12 years, and Age Group 3:2 to < 6 years) were removed and all subjects followed the above updated dosing scheme.

Source: Table 3, CSR for Study M15-340 CSR

**Table 7. Geometric Mean (Mean, % CV) PK Parameters of Upadacitinib in Pediatric Patients with JIA with Active Polyarthritis (≥2 years) by Cohort Following the Initial and Revised Dosing Regimens in Study M15-340 Part 1**

| Pharmacokinetic Parameters (units) | Cohort 1 Low Dose QD (N = 9) | Cohort 2 High Dose QD (N = 9) | Cohort 3 Low Dose | | | Cohort 5 Low Dose BID (N = 12)[i] |
|---|---|---|---|---|---|---|
| | | | QD (N = 12) | BID (N = 7) | Total[g] (N = 19) | |
| $C_{max}$ (ng/mL) | 35.1 (37.2, 35) | 69.8 (71.2, 19) | 46.9 (52.3, 46) | 58.9 (62.5, 35) | 51.0 (56.1, 41) | 46.6 (55.8, 56) |
| $T_{max}$[a] (h) | 3.0 (1.0 – 6.0) | 4.0 (2.0 – 6.0) | 3.0 (1.0 – 6.0) | 1.0 (0.5 – 1.0) | -- | 1.0 (0.5 – 2.0) |
| Functional $t_{1/2}$[b] (h) | 5.53 (1.77)[e] | 4.79 (1.12) | 5.20 (0.949)[f] | 2.39 (0.277) | -- | 2.33 (0.351)[j] |
| $AUC_{tau}$[c] (ng•h/mL) | 269 (282, 32)[e] | 553 (572, 26) | 318 (351, 41)[f] | 198 (209, 36) | -- | 184 (217, 61)[j] |
| $AUC_{0-24}$[c] (ng•h/mL) | 269 (282, 32)[e] | 553 (572, 26) | 318 (351, 41)[f] | 397 (417, 36) | 346 (377, 39)[h] | 369 (433, 61)[j] |
| $CL_{ss}/F$ (L/h) | 55.7 (58.2, 32)[e] | 46.5 (49, 38) | 41.6 (46.7, 67)[f] | 19.7 (20.2, 25) | -- | 15.0 (16.8, 49)[j] |
| Bioavailability-Adjusted $CL_{ss}/F$[d] (L/h) | 38.1 (39.8, 32)[e] | 31.8 (33.5, 38) | 28.5 (32.0, 67)[f] | 19.7 (20.2, 25) | 24.7 (27.4, 65)[h] | 15.0 (16.8, 49)[j] |
| $C_{trough}$ (ng/mL)[k] | 1.68 (2.07, 52)[e] | 2.17 (2.68, 59) | 2.02 (2.37, 54)[f] | 1.81 (2.00, 58) | -- | 1.38 (1.71, 70)[j] |
| $C_{min}$ (ng/mL) | 1.46 (1.83, 59)[e] | 2.19 (2.92, 82) | 1.56 (1.95, 67)[f] | 1.81 (2.00, 58) | -- | 1.94 (2.95, 107)[j] |

Subjects who received initial dosing regimen (Protocol Version 1.0 to 7.0): Cohort 1 low dose QD (N=9), Cohort 2 high dose QD (N=9), Cohort 3 low dose QD (N=6), Cohort 3 low dose BID (N=1), Cohort 5 low dose BID (N=2)
Subjects who received revised dosing regimen (Protocol Version 8.0): Cohort 3 low dose QD (N=6), Cohort 3 low dose BID (N=6), Cohort 5 low dose BID (N=12)
Cohort 1: Age Group 1 (12 to < 18 years), Low Dose (15 mg QD)
Cohort 2: Age Group 1 (12 to < 18 years), High Dose (30 mg QD)
Cohort 3: Age Group 2 (6 to < 12 years), Low Dose (BID or 15 mg QD)
Cohort 5: Age Group 3 (2 to < 6 years), Low Dose (BID)

a. Median (minimum through maximum).
b. Harmonic mean (pseudo-standard deviation).
c. For QD regimens, $AUC_{tau} = AUC_{0-24}$; for BID regimens, $AUC_{tau} = AUC_{0-12}$ and $AUC_{0-24} = AUC_{0-12} \times 2$.
d. $CL_{ss}/F$ adjusted for the difference in bioavailability between formulations. For extended-release QD regimens, bioavailability-adjusted $CL_{ss}/F = 0.684*CL_{ss}/F$; For immediate-release BID regimens, bioavailability-adjusted $CL_{ss}/F = CL_{ss}/F$.
e. N = 8; Concentration at 24 hour was missing and the elimination phase rate constant could not be determined for one subject.
f. N = 11; Concentration at 24 hour was missing and the elimination phase rate constant could not be reliably estimated for one subject.
g. QD and BID regimens summarized together.
h. N = 18; Concentration at 24 hour was missing and the elimination phase rate constant could not be reliably estimated for one subject.
i. One subject was excluded for receiving an incorrect dose during the entire Part 1 period, and another subject that did not receive a dose on Day 7 due to an AE of vomiting was also excluded.
j. N = 10; Concentrations at 12 hour was missing and the elimination phase rate constant could not be determined or reliably estimated for two subjects.
k. Includes estimated $C_{trough}$ based on elimination half-life.

Source: Table 14, CSR for Study M15-340

**Table 8. Mean (SD) PK Parameters of Upadacitinib in Pediatric Patients 2 Years and Older with JIA with Active Polyarthritis by Body Weight Following the Proposed Dosing Regimen in Study M15-340 Part 1**

| Body weight subgroup | N | Body Weight[a] (kg) | Dosing regimen | Formulation | $AUC_{0-24h}$ (ng·h/mL) | Cmax (ng/mL) | Ctrough (ng/mL) |
|---|---|---|---|---|---|---|---|
| 10 to <20 kg | 11 | 14.6 (11.0, 19.7) | 3 mg BID | Solution | 468 (236) (n=10) | 61.1 (27.9) (n=11) | 1.64 (1.21) (n=10) |
| 20 to <30 kg | 3 | 25.2 (20.6, 29.4) | 4 mg BID | Solution | 410 (75) (n=3) | 73.0 (18.7) (n=3) | 1.58 (0.06) (n=3) |
| ≥ 30 kg | 2 | 32.9 (31.0, 34.8) | 6 mg BID | Solution | 552 (219) (n=2) | 73.5 (7.2) (n=2) | 3.22 (1.87) (n=2) |
| | 21 | 51.4 (32.4, 92.9) | 15 mg QD | Tablet | 340 (129) (n=20) | 49.5 (21.3) (n=21) | 2.36 (1.28) (n=20) |

a: Mean (range)

Source: FDA analysis

**Table 9. Mean (SD) PK Parameters of Upadacitinib in Pediatric Patients 2 Years and Older with JIA with Active Polyarthritis by Age Group Following the Proposed Dosing Regimen in Study M15-340 Part 1**

| Age subgroup | $AUC_{0\text{-}24h}$ (ng·h/mL) | Cmax (ng/mL) | Ctrough (ng/mL) |
|---|---|---|---|
| 2 to <6 years | 480 (246) (n=9) | 63.2 (28.4) (n=10) | 1.62 (1.28) (n=9) |
| 6 to <12 years | 394 (146) (n=16) | 60.9 (22.0) (n=16) | 2.27 (1.32) (n=16) |
| 12 to <18 years | 318 (111) (n=10) | 42.7 (16.9) (n=11) | 2.38 (1.15) (n=10) |

Source: FDA analysis

Upadacitinib population PK analysis in pediatric subjects

Upadacitinib PK in pediatric subjects was characterized using population PK analysis with data from phase 1 Study M15-340 in pediatric subjects with JIA with active polyarthritis and an ongoing Phase 1 Study M16-049 in pediatric subjects with AD aged 2 to less than 12 years old and leveraging prior information from healthy subjects and adults with RA, PsA, or AD through a Bayesian approach. Upadacitinib PK in pediatric subjects was described by a two-compartment model with first-order absorption for the IR oral solution formulation, mixed zero- and first-order absorption for the ER tablet formulation, and linear first-order elimination. Refer to Pharmacometrics Review by Dr. Da Zhang in Appendix 15.3 for more detailed information.

Note that while the PK data from Study M16-049 in pediatric subjects 2 to less than 12 years of age with AD was included in the population PK analysis, the scope of this review only focuses on the proposed pediatric indications of pJIA and PsA and no relevant conclusion will be made regarding the use of upadacitinib for the treatment of pediatric subjects 2 to less than 12 years of age with AD.

- *Pediatric patients with pJIA*

To compare upadacitinib exposure in pediatric patients with pJIA and adults with RA, the developed pediatric population PK model was used to simulate upadacitinib exposure in pJIA following the administration of the proposed dosing regimen. The model-predicted upadacitinib plasma exposures (Cmax,ss and AUC24,ss) by body weight or age group in pediatric subjects with JIA with active polyarthritis with the proposed dosing regimen were comparable to the predicted exposures in adults with RA with the approved dosing regimen (15 mg QD with ER tablet) (Table 10, Table 11, Figure 2).

**Table 10. Summary Statistics of Model-Predicted Upadacitinib Exposures in Pediatric Subjects by Body Weight Groups Compared to Adult Subjects with RA**

| Dose Level | Body Weight Group | $AUC_{24,ss}$ (ng hr/mL) Median (90% PI) | Ratio to Adults RA ($AUC_{24,ss}$) | $C_{max,ss}$ (ng/mL) Median (90% PI) | Ratio to Adults RA ($C_{max,ss}$) |
|---|---|---|---|---|---|
| Dose corresponding to 15 mg QD extended-release in adults | Adults RA | 376 (186, 780) | - | 42.1 (24.0, 72.9) | - |
| | 10 to < 20 kg | 299 (168, 542) | 0.796 | 37.6 (15.7, 92.3) | 0.895 |
| | 20 to < 30 kg | 334 (187, 660) | 0.889 | 39.7 (17.3, 113) | 0.944 |
| | ≥ 30 kg | 319 (171, 625) | 0.848 | 44.5 (19.9, 91.7) | 1.06 |

Cross reference: R&D/22/1451 Table 7

Source: Table 5, Summary of Clinical Pharmacology Studies, NDA211675-S21

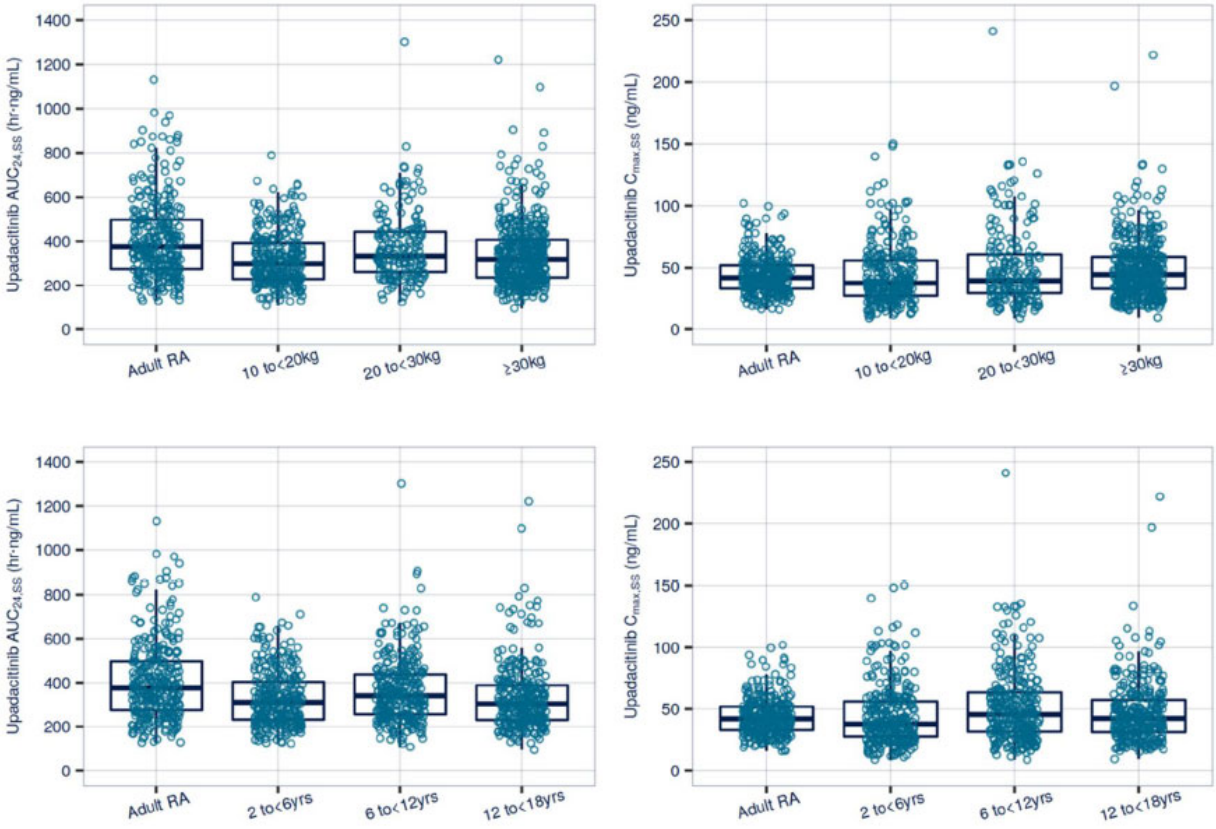
**Table 11. Summary Statistics of Model-Predicted Upadacitinib Exposures in Pediatric Subjects by Age Groups Compared to Adult Subjects with RA**

| Dose Level | Age Group | $AUC_{24,ss}$ (ng hr/mL) Median (90% PI) | Ratio to Adults RA ($AUC_{24,ss}$) | $C_{max,ss}$ (ng/mL) Median (90% PI) | Ratio to Adults RA ($C_{max,ss}$) |
|---|---|---|---|---|---|
| Dose corresponding to 15 mg QD extended-release in adults | Adults RA | 376 (186, 780) | - | 42.1 (24.0, 72.9) | - |
| | 2 to < 6 yrs | 311 (168, 571) | 0.827 | 37.8 (16.3, 97.3) | 0.899 |
| | 6 to < 12 yrs | 340 (184, 631) | 0.907 | 45.5 (18.7, 108) | 1.08 |
| | 12 to < 18 yrs | 304 (171, 652) | 0.808 | 42.4 (19.7, 85.9) | 1.01 |

Cross reference: R&D/22/1451 Table 8

Source: Table 6, Summary of Clinical Pharmacology Studies, NDA211675-S21

**Figure 2. Distribution of Model-Predicted Upadacitinib Exposures in Pediatric Subjects by Body Weight and Age Groups Compared to Adult Subjects with RA**




Cross reference: R&D/22/1451 Figure 6

Source: Figure 7, Summary of Clinical Pharmacology Studies, NDA211675-S21

- *Upadacitinib PK in pediatric patients 2 years and older with PsA*

While upadacitinib PK in pediatric patients 2 years and older with PsA has not been characterized, it is expected to be comparable to pediatric subjects with pJIA given the comparable PK between adults with RA and PsA.

To compare upadacitinib exposure in pediatric subjects and adults with PsA, the developed pediatric population PK model was used to simulate upadacitinib exposure in pediatric subjects with PsA following the administration of the proposed dosing regimen. The model-predicted upadacitinib plasma exposures (Cmax,ss and AUC24,ss) by body weight or age group in pediatric subjects with PsA with the proposed dosing regimen were comparable to the predicted exposures in adults with PsA with the approved dosing regimen (15 mg QD with ER tablet) (Table 12, Table 13, Figure 3, Figure 4).

**Table 12. Summary Statistics of Model-Predicted Exposures in Pediatric Subjects by Body Weight Groups Compared to Adult Subjects with PsA**

| Dose Level | Body Weight Group | $AUC_{24,ss}$ (ng hr/mL) Median (90% PI) | Ratio to Adults PsA ($AUC_{24,ss}$) | $C_{max,ss}$ (ng/mL) Median (90% PI) | Ratio to Adults PsA ($C_{max,ss}$) |
|---|---|---|---|---|---|
| Dose corresponding to 15 mg QD extended-release in adults | Adult PsA | 356 (169, 710) | - | 38.2 (21.7, 68.4) | - |
| | 10 to < 20 kg | 299 (168, 542) | 0.839 | 37.6 (15.7, 92.3) | 0.986 |
| | 20 to < 30 kg | 334 (187, 660) | 0.937 | 39.7 (17.3, 113) | 1.04 |
| | ≥ 30 kg | 319 (171, 625) | 0.894 | 44.5 (19.9, 91.7) | 1.17 |

Cross reference: R&D/22/1451 Table 7

Source: Table 5, Summary of Clinical Pharmacology Studies, NDA211675/S-022

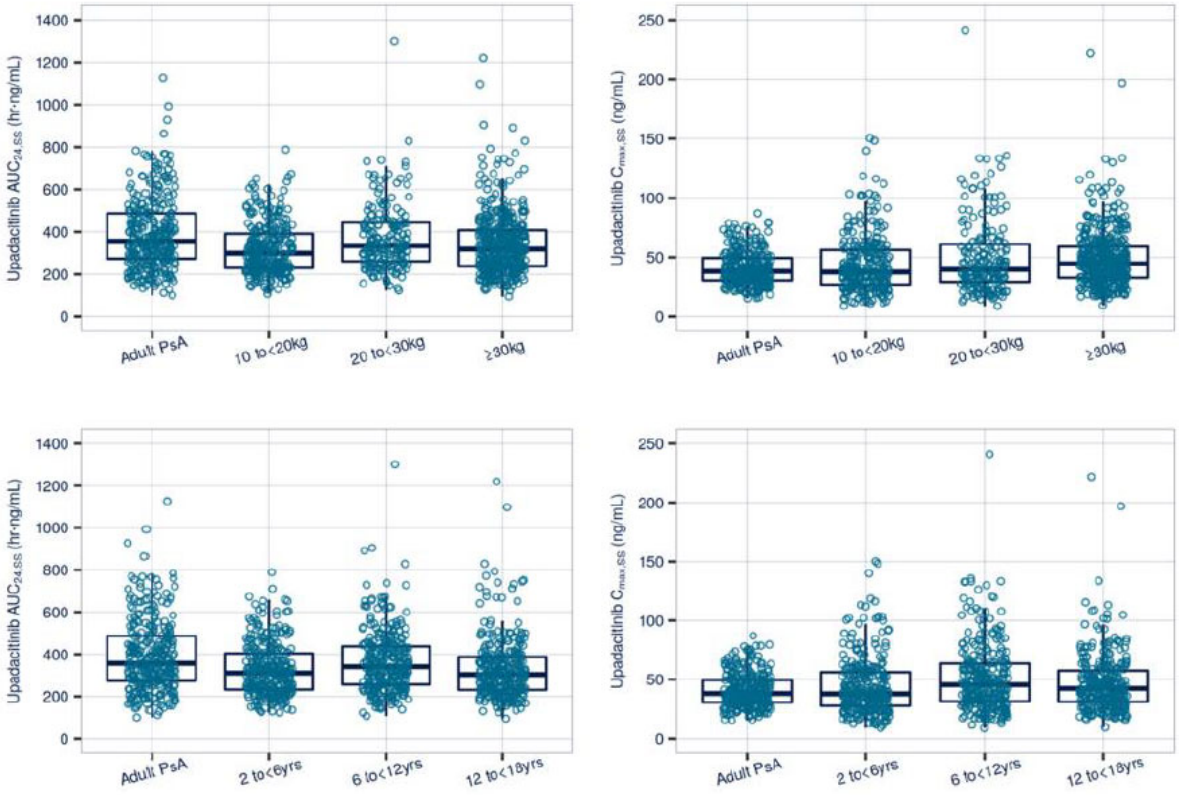
**Table 13. Summary Statistics of Model-Predicted Upadacitinib Exposures in Pediatric Subjects by Age Groups Compared to Adult Subjects with PsA**

| Dose Level | Age Group | $AUC_{24,ss}$ (ng hr/mL) Median (90% PI) | Ratio to Adults PsA ($AUC_{24,ss}$) | $C_{max,ss}$ (ng/mL) Median (90% PI) | Ratio to Adults PsA ($C_{max,ss}$) |
|---|---|---|---|---|---|
| Dose corresponding to 15 mg QD extended-release in adults | Adult PsA | 356 (169, 710) | - | 38.2 (21.7, 68.4) | - |
| | 2 to < 6 yrs | 311 (168, 571) | 0.871 | 37.8 (16.3, 97.3) | 0.991 |
| | 6 to < 12 yrs | 340 (184, 631) | 0.955 | 45.5 (18.7, 108) | 1.19 |
| | 12 to < 18 yrs | 304 (171, 652) | 0.852 | 42.4 (19.7, 85.9) | 1.11 |

Cross reference: R&D/22/1451 Table 8

Source: Table 6, Summary of Clinical Pharmacology Studies, NDA211675/S-022

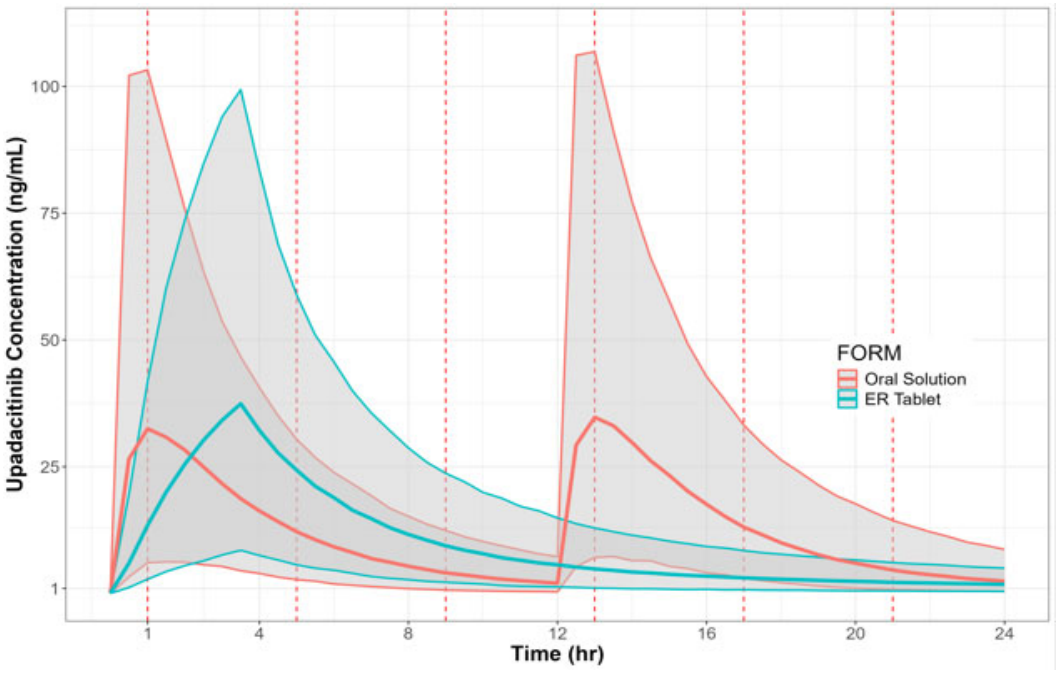
**Figure 3. Distribution of Model-Predicted Upadacitinib Exposures in Pediatric Subjects by Body Weight and Age Groups Compared to Adult Subjects with PsA**

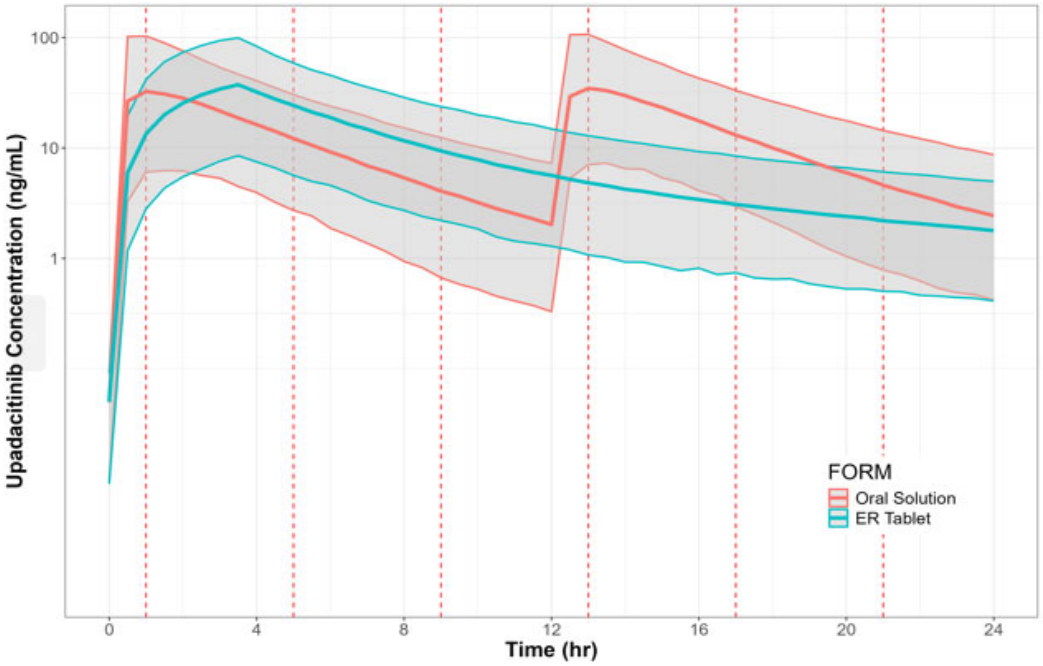



Cross reference: R&D/22/1451 Figure 6

Source: Figure 7, Summary of Clinical Pharmacology Studies, NDA211675/S-022

**Figure 4. Model-Predicted Upadacitinib Plasma Concentration-Time Profiles After Administration of QD and BID Regimens in Pediatric Patients (Linear (Upper Panel) and Log-Linear (Lower Panel) Scales)**



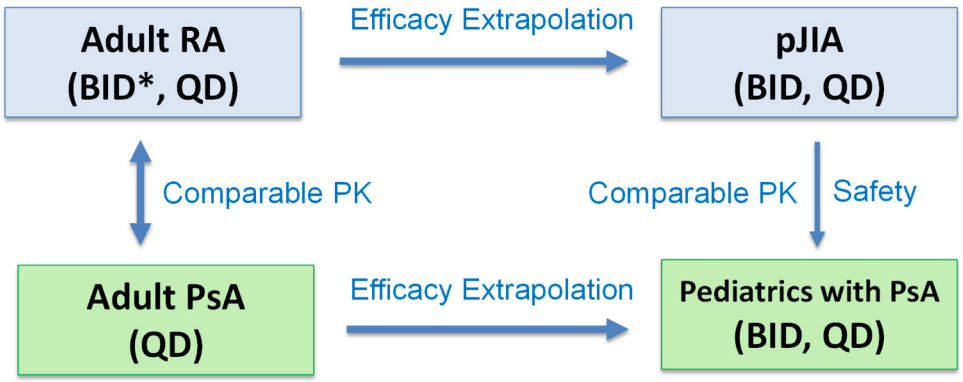

Source: FDA analysis

### 6.3.1. Clinical Pharmacology Questions

**Does the clinical pharmacology program provide supportive evidence of effectiveness?**

Yes, the predicted upadacitinib exposure in pediatric subjects with pJIA and PsA with the proposed dosing regimen are comparable to the exposure in adults with RA and PsA with the approved dosing regimen, respectively, supporting the extrapolation of efficacy from adults with RA and PsA to pediatric subjects with pJIA and PsA, respectively (Figure 5).

**Figure 5. Bridging Strategy Between Adults with RA and PsA and Pediatric Subjects with pJIA and PsA**




*Phase 2 dose-ranging study

Source: FDA reviewer

Pediatric patients with pJIA

The proposed upadacitinib pediatric dosing regimen in pJIA includes BID dosing with IR oral solution and QD dosing with ER tablet. While only upadacitinib QD dosing with ER tablet was approved in adults with RA, the treatment effect of upadacitinib BID dosing (ACR response at Week 12 as primary endpoint) with IR formulation was explored in two phase 2 dose-ranging studies in RA patients (Studies M13-537 and M13-550), in which 6 mg BID and 12 mg BID dosing were selected as the target exposure for phase 3 studies (Table 14). With the development of ER tablet formulation, upadacitinib 15 mg QD dosing with ER formulation provided comparable steady state systemic exposure to 6 mg BID using IR formulation and, therefore, was evaluated in the phase 3 studies in RA. Refer to the NDA 211675 Clinical Pharmacology Review by Dr. Lei He dated May 17, 2019, for more details.

The population PK model in pediatrics and exposure-response models in adults with RA were used to simulate the efficacy of upadacitinib in pediatric subjects with pJIA. Simulation results indicate that the proposed upadacitinib pediatric dosing regimen is predicted to provide similar efficacy in pJIA as compared to the approved 15 mg QD regimen in adults with RA, and the efficacy in pJIA is also predicted to be similar across all age groups in pJIA (2 to <6 years, 6 to <12 years, and 12 to <18 years) (Figure 6, Figure 7).

Overall, the comparable PK exposures between pediatric subjects with JIA with active polyarthritis and adult patients with RA are considered to be adequate to support the extrapolation of efficacy from adults with RA to pediatric subjects with pJIA.

**Table 14. Summary of the Primary Efficacy Results from Three Phase 2 Dose-Ranging Studies in Adults with RA**

| Study ID | Patient Population | Formulation | ACR Response Rate at Week 12* | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | placebo | 3 mg BID | 6 mg BID | 12 mg BID | 18 mg BID | 24 mg QD |
| M13-537 | RA with inadequate resp. to MTX (n=299) | IR | 50% (23/46) | 64.6% (31/48) (n.s.) | 73.5% (36/49) (p=0.018) | 81.6% (40/49) (p=0.001) | 76.6% (36/47) (p=0.008) | 81.6% (40/49) (p=0.001) |
| M13-550 | RA on MTX, inadequate resp. to anti-TNF biologics (n=276) | IR | 35.2% (19/54) | 55.6% (30/54) (p=0.033) | 63.5% (33/52) (p=0.004) | 72.7% (40/55) (p<0.001) | 70.9% (39/55) (p<0.001) | -- |

* listed as response rate (%) calculated by response patient number/total patient number; p value is the comparison of ACR 20 between treatment group and placebo.

Source: Table 4, NDA211675 Clinical Pharmacology Review

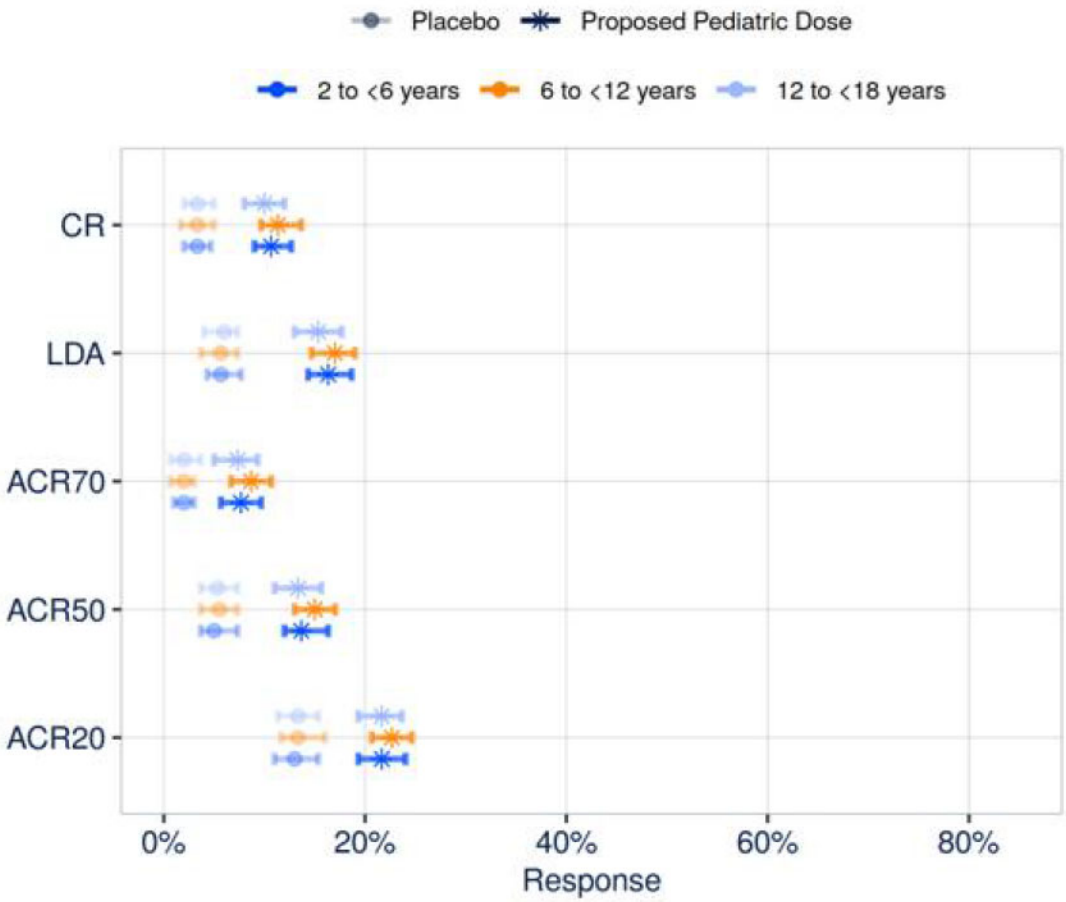
**Figure 6. Exposure-Response Simulation in Pediatric Subjects with pJIA in Comparison to Adults with RA**


Dot and Star: Median response; Error bars: 90% PIs of the response.

Cross reference: R&D/22/1711 Figure 1

Source: Figure 8, Summary of Clinical Pharmacology Studies, NDA211675/S-021

**Figure 7. Exposure-Response Simulation in Pediatric Subjects with pJIA Stratified by Age Group**




Dot and Star: Median response; Error bars: 90% PIs of the response.
Cross reference: R&D/22/1711 Figure 3
Source: Figure 9, Summary of Clinical Pharmacology Studies, NDA211675/S-021

Pediatric patients with PsA

While upadacitinib PK in pediatric patients 2 years and older with PsA has not been characterized, it is expected to be comparable to pediatric subjects with pJIA given the comparable PK between adults with RA and PsA.

The proposed upadacitinib pediatric dosing regimen in pediatric PsA includes BID dosing with IR oral solution and QD dosing with ER tablet. However, only upadacitinib QD dosing with ER tablet was investigated and approved in adults with PsA. The population PK model in pediatrics was used to simulate the plasma concentration-time profiles with the QD and BID regimens in

pediatric subjects weighing ≥30 kg, who are eligible for receiving either 6 mg BID oral solution or 15 mg QD ER tablets. Simulation results indicate that 15 mg QD using the ER formulation and 6 mg BID using the IR oral solution provide similar upadacitinib daily plasma exposures (Cmax,ss, AUC0-24,ss, Ctrough,ss) (Figure 4, Table 15). In the exposure-response analyses including adults with PsA, a significant relationship between upadacitinib Cavg and the key efficacy endpoints was observed (Figure 8). Given that BID IR regimens and the QD ER regimens provide similar Cavg, Cmax and Ctrough, it is expected that upadacitinib efficacy will be similar between the proposed BID and QD regimens.

The population PK model in pediatrics and exposure-response models in adults with PsA were used to simulate the efficacy of upadacitinib in pediatric subjects with PsA. Simulation results indicate that the proposed upadacitinib pediatric dosing regimen is predicted to provide similar efficacy in pediatric subjects with PsA as compared to the approved 15 mg QD regimen in adults with PsA and the efficacy in PsA is also predicted to be similar across all age groups in pediatric PsA (2 to <6 years, 6 to <12 years, and 12 to <18 years) (Figure 9, Figure 10).

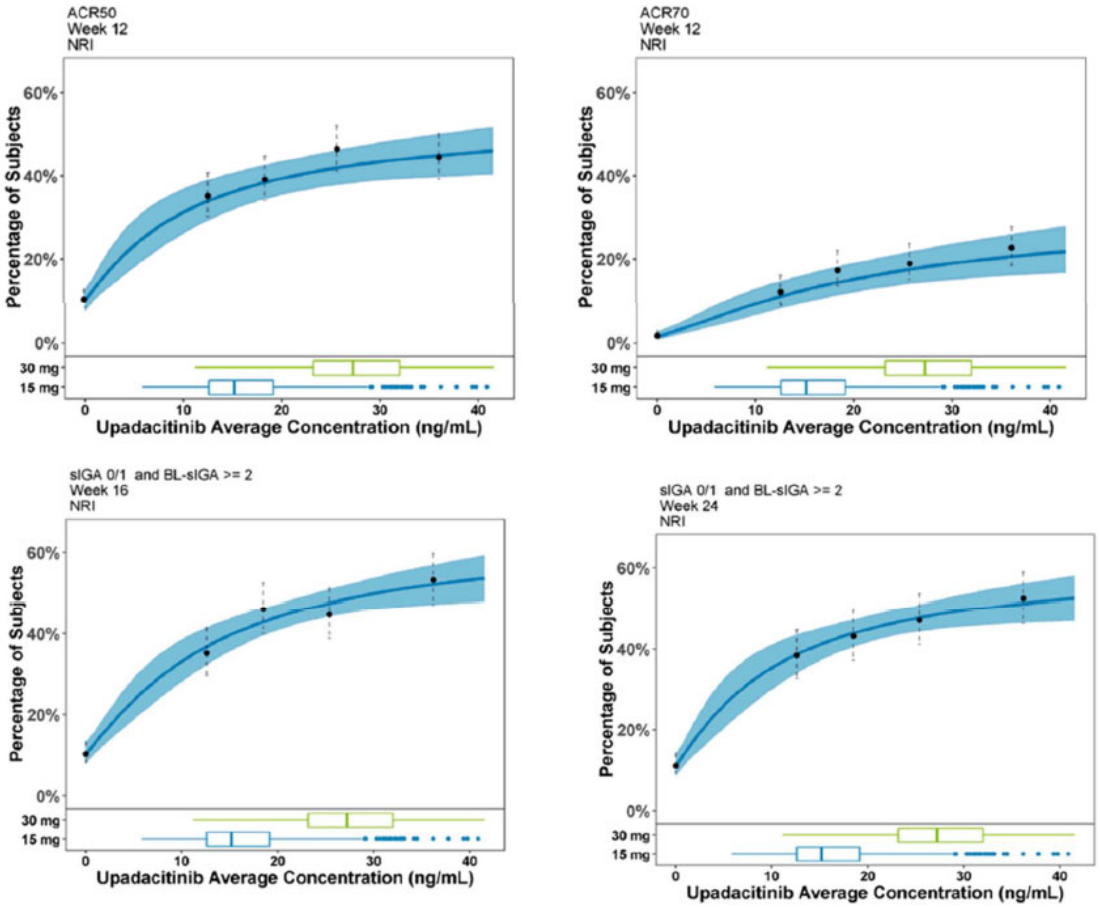
Overall, the comparable PK exposures between pediatric subjects with PsA and adults with PsA are considered to be adequate to support the extrapolation of efficacy from adults with PsA to pediatric subjects with PsA.

**Table 15. Summary Statistics of Model-Predicted Upadacitinib Exposures After Administration of QD and BID Regimens in Pediatric Subjects**

| Formulation | $AUC_{0\text{-}24}$ (ng·hr/mL) Median (90% PI) | $C_{max}$ (ng/mL) Median (90% PI) | $C_{trough}$ (ng/mL) Median (90% PI) |
|---|---|---|---|
| 15 mg QD Tablet | 319 (171, 625) | 44.5 (19.9, 91.7) | 2.94 (1.17, 7.15) |
| 6 mg BID Oral Solution | 380 (203, 754) | 44.6 (18.7, 111) | 2.91 (0.887, 8.24) |

Source: Table 1, Response to FDA's Filing Letter Request dated September 8, 2023

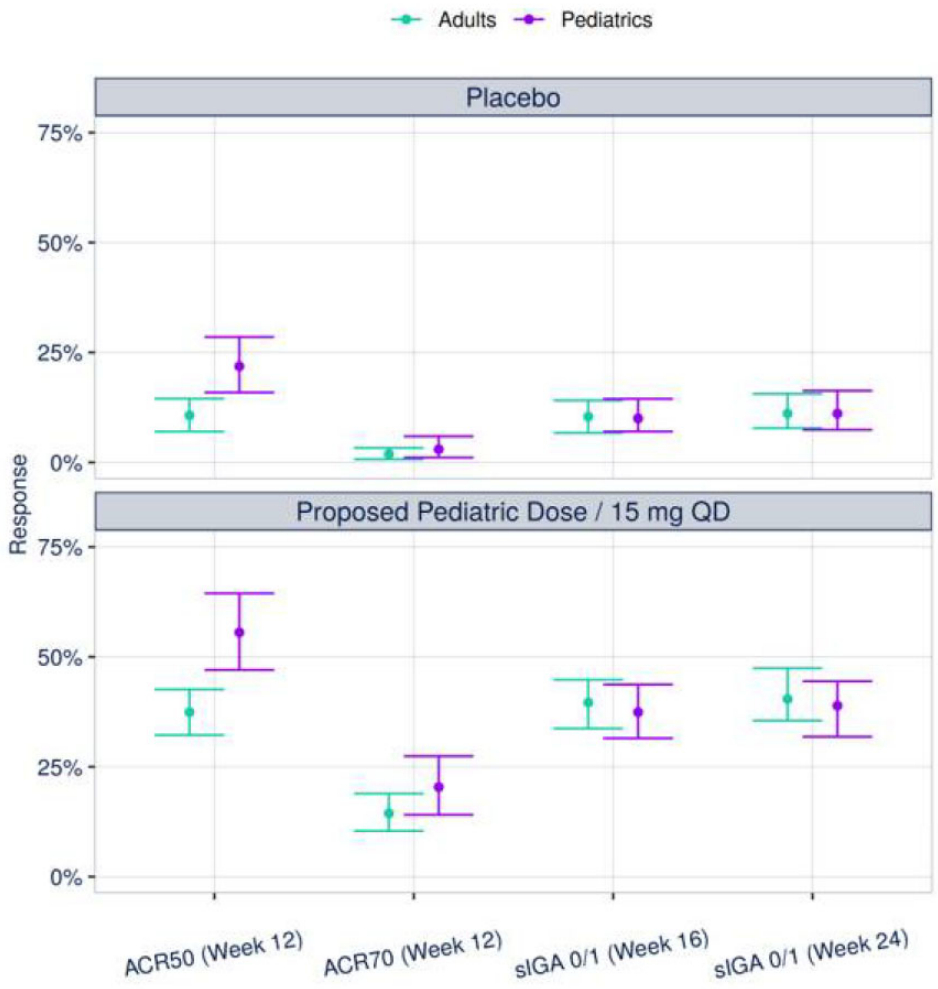
**Figure 8. Observed and Model-Predicted Efficacy Responses vs. Upadacitinib Cavg**




Note: The blue solid line represents the median predicted response, and the blue shaded area represents 95% confidence intervals of the predicted response. The dots and error bars represent median and 95% binomial CIs of binned observed rates. Reference: R&D/19/1199

Source: Figure 2, Response to FDA's Filing Letter Request dated September 8, 2023

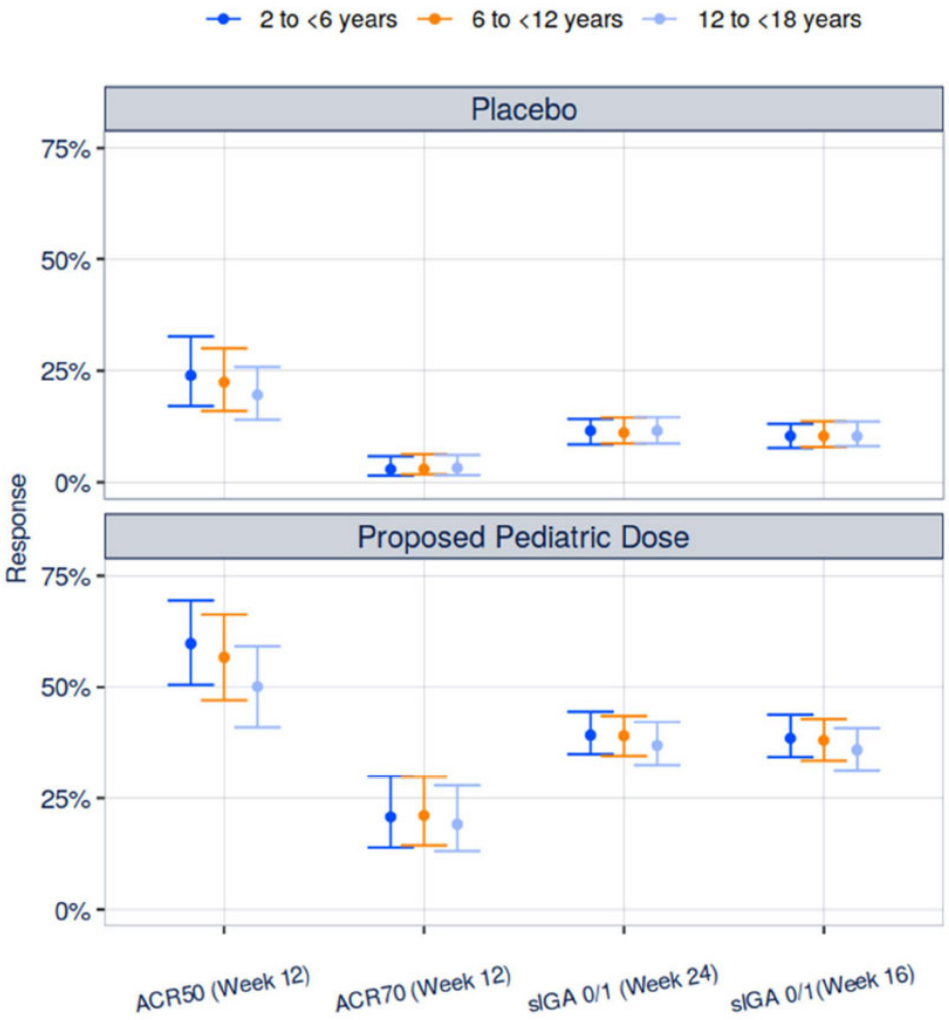
**Figure 9. Exposure-Response Simulation in Pediatric Subjects with PsA in Comparison to Adults with PsA**




Cross reference: R&D/22/1712 Figure 1

Source: Figure 8, Summary of Clinical Pharmacology Studies, NDA211675./S-022

**Figure 10. Exposure-Response Simulation in Pediatric Subjects with PsA Stratified by Age Group**




Cross reference: R&D/22/1712 Figure 3

Source: Figure 9, Summary of Clinical Pharmacology Studies, NDA211675/S-022

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

The proposed dosing regimen for pediatric patients 2 years and older with pJIA and PsA is appropriate.

- 10 to <20 kg: 3 mg (3 mL oral solution) BID

- 20 to <30 kg: 4 mg (4 mL oral solution) BID
- ≥30 kg: 6 mg (6 mL oral solution) BID or 15 mg (one 15 mg ER tablet) QD

The proposed pediatric dosing regimen is predicted to provide comparable PK exposure as well as efficacy in pediatric subjects with pJIA and PsA as compared to adults with RA and PsA, respectively. See above for details regarding PK and efficacy comparison. In addition, given the comparable PK exposure in pediatric subjects with pJIA, AD and PsA, the safety profile in pediatric PsA is expected to similar to pediatric subjects with pJIA and AD. See section 8 for more details of safety assessment.

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

Renal and hepatic impairment
In adult patients with RA or PsA, no dosage adjustment is needed in patients with mild (eGFR 60 to <90 mL/min/1.73 $m^2$), moderate (eGFR 30 to <60 mL/min/1.73 $m^2$), or severe renal impairment (eGFR 15 to <30 mL/min/1.73 $m^2$). Rinvoq has not been studied in patients with end stage renal disease (eGFR <15 mL/min/1.73$m^2$). 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. The proposed upadacitinib dosing recommendation for pediatric patients 2 years and older with pJIA and pediatric PsA regarding renal and hepatic impairment are consistent with the approved recommendations for RA and PsA, which is reasonable.

Body weight, age, disease, race, and sex
In population PK analysis, body weight has been identified a significant covariate on upadacitinib apparent clearance and volume of distribution in pediatric patients, supporting the proposed weight-tiered dosing regimen of upadacitinib in pediatric patients. After accounting for the body weight effect, age had no additional effect on upadacitinib PK in pediatrics. Upadacitinib PK is comparable between pediatric subjects with pJIA and pediatric AD.

Race and sex had no relevant effects on upadacitinib PK parameters in adult subjects with RA or PsA and, therefore, are not expected to have effects on upadacitinib PK in pediatrics.

**Is the formulation(s) used in clinical studies adequately bridged to the proposed commercial formulation?**

The 15 mg ER tablet formulation (ER17Y) used in the pediatric study M15-340 has been adequately bridged to the commercial 15 mg ER tablet formulation (ER17) under fasted and fed conditions in phase 1 Study M20-017, which was previously reviewed in the NDA submission for upadacitinib in PsA (Table 16) (Refer to NDA211675/S-002 Unireview dated February 13, 2021).

Three different formulations of upadacitinib oral solution (1 mg/mL) (F1, S1, and F2) were used in the phase 1 study (M15-340) in JIA with active polyarthritis, of which formulation F2 is the proposed commercial formulation (Table 18). The relative bioavailability of another upadacitinib IR oral solution (1 mg/mL) (F0) has been characterized in Study M16-552 in healthy subjects comparing to the phase 3 study 15 mg ER tablet (ER7) (Table 17), which was adequately bridged to the commercial 15 mg ER tablet in Study M15-878. Results of Study M16-552 indicated that under fasted condition, administration of two 6 mg doses of upadacitinib oral solution (Formulation F0; 1 mg/mL) 12 hours apart resulted in 30% higher Cmax and 17% higher AUC as compared to administration of a single dose of the 15 mg upadacitinib ER tablet (ER7). For details of Studies M16-552 and M15-878, refer the NDA 211675 Clinical Pharmacology Review by Dr. Lei He dated May 17, 2019. The Applicant requested a biowaiver (R&D/23/0111) for conducting a bioavailability study to support the bioequivalence among these oral solution formulations (F1, S1, F2, and F0). From Biopharmaceutics perspective, it was considered that the bridge (bioavailability/bioequivalence) between the formulations F0, F1, S1, and proposed commercial drug product formulation F2 has been established. Refer to the Biopharmaceutics Review by Dr. Kalpana S. Paudel for more details.

**Table 16. Summary of Formulations Used in Clinical Development in Upadacitinib Studies**

| | Study Number | | | | |
|---|---|---|---|---|---|
| **Formulation and Devices** | M15-340 | M15-878 | M16-049 | M16-552 | M20-017 |
| Phase 3 RA formulation (ER8), 30 mg tablet | | X | | | |
| Commercial formulation (ER18), 30 mg tablet | | X | | | X |
| Phase 3 RA formulation (ER7), 15 mg tablet | | X | | X | |
| Commercial formulation (ER17), 15 mg tablet | | X | | | X |
| Pediatric study formulation (ER16Y), 7.5 mg tablet | X | | X | | |
| Pediatric study formulation (ER17Y), 15 mg tablet | X | | X | | X |
| Pediatric study formulation (ER18Y), 30 mg tablet | X | | X | | X |
| 1 mg/mL oral solution (F0) | | | | X | |
| 1 mg/mL oral solution (F1) | X | | X | | |
| 0.5 mg/mL oral solution (S1) | X | | X | | |
| 1 mg/mL oral solution (F2) | X | | X | | |

ER = extended-release

Note: The composition of the ER7, ER8, and ER18 tablet formulations were included in the original regulatory application for the use of upadacitinib in the treatment of RA (R&D/17/0611).

Source: Table 3, Biopharmaceutic Studies and Analytical Methods, NDA211675/S-021

**Table 17. PK Comparison between Two 6 mg Doses of Upadacitinib Oral Solution Formulation (1 mg/mL, F0) and a Single 15 mg Dose of Upadacitinib ER Tablet Formulation (ER7) under Fasted Conditions in Healthy Subjects in Study M16-552**

| Regimens Test vs. Reference | Pharmacokinetic Parameter | Point Estimate | 90% Confidence Interval |
|---|---|---|---|
| Regimen A vs. Regimen B | $C_{max}$ (ng/mL)[a] | 1.301 | 1.164, 1.453 |
| | $AUC_t$ (ng•h/mL) | 1.184 | 1.102, 1.272 |
| | $AUC_{inf}$ (ng•h/mL) | 1.169 | 1.087, 1.258 |

In Study M16-552, two 6 mg doses of upadacitinib oral solution (1 mg/mL, F0) were administered 12 hours apart under fasted condition, and a single 15 mg dose of upadacitinib ER tablet (ER7) was administered under fasted condition.
Source: Table 4.1.2-17 of NDA211675 Clinical Pharmacology Review dated May 17, 2019

**Table 18. Composition of Upadacitinib Immediate-Release Oral Solution Formulations**

| | | Quantities (g) | | | |
|---|---|---|---|---|---|
| Component | Function | Formulation F0: 1 mg/mL | Formulation F1: 1 mg/mL | Formulation S1: 0.5 mg/mL | Formulation F2: 1 mg/mL (proposed commercial formulation) |
| Upadacitinib | Active | 0.100 | 0.100 | 0.050 | 0.100 |
| (b) (4) | (b) (4) | (b) (4) | | | (b) (4) |
| Sodium Benzoate | | | | | |
| Sucralose | | | | | |
| Water | | q.s. to 100 | q.s. to 100 | q.s. to 100 | q.s. to 100 |
| Specified pH range | | (b) (4) | To be monitored | (b) (4) | (b) (4) |
| Measured pH range | | NA[a] | (b) (4) | | |

NA = not applicable; q.s. = sufficient quantity
F0 = the extemporaneous dose preparation formulation evaluated in a relative bioavailability study (M16-552).
F1 = the first formulation used in Studies M15-340 and M16-049, in glass bottle.
S1 = the second formulation used in Studies M15-340 and M16-049, in glass bottle.
F2 = the third formulation used in Studies M15-340 and M16-049, in glass bottle; proposed commercial formulation will be supplied in high-density polyethylene (HDPE) bottle.
a. pH of Formulation F0 was not measured as part of the extemporaneous dose preparation process.
Source: FTR-17-0014, NDA 218347, Module 3, Section 3.2.P.2.2, Table 2 and Table 4

Source: Table 5, Biopharmaceutic Studies and Analytical Methods, NDA211675/S-021

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

Food-drug interactions

Coadministration of upadacitinib Rinvoq ER tablets with a high-fat/high-calorie meal had no clinically relevant effect on upadacitinib exposures (increased AUCinf by 29% and Cmax by 39%). Rinvoq ER tablets could be administered with or without food.

Upadacitinib oral solution has been administered in Study M15-340 30 minutes after a meal on Day 7 (the intensive PK sampling day) and regardless food intake on any other days. In the previously submitted Study M13-401, administration of a upadacitinib IR capsule (3 mg) formulation approximately 30 minutes after a high-fat/high-calorie meal resulted in ~23% decrease in Cmax and comparable AUC as compared to fasting conditions (For details of Study M13-401, refer the NDA 211675 Clinical Pharmacology Review by Dr. Lei He dated May 17, 2019). Therefore, coadministration with food is not expected to have a clinically relevant effect on upadacitinib exposure with the proposed IR solution. Upadacitinib oral solution could be administered with or without food in pediatric patients with pJIA and PsA.

Drug-drug interactions

In adult patients with RA or PsA, it was recommended to monitor patients closely for adverse reactions when co-administering Rinvoq 15 mg QD with strong CYP3A4 inhibitors. Food or drink containing grapefruit should be avoided during treatment with RINVOQ. Coadministration of Rinvoq with strong CYP3A4 inducers is not recommended.

The proposed upadacitinib dosing recommendation for pediatric patients 2 years and older with pJIA and pediatric PsA regarding drug-drug interactions are consistent with the approved recommendations for RA and PsA, which is reasonable.

**Question on clinically relevant specifications (TBD)?**

None

# 7 Sources of Clinical Data and Review Strategy

## 7.1. Table of Clinical Studies

The primary clinical study submitted to support upadacitinib for the proposed indications of pJIA and pediatric PsA is Study M15-340. This study is a multipart, open-label safety and PK study in pediatric subjects with JIA with active polyarthritis. Supportive PK and safety data were also submitted from an interim analysis of Study M16-049, an ongoing study in pediatric subjects with AD ages 2 to less than 12 years old. As described in Section 6, population-PK analyses reports based on PK data from Studies M15-340 and M16-049 were used to support PK-based efficacy extrapolations for pJIA from adult RA and pediatric PsA from adult PsA, respectively. Supporting safety information for upadacitinib in pediatric subjects was also submitted from the pooled long-term follow up of adolescent subjects with AD ages 12 to less than 18 years from the pivotal studies previously used to support the approval of upadacitinib for AD in patients 12 years and older (NDA 211675/S-004). Table 19 presents a summary of the objectives, designs, study populations, and treatment groups for each of the clinical studies used to support upadacitinib for the proposed indications of pJIA and pediatric PsA.

Upadacitinib for adults with moderately to severely active RA was previously supported by efficacy, safety, and PK data from 5 randomized, placebo-controlled studies: M13-549, M13-542, M14-465, M13-545, and M15-555. See the Cross-Discipline Team Leader (CDTL) review for the original NDA application dated July 19, 2019, for full details.

Upadacitinib for adults with active PsA was previously supported by efficacy, safety, and PK data from 2 randomized, placebo-controlled studies: M15-554 and M15-572. See the Unireview for supplemental NDA application NDA 211675/S-002 dated December 10, 2021, for full details.

**Table 19. Listing Clinical Trials Relevant to this NDA**

| Trial Identity | NCT no. | Trial Design | Regimen/ schedule/ route | Study Endpoints | Treatment Duration/ Follow Up | No. of patients enrolled | Study Population | No. of Centers and Countries |
|---|---|---|---|---|---|---|---|---|
| | | ***Studies to Support Efficacy and Safety*** | | | | | | |

<table>
<tr>
<td>M15-340</td>
<td>NCT03725007</td>
<td>Multipart , multiple dose, OL study<br><br><u>Part 1</u>: PK eval of low and high doses in 3 different age groups (12 to < 18 yrs; 6 to < 12 yrs; 2 to < 6 yrs) (completed)<br><br><u>Part 2</u>: OLE for Part 1 subjects to receive low dose upadacitinib for additional 155 weeks (ongoing)<br><br><u>Part 3</u>: Additional OL cohort to receive upadacitinib for 156 weeks (ongoing)</td>
<td>
<table>
<tr><th></th><th>10 to <20 kg</th><th>20 to <30 kg</th><th>≥30 kg</th></tr>
<tr><td>Low dose</td><td>3 mg BID oral solution</td><td>4 mg BID oral solution</td><td>15 mg QD Tablet (or 6 mg BID oral solution if unable to swallow tablet)</td></tr>
<tr><td>High dose</td><td>6 mg BID oral solution</td><td>8 mg BID oral solution</td><td>30 mg QD Tablet (or 12 mg BID oral solution if unable to swallow tablet)</td></tr>
</table>
</td>
<td>PK: $C_{max}$, $T_{max}$, and $AUC_{tau}$ at Day 7; $T1_{/2}$; CL/F; V/F<br><br>Safety: TEAEs, physical exam, change in vitals, clinical labs<br><br>Descriptive efficacy at Week 12: ACR 30/50/70/90/100; JADAS 10/27/71; changes in ACR and JADAS components; number of active joints, C-HAQ, PGA, PtGA, ESR, CRP</td>
<td>Part 1: 7 days<br><br>Part 2: 155 weeks<br><br>Part 3: 156 weeks</td>
<td>83</td>
<td>Pediatric subjects 2 to less than 18 years with JIA with active polyarthritis</td>
<td>14 sites in 5 countries</td>
</tr>
</table>

| | | ***Studies to Support Safety*** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| M16-049 | NCT03646604 | Multipart , multiple dose, OL study<br><br><u>Part 1</u>: PK eval of low and high doses in 2 different age groups (6 to < 12 yrs; 2 to < 6 yrs) (completed)<br><br><u>Part 2</u>: OLE for Part 1 subjects to receive low dose upadacitinib for additional 104 weeks (ongoing) | | 10 to <20 kg | 20 to <30 kg | ≥30 kg | PK: $C_{max}$, $T_{max}$, and $AUC_{tau}$ at Day 7; $T1_{/2}$; CL/F; V/F<br><br>Safety: TEAEs, physical exam, change in vitals, clinical labs | Part 1: 7 days<br><br>Part 2: 104 weeks | 35 | Pediatric subjects 2 to less than 12 years with AD who had an inadequate response to treatment with TCS, TCI | 18 sites in 3 countries |
| | | | Low dose | 3 mg BID oral solution | 4 mg BID oral solution | 15 mg QD Tablet (or 6 mg BID oral solution if unable to swallow tablet) | | | | | |
| | | | High dose | 6 mg BID oral solution | 8 mg BID oral solution | 30 mg QD Tablet (or 12 mg BID oral solution if unable to swallow tablet) | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| M16-045 | NCT03569293 | Multicenter 2-period: 16-week randomized, DB, parallel-group, controlled treatment period followed by a long-term BE period up to Week 260 | DB Period: 15 mg, 30 mg UPA or placebo QD, PO<br><br>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<br><br>BE Period: Up to Week 260 | 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 | NCT03568318 | Multicenter 2-period: 16-week randomized, DB, parallel-group, controlled treatment period followed by a long-term BE period up to Week | DB Period: 15 mg, 30 mg UPA or placebo QD, PO with TCS or TCI<br><br>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 | DB Period: 16 weeks<br><br>BE Period: Up to Week 260 | 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 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 260 | | (clear or almost clear) with at least two grades of reduction from Baseline at Week 16. | | | | |
| M18-891 | NCT03607422 | Multicenter 2-period: 16-week randomized, DB, parallel-group, controlled treatment period followed by a long-term BE period up to Week 260 | DB Period: 15 mg, 30 mg UPA or placebo QD, PO<br><br>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<br><br>BE Period: Up to Week 260 | 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 |

Abbreviations: AD = Atopic Dermatitis; BID = twice daily; DB = double-blind; EASI = Eczema Area and Severity Index; OL = open-label; OLE = open-label extension; 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

### 7.2.1. NDA 211675/S-021

The Applicant conducted a single clinical study in pediatric subjects with JIA with active polyarthritis. Study M15-340 is an open-label, multiple-dose, multicenter, multipart, PK, safety, and tolerability study in pediatric subjects ages 2 to less than 18 years old with JIA with active polyarthritis. All subjects received weight-tiered daily dosing with upadacitinib oral extended-release tablets or twice daily dosing with an oral immediate-release solution formulation for up to 156 weeks. The primary objectives were to evaluate the PK, safety, and tolerability of multiple doses of upadacitinib in pediatric subjects with JIA with active polyarthritis. The secondary objective was to evaluate the descriptive efficacy of upadacitinib in JIA with active polyarthritis.

The proposed basis of approval for S-021 is the extrapolation of efficacy from RA patients to JIA with active polyarthritis patients based on PK exposure matching. As discussed in Section 6, review of the PK data from Study M15-340 demonstrated a similar range of observed exposures as in adult RA subjects in the adult RA development program. In addition, Study M15-340 provides open-label, uncontrolled descriptive efficacy data to support the efficacy of upadacitinib in JIA with active polyarthritis. Descriptive efficacy analyses were performed using data from the 51 subjects in Parts 1 and 2 available through a data cutoff date of September 22, 2022. Data from subjects in Part 3 were not used since enrollment for Part 3 started just shortly before the data cutoff date (June 17, 2022).

The safety assessment of upadacitinib in JIA with active polyarthritis indication is based primarily on the safety data from subjects in Study M15-340. The safety analyses were based on all subjects who received at least one dose of study drug administration. As of the data cutoff of the 4-Month SUR, a total of 83 subjects, including subjects from Part 3, met this criterion for inclusion in the safety analyses. Additional supportive safety data for upadacitinib in pediatric subjects were provided in an interim report for Study M16-049, ongoing PK and safety study in pediatric subjects with AD ages 2 to less than 12 years old, and in the pooled long-term follow up safety data in adolescent subjects with AD ages 12 to less than 18 years from Studies M16-045, M16-047, and M18-089.

The data from Study M15-340 analyzed for this review were evaluated according to Protocol Version 11.0 and the corresponding Statistical Analysis Plan, Version 8.0. See Section 8.1.1 for a full description of the study protocol and statistical analysis plan, including amendments.

### 7.2.2. NDA 211675/S-022

No clinical studies of upadacitinib in pediatric patients with active pediatric PsA were submitted.

As permitted under 21 CFR 314.55 and per written interactions with the Applicant, an assessment of upadacitinib treatment in children aged 2 to less than 18 years old with active pediatric PsA was conducted via a full efficacy extrapolation approach from existing efficacy and PK/PD data in adults with PsA and children with JIA with active polyarthritis treated with upadacitinib. The proposed extrapolation of efficacy from adult PsA patients to pediatric PsA patients is based on support for disease similarity between pediatric PsA and adult PsA together with justification for PK similarity between pediatric PsA and JIA with active polyarthritis and for the PK bridge between adult PsA and pediatric PsA. As discussed in Section 6, review of these PK data demonstrated a similar range of exposures observed in Study M15-340 in subjects with JIA with active polyarthritis (cross-referenced from S-021) as observed in adult PsA subjects in the upadacitinib adult PsA development program.

The safety assessment of upadacitinib for the proposed pediatric PsA indication is based on the leveraging of cross-referenced safety data submitted in S-021 from JIA with active polyarthritis patients in Study M15-340 and supportive safety data from the pediatric AD development program.

### 7.2.3. NDA 218347

No new clinical information was submitted in this Type 3 NDA. The efficacy and safety of upadacitinib 1 mg/mL oral solution for administration to patients with pJIA and pediatric PsA weighing less than 30 kg or unable to swallow solid dosage forms are based on cross-references to the clinical information submitted in NDA 211675/S-021 and S-022.

# 8 Statistical and Clinical and Evaluation

## 8.1. Review of Relevant Individual Trials Used to Support Efficacy

### 8.1.1. Study M15-340

**Trial Design**

***Overall Design***

Study M15-340 is a multiple-dose, open-label, three-part study in pediatric subjects with JIA with active polyarthritis ages 2 to less than 18 years of age. Eligible subjects had to have JIA with active polyarthritis with arthritis affecting at least 5 joints within the first 6 months of disease and 5 or more active joints at the time of screening. Methotrexate, low-dose glucocorticoids (prednisone ≤ 10 mg/day), and NSAIDs were permitted provided that the dose had been stable for a least 12 weeks prior to the first dose of upadacitinib.

The overall study design, summarized in Figure 1 in Section 6.1, consisted of 3 parts:

- Part 1: Part 1 evaluated PK as well as safety and tolerability and is now completed. Subjects received "low" and "high" weight-tiered doses of open-label upadacitinib for 7 consecutive days. See Section 8.1.1 Study M15-340/Study Treatments for full dosing details. The 2 dose levels were selected to evaluate comparable plasma exposures to 15 mg daily and 30 mg daily upadacitinib oral extended-release tablets in adults with RA. Initially, the Applicant intended to sequentially evaluate the two dose levels in 3 different age groups: 2 to <6 years, 6 to <12 years, and 12 to <8 years. However, the high dose was evaluated only in subjects 12 to <18 years because of a protocol revision (protocol version 9.0) that removed the high dose treatment cohorts for the other age groups. The change was made to reflect results of an interim PK analysis and to align with Agency advice that dosing in Study M15-340 should not exceed comparable approved dosing in adults with RA. See Sections 3.2, 6.3.1, and 8.1.1 Study M15-340/Protocol Amendments for full details.

- Part 2: Part 2 evaluated long-term safety and tolerability and is ongoing. Subjects who completed Part 1 are receiving up to an additional 155 weeks of open-label treatment with upadacitinib in this long-term extension to evaluate long-term safety. All subjects received only the "low dose" according to weight.

- Part 3: Part 3 also evaluated long-term safety and tolerability and is ongoing. An additional cohort of subjects with JIA with active polyarthritis ages 2 to <18 years was

added in protocol version 10.0 to obtain additional long-term safety data. Subjects in Part 3 are receiving up to 156 weeks of open-label treatment with upadacitinib.

***Study Location***

Study M15-340 was a multinational study. Subjects were enrolled from 14 sites in the United States, Hungary, Puerto Rico, and Spain.

***Study Subjects***

Pediatric subjects with active JIA with active polyarthritis were defined by the following key eligibility criteria:

Demographics

- Individuals, ages 2 to <18 years, and total body weight of 10 kg or higher at the time of screening

Disease History

- Diagnosed with JIA with active polyarthritis (RF-positive or RF-negative polyarticular JIA, extended oligoarticular JIA, or sJIA with active arthritis and without active systemic features) with arthritis affecting at least 5 joints within the first 6 months of disease (for extended oligoarticular JIA: ≤4 joints within the first 6 months of disease and >4 joints thereafter)
- Subjects must not have a diagnosis of ERA or pediatric PsA
- Have 5 or more active joints at the time of Screening, defined as the presence of swollen joints (not due to deformity) or, in the absence of swelling, joints with limitation of motion (LOM) plus pain on motion and/or tenderness with palpation, with LOM present in at least three of the active joints

Laboratory Assessments and Electrocardiogram (ECG) Criteria

- Screening laboratory values meeting the following criteria:
    - Serum aspartate transferase (AST) or alanine transferase (ALT) ≤1.5 x upper limit of normal (ULN) for age and sex;
    - Estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 $m^2$ by modified Schwartz equation for ages ≤ 12 years, and ≥60 mL/min by Cockcroft-Gault equation for ages >12 years;
    - Total white blood cell count (WBC) ≥3000/µL;
    - Absolute neutrophil count (ANC) ≥1200/µL;
    - Platelet count ≥100,000/µL;
    - Absolute lymphocyte count (ALC) ≥750/µL;
    - Hemoglobin ≥9.0 g/dL

- No clinically relevant or significant ECG abnormalities
- Subject has a negative tuberculosis (TB) Screening Assessment defined as negative QuantiFERON-TB Gold Test or tuberculin purified protein derivative (PPD) Skin Test at Screening. If the subject has evidence of latent TB infection, the subject must initiate and complete a minimum of 2 weeks (or per local guidelines, whichever is longer) of an ongoing TB prophylaxis or have documented completion of a full course of TB prophylaxis, prior to Study Day 1

Subject History/Physical Exam and Vital Signs

- No ongoing or active uveitis within 3 months prior to Study Day 1
- Subject has not been treated with intra-articular or parenteral administration of corticosteroids in the preceding 4 weeks prior to Study Day 1
- No history of any malignancy except for successfully treated non-melanoma skin cancer or localized carcinoma *in situ* of the cervix
- No history of an allergic reaction or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class
- No current or past history of infection including:
    - No history of recurrent or disseminated (even a single episode) herpes zoster
    - No history of disseminated (even a single episode) herpes simplex
    - No human immunodeficiency virus (HIV) infection
    - Subject does not have active TB
    - No anti-infectives within 14 days prior to Study Day 1
    - No chronic recurring infection and/or active viral infection that, based on the Investigator's clinical assessment, makes the subject an unsuitable candidate for the study
    - Confirmed COVID-19: the Baseline visit must be at least 10 days from onset of signs/symptoms or positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test; symptomatic subjects must have recovered, defined as resolution of fever without use of antipyretics and improvement in symptoms
    - Suspected COVID-19: subjects with signs/symptoms suggestive of COVID-19, known exposure, or high risk behavior should undergo molecular (e.g., polymerase chain reaction [PCR]) testing to rule out SARS-CoV-2 infection or must be asymptomatic for 10 days from a potential exposure
    - No active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection defined as:
        - HBV: hepatitis B surface antigen (HBs Ag) positive (+) or detected sensitivity on the HBV deoxyribonucleic acid (DNA) PCR qualitative test for subjects who are hepatitis B core antibody (HBc Ab) positive (+);
        - HCV: HCV ribonucleic acid (RNA) detectable in any subject with anti-HCV antibody (HCV Ab)
- Subject has not been a previous recipient of an organ transplant that requires continued immunosuppression

- No history of gastrointestinal perforation (other than appendicitis or penetrating injury), diverticulitis, or significantly increased risk for gastrointestinal perforation per Investigator judgment
- No conditions that could interfere with drug absorption including, but not limited to, short bowel syndrome
- No history of clinically significant medical conditions or any other reason that the
- investigator determines would interfere with the subject's participation in this study, would make the subject an unsuitable candidate to receive study drug or would put the subject at risk by participating in the protocol

Contraception

- A negative serum pregnancy test for all female subjects in Tanner stages ≥3 only or onset of menses at the screening visit and a negative urine pregnancy test at baseline prior to the first dose of study drug
- If female of childbearing potential (subjects in Tanner stages ≥3 only or onset of menses), must be practicing at least 1 protocol-specified method of birth control (see Section 8.1.1 Study M15-340/Medications), that is effective from Study Day 1 (or earlier) through at least 30 days after the last dose of study drug

Medications

- No prior exposure to JAK inhibitor
- If receiving MTX, have been taking MTX for at least 12 weeks immediately before and including Study Day 1 and on a stable dose of ≤20 mg/m$^2$ for at least 8 weeks before and including Study Day 1; in addition, subjects should take either folic acid or folinic acid according to local standard of care
- If on oral glucocorticoids, must have been taking oral glucocorticoids at a stable dose (no greater than 10 mg/day or 0.2 mg/kg/day, whatever is lower) for at least 1 week before and including Study Day 1)
- No current use of known moderate or strong inhibitors (e.g., amiodarone, clarithromycin, fluconazole, ciprofloxacin, itraconazole, ketoconazole, quinidine, fluoxetine, and paroxetine) or inducers (e.g., carbamazepine, rifampin, phenobarbital, and phenytoin) of drug metabolizing enzymes within 30 days prior to the first dose of study drug through the end of the Part 1 of the study. No systemic use of known strong cytochrome P450 3A isoform subfamily (CYP3A) inhibitors or inducers from the start of Part 2 or Part 3 of the study through study completion
- No receipt of any live or live-attenuated vaccine within 30 days (or longer if required locally) prior to the screening visit
- Subject must not have been treated with any investigational drug within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug or is currently enrolled in another clinical study

***Study Treatments***

Upadacitinib was administered daily as oral extended-release tablets or twice daily as an oral immediate-release formulation according to weight as already summarized in Table 6 in Section 6.2.2. General Dosing and Therapeutic Individualization. Change in the subject's body weight category was assessed by the Investigator at each Part 2 or Part 3 study visit. The duration of treatment in Parts 1, 2, and 3 was as described under Section 8.1.1 Study M15-340/Overall Study Design.

High dose treatment was limited to the 9 subjects enrolled in Cohort 1 (12 to <18 years age group) of Part 1 since high dose treatment was eliminated in protocol versions 8.0 and 9.0 (see Section 8.1.1 Study M15-340/Protocol Amendments). As noted in Section 3.2, the removal of high dose treatment was intended to reflect Agency advice provided in the April 14, 2021, Type C Meeting Final Written Responses that study dosing should not exceed comparable approved dosing in adults. Only low dose treatment was administered in Parts 2 and 3.

Three (3) oral extended-release tablet strengths were originally used in the study (7.5, 15, and 30 mg). The 7.5 mg tablet was no longer used in the study after the body weight categories and dose levels were adjusted in protocol version 8.0, and the 30 mg tablet was no longer used after the High Dose levels were removed for the younger age groups in protocol version 9.0.

Three (3) different oral solution formulations were developed and used in the study. A 1 mg/mL (pH (b) (4)) solution was initially used in the study. A 0.5 mg/mL (pH (b) (4)) solution was later developed (b) (4) another 1 mg/mL (pH (b) (4)) solution was developed (b) (4). This 1 mg/mL (pH (b) (4)) oral solution formulation is submitted in NDA 218347 as the proposed commercial oral solution formulation for pediatric use.

***Medications***

Permitted Medications

- Methotrexate (MTX): stable doses of methotrexate ≤20 mg/m$^2$ body surface area/week
- Low-dose glucocorticoids: stable doses ≤0.2 mg/kg/day prednisone with a daily maximum of 10 mg
- NSAIDs: stable doses
- COVID-19 vaccination: non-live vaccines (e.g., messenger ribonucleic acid [mRNA], non-replicating viral vector, protein subunit, etc.) to prevent SARS-CoV-2 infection could be administered during the screening or treatment periods. However, subjects were asked, if possible, to avoid receiving a COVID-19 vaccination in the 7 days prior to enrollment or

within the first 7 days after initiation of study drug.

In Parts 2 and 3, initiation of, change in dosing of, or as needed (PRN) use of NSAIDs, glucocorticoids, and MTX were allowed as per local approved labeling.

Prohibited Medications

- Biologics: prior use of biologic treatment was discontinued prior to Study Day 1 (etanercept, 4 weeks; infliximab, adalimumab or abatacept, 8 weeks; golimumab, 10 weeks; tocilizumab, ustekinumab, and certolizumab pegol, 12 weeks; canakinumab, 10 weeks; anakinra, 1 week) and is also prohibited during the study. However, if there was documentation of undetectable drug level measured by a commercially available assay for any of the approved biologics above, there was no minimum washout prior to baseline.
- Immunosuppressants: aside from glucocorticoids or MTX as described above, immunosuppressants were discontinued at least 30 days or 5-half-lives prior to study drug administration through the end of the study.
- JAK inhibitors: aside from study drug, JAK inhibitors (e.g., commercially available upadacitinib, tofacitinib, ruxolitinib, baricitinib peficitinib, abrocitinib, and filgotinib) were prohibited
- Inhibitors and inducers of drug-metabolizing enzymes: moderate or strong inhibitors (e.g., amiodarone, clarithromycin, fluconazole, ciprofloxacin, itraconazole, ketoconazole, quinidine, fluoxetine, and paroxetine) or inducers (e.g., carbamazepine, rifampin, phenobarbital, and phenytoin) of drug metabolizing enzymes within 30 days prior to the first dose of study drug and through the end of Part 1 of the study. Systemic use of known strong CYP3A inhibitors or inducers from the start of Part 2 or Part 3 through the end of the study was also prohibited.
- Live vaccines: not permitted during Part 1 of the study. If a subject and Investigator chose to administer live vaccines, these vaccinations had to be completed, when possible (per local label), at least 4 weeks (or longer if required locally) before first dose of study drug with appropriate precautions. Although not mandated by the protocol, vaccines recommended by local guidelines were recommended. If a live vaccine had to be administered during Part 2 or Part 3, study drug had to be held for at least 4 weeks (or longer if required locally) prior to the vaccination and at least 4 weeks (or longer if required locally) after the vaccination. Thereafter, study drug could be resumed at the Investigator's discretion with appropriate precautions.
- Investigational drugs: had to be discontinued within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug. Investigational drugs are also prohibited during the study

***Individual study drug discontinuation and study stopping criteria***

Individual study drug discontinuation criteria

- Clinically significant abnormal laboratory results or adverse events (AEs), which ruled out continuation of the study drug, as determined by the investigator or the AbbVie Therapeutic Area Medical Director (TA MD)
- Serious infections (e.g., sepsis) that could not be adequately controlled within 2 weeks by anti-infective treatment or would put the subject at risk for continued participation in the trial, as determined by the Investigator
- Investigator believed that discontinuation was in the best interest of the subject
- Subject or subject's legal authorized representative requested withdrawal from the study
- An eligibility criteria violation was noted after the subject started study drug, when continuation of the study drug would place the subject at risk, as determined by the AbbVie TA MD
- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk, as determined by the AbbVie TA MD
- Subject was noncompliant with TB prophylaxis (if applicable) or developed active TB at any time during the study
- Subject became pregnant while on study drug
- Malignancy, except for localized non-melanoma skin cancer or carcinoma in situ of the cervix
- Subject was significantly noncompliant with study procedures, putting the subject at risk for continued participation in the trial, as determined by the investigator or the TA MD
- Subject developed a gastrointestinal perforation (defined as acute, spontaneous perforation of the gastrointestinal tract that requires inpatient medical care or urgent surgical intervention other than appendicitis or mechanical injury)
- Confirmed diagnosis of deep vein thrombosis, pulmonary embolus, or non-cardiac, non-neurologic arterial thrombosis

Study Discontinuation Criteria (Part 1 Only)

For any of the following safety criteria met, a safety review would be triggered, enrollment of new subjects would be discontinued, and no further dose escalations would occur until completion of the safety review.

Clinical and post-dose systemic adverse events:

- Any subject administered active study drug experienced a severe (Grade 3 or higher, according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 [NCI-CTCAE v5) clinical adverse event, considered related to study drug
- Two (2) or more subjects administered active study drug experienced a Grade 2 clinical

adverse event of a similar nature, considered related to study drug

- Two (2) or more subjects administered active study drug experienced Grade 2 suspected hypersensitivity reactions or one subject administered active study drug experiences ≥ Grade 3 suspected hypersensitivity reaction. Events were graded by the level of intervention described in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 5.0) allergic reaction/cytokine release syndrome adverse event categories or, if applicable, anaphylaxis or serum sickness adverse event categories.

Laboratory or vital sign abnormalities, ECG changes:

- Two (2) or more subjects administered active study drug experienced a confirmed Grade 3 or higher hematologic laboratory abnormality-related adverse event of similar nature, considered related to study drug
- Two (2) or more subjects administered active study drug experienced a confirmed Grade 2 or higher non-hematologic, non-creatine phosphokinase (CPK) laboratory or vital sign abnormality-related adverse event of similar nature considered related to study drug
- Two (2) or more subjects administered study drug experienced a confirmed symptomatic CPK elevation ≥4x ULN, considered related to study drug
- Any subject administered active study drug having confirmed ALT or AST >3x ULN, and total bilirubin >2x ULN or international normalized ratio (INR) >1.5, for which no alternative etiology was identified
- Any subject administered active study drug with confirmed ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia for which no alternative etiology was identified
- Any subject administered active study drug has a confirmed ALT or AST >8x ULN, for which no alternative etiology was identified
- Any subject administered active study drug with confirmed ECG changes that considered clinically significant and considered related to study drug or a confirmed absolute QT interval corrected for heart rate using Fridericia's correction formula (QTcF) value >500 msec that the Investigator considered related to study drug or a confirmed absolute QTcF value change from baseline >60 msec

***Rescue***

For Parts 2 and 3, subjects who did not achieve at least 20% improvement in total number of active joints (joints with swelling not due to deformity or joints with LOM and with pain, tenderness, or both) compared to baseline at 2 consecutive visits on or after Week 8 had to discontinue study drug and receive treatment at the Investigator's discretion in accordance with local standard-of-care. However, rescue therapy utilization was not reported, as specific rescue therapies were not defined for the study.

**Study Endpoints**

PK: $C_{max}$, $T_{max}$, and $AUC_{tau}$ at Day 7; $T_{1/2}$; CL/F; V/F

Safety: treatment-emergent adverse events (TEAEs), physical exam, change in vitals, clinical labs

Descriptive efficacy at Week 12: American College of Rheumatology (ACR) 30/50/70/90/100 Pediatric Responses; Juvenile Arthritis Disease Activity Scales (JADAS) 10/27/71; changes in ACR and JADAS components; number of active joints, Childhood Health Activity Questionnaire (C-HAQ), Physician Global Assessment (PGA), Patient Global Assessment (PtGA), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)

**Statistical Analysis Plan**

No formal hypothesis testing was planned for this study. Tabular data summaries, graphical data displays, and subject listings were used to summarize the data.

Available data from 49 subjects in Part 1 were used in the PK analyses. All subjects who received at least one dose of study drug as of the data cutoff date for the Clinical Study Report (CSR) (September 22, 2022) were included in the efficacy analyses (intention-to-treat (ITT) analysis set). The descriptive efficacy analyses included data from Part 1 and Part 2 but not Part 3 since enrollment for Part 3 started just shortly before the data cutoff date (June 17, 2022). All subjects who received at least one dose of study drug as of the data cutoff date for the 4-Month Safety Update Report (SUR) (June 20, 2023) were included in the safety analyses (safety analysis set).

**Protocol Amendments**

The original protocol (Version 1.0, dated March 23, 2018) had 10 amendments and 6 administrative changes. Substantive in each version and the number of subjects enrolled under each version were as follows:

- Version 2.0 (June 26, 2018, 0 subjects): Modified study activities to reduce subject burden to participate in the study, updated eligibility criteria to align diagnosis criterion language with ILAR Classification of JIA, specify that subjects must not have diagnosis of ERA or pediatric PsA, align language for active joints with ACR definition, update criterion for active uveitis to 3 months prior to Study Day 1, and make minor

clarifications to the language of concomitant medications eligibility criteria, clarified dose adjustment criteria, specified study drug supply after study completion, updated prohibited medications and therapy details to update discontinuation criteria for canakinumab to 10 weeks and anakinra to 1 week prior to Study Day 1, make minor clarification to language for use of inhibitors, and add criteria for live vaccine usage, added missing drug dispensation visit for BID regimens in Part 2, added Juvenile Arthritis Disease Activity Scales (JADAS) to efficacy parameters, removed patient's/caregiver's visual analog scale (VAS) since included in the C-HAQ, and updated investigational product descriptions for consistency.

- Version 3.0 (August 21, 2018, 0 subjects): Corrected description for AE severity grading, added urine pregnancy test to follow-up visit in Part 1, added the Operations Manual as an appendix to the protocol, and made clarifications throughout the Operations Manual
- Version 4.0 (September 14, 2018, 1 subject): Added palatability evaluation for oral solution, updated number of active joints in eligibility criteria to align with commitments in the EMA's PIP, updated number of subjects to be enrolled, added an additional pharmacokinetic parameter to be calculated, specified criteria for ≥ Grade 3 AEs, and made clarifications to toxicity management language.
- Version 5.0 (December 6, 2018, 24 subjects): Added details on dose selection, provided details on discontinuation of study, and specified oral solution excipients
- Version 6.0 (April 7, 2020, 2 subjects): Specified use of new 0.5 mg/mL oral solution formulation, clarified definition of active joints, specified that biologic treatments, investigational drugs, and JAK inhibitors are prohibited during study, updated details for live vaccine guidance and allowed background medications for Part 2, removed collection of pregnant partner information, added guidance for elective and emergency surgeries, added Cardiovascular Adjudication Committee, clarified interim analysis, added flexibility to Part 2 study visits, added guidance on screening and rescreening procedures, and added clarification to HBV DNA PCR testing, pregnancy testing, and global assessment of disease activity.
- Version 7.0 (October 15, 2020, 0 subjects): Added COVID-19 considerations, updated minimum number of subjects under 25 kg to be enrolled, added 'review dosing card' activity for Part 2, and added the option to ship study drug from site to subjects on BID regimen for visits intended for drug dispensation only.
- Version 8.0 (December 9, 2020, 15 subjects): Adjusted body weight categories and dose levels based on review of Cohorts 1 (12 to <18 years, low dose), 2 (12 to < 18 years, high dose), and 3 (6 to <12 years, low dose) data, updated blood sample collection details and added an unscheduled visit for when dose adjustment occurs in Part 2, updated COVID-19 toxicity management language, clarified stopping criteria specific to CPK elevations, and clarified that all subjects will be dispensed Low Dose in Part 2.
- Version 9.0 (July 2, 2021, 6 subjects): Updated dosing to remove 30 mg and equivalent dosing regimen and High Dose Cohorts 4 (6 to <12 years, high dose) and 6 (2 to <6 years, high dose) in Part 1, expanded Low Dose Cohorts 3 (6 to <12 years) and 5 (2 to <6 years)

from 9 to 18 subjects each, extended the study to add additional visits following Week 156 for active subjects benefiting from upadacitinib, updated body weight criteria for minimum of subjects to be enrolled to align with body weight categories, added language to address potential use of SARS-CoV-2 vaccines, updated sample size estimation based on phase 3 RA patient results, removed option to continue in study after drug discontinuation, and removed additional visits required for BID regimens.

- Version 10.0 (December 20, 2021, 11 subjects): Added Part 3 which is an additional safety cohort, added plan for population pharmacokinetic analysis, clarified efficacy evaluations, specified description for gastrointestinal perforation, and clarified objective for Part 2.
- Version 11.0 (November 15, 2022, 0 subjects): Updated language throughout to align with new European Union/Clinical Trial Regulation, added additional objective to clarify descriptive efficacy endpoints will be reported, clarified end of study at Week 156 and defined Post-Trial Access details, clarified definition of JIA with active polyarthritis, removed minimum dose of methotrexate in eligibility criteria since used in some countries and younger children, updated eligibility criteria for COVID-19, specified requirements for Japan throughout, changed contraception requirement for premenarchal girls from Tanner Stage 2 to 3 throughout to align with definition of women of childbearing potential, aligned toxicity management details to align with standards across upadacitinib program, and added collection of full date of birth and historical height

Overall, the study design of Study M15-340, including protocol amendments, was reasonable to address the pre-specified primary objectives to characterize the PK profile of upadacitinib in JIA with active polyarthritis and the secondary safety and descriptive efficacy objectives.

### 8.1.2. Study Results

**Compliance with Good Clinical Practices**

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices (GCP) and applicable regulatory requirements.

**Financial Disclosure**

Financial disclosures were reported by one principal investigator in Study M15-340. A total of 5 subjects were enrolled at the study site. As the primary endpoint of Study M15-340 was PK, the study was conducted in an open-label manner, and the number of subjects enrolled at the study site was small. Given these considerations, the disclosable interest is unlikely to influence the outcomes of the study. See Section 15.2 for full details.

**Data Quality and Integrity**

NDA211675/S-021, NDA 211675/S-022, and NDA 218347 were reviewed for content, format, and overall data quality and integrity and were each found acceptable during the filing review.

**Patient Disposition**

Eighty-three (83) pediatric subjects with JIA with active polyarthritis were enrolled across 14 sites in the United States, Germany, Hungary, Puerto Rico, and Spain. Table 20 summarizes the disposition of subjects enrolled in Study M15-340.

**Table 20. Subject Disposition, Study M15-340**

| | Age 2 to <6 years N=22 n (%) | Age 6 to <12 years N=36 n (%) | Age 12 to <18 years N=25 n (%) | Total N=83 N (%) |
|---|---|---|---|---|
| **Completed Study** | **0** | **0** | **2 (8.0)** | **2 (2.4)** |
| Completed Part 1 | 14 (63.6) | 19 (52.8) | 18 (72.0) | 51 (61.4) |
| Completed Part 2 | 0 | 0 | 2 (8.0) | 2 (2.4) |
| Completed Part 3 | 0 | 0 | 0 | 0 |
| **Ongoing Study** | 21 (95.5) | 32 (88.9) | 15 (60.0) | 68 (81.9) |
| Ongoing Part 1 | 0 | 0 | 0 | 1 (1.2) |
| Ongoing Part 2 | 14 (63.6) | 16 (44.4) | 8 (32.0) | 38 (45.8) |
| Ongoing Part 3 | 7 (31.2) | 16 (44.4) | 7 (28.0) | 30 (36.1) |
| **Study Drug Discontinuation*** | **1 (4.5)** | **5 (13.9)** | **8 (32.0)** | **14 (16.9)** |
| Adverse event | 0 | 1 (2.8) | 1 (4.0) | 2 (2.4) |
| Withdrawal by subject | 0 | 1 (2.8) | 2 (8.0) | 3 (3.6) |
| Lost to follow-up | 0 | 0 | 1 (4.0) | 1 (1.2) |
| Lack of efficacy | 1 (4.5) | 3 (8.3) | 3 (12.0) | 7 (8.4) |
| COVID-19 logistical restrictions | 0 | 0 | 0 | 0 |
| Other | 0 | 0 | 1 (4.0) | 1 (1.2) |
| COVID-19 infection | 0 | 0 | 0 | 0 |
| Terminated by Sponsor | 0 | 0 | 0 | 0 |
| **Study Discontinuation*** | 1 (4.5) | 4 (11.1) | 8 (32.0) | 13 (15.7) |
| Adverse event | 0 | 1 (2.8) | 0 | 1 (1.2) |
| Withdrawal by subject | 0 | 1 (2.8) | 2 (8.0) | 3 (3.6) |
| Lost to follow-up | 0 | 0 | 1 (4.0) | 1 (1.2) |
| Lack of efficacy | 0 | 0 | 0 | 0 |
| COVID-19 logistical restrictions | 0 | 0 | 0 | 0 |
| Other | 1 (4.5) | 2 (5.6) | 5 (20.0) | 8 (9.6) |
| COVID-19 infection | 0 | 0 | 0 | 0 |
| Terminated by Sponsor | 0 | 0 | 0 | 0 |

* Subjects could have had more than 1 reason for discontinuing study drug or the study. The primary reason for discontinuation is presented.
Source: Tables 2.1__1.2 and 2.1__2.2, SUR for Study M15-340 and Applicant response to the clinical information request dated February 2, 2024

All 51 subjects enrolled in Part 1 completed Part 1. Among the 51 subjects in Part 1, 40 continued into Part 2. Among Part 2 subjects, 2 have completed Part 2, and 38 subjects are

receiving ongoing treatment. An additional 30 subjects have been enrolled in Part 3, all of whom are receiving ongoing treatment. Enrollment for Parts 1 and 2 is closed, but enrollment for Part 3 enrollment is ongoing.

As of the June 20, 2023, data cutoff date for the 4-Month SUR, 68 subjects (81.9%) continue to receive ongoing treatment (Table 20). Sixty (72.3%) of subjects completed at least 26 weeks of treatment (2 to <6 years: 15, 6 to <12 years: 27, 12 to <18 years: 18), and 48 subjects (57.8%) completed at least 52 weeks of treatment (2 to <6 years: 13, 6 to <12 years: 20, 12 to <18 years: 15).

Fourteen (14) subjects (16.9%) discontinued study drug, including 1 subject (4.5%) age 2 to <6 years, 5 subjects (13.9%) age 6 to <12 years, and 8 subjects (32.0%) age 12 to <18 years. The most common primary reason for study drug discontinuation overall and in all age groups was lack of efficacy (2 to <6 years: 1 [4.5%], 6 to <12 years: 3 [8.3%], 12 to <18 years: 3 [12%]). Adverse event was the primary reason for study drug discontinuation for 2 subjects (2.4%), including single subjects age 6 to <12 years and age 12 to <18 years, respectively.

The numbers and proportions of subjects overall and within each age group who discontinued the study were similar to numbers and proportions of subjects who discontinued study drug. Thirteen (13) subjects (15.7%) overall discontinued the study, including 1 subject (4.5%) age 2 to < 6 years, 4 subjects (11.1%) age 6 to <12 years, and 8 subjects (32.0%) age 12 to <18 years. A single subject (1.2%) in the 6 to <12 years age group had adverse event as the primary reason for study discontinuation.

**Protocol Violations/Deviations**

Nineteen (19) subjects (22.9%) had ≥1 major protocol deviation. Six (6) subjects had deviations related to exclusion criteria (such as informed consent/assent). Four (4) subjects had other protocol deviations related errors in the timing of sample collection relative to dosing. Three (3) subjects received prohibited medications. Single subjects had deviations due to accidentally spitting part of a dose and use of a prohibited medication. Four (4) subjects had deviations related to wrong study drug or incorrect dosage of upadacitinib as follows:

- Two (2) subjects in the body weight category for 25 to 40 kg (3 mg of oral solution BID) received the dose for body weight category 15 to <25 kg (2 mg of oral solution BID) at Week 48 due to site error.
- A subject was not dispensed a new drug kit for Day 8 since the completion call for Part 1 was not completed and the subject continued on High Dose instead of Low Dose until Week 2.

- A subject received an incorrect dose of 1.5 mg BID, instead of 3 mg BID, in Part 1 due to Investigator error. This subject was excluded from the PK summaries.

However, none of these deviations were likely to have affected the integrity of the study or introduced significant bias into the study results.

**Table of Demographic Characteristics**

The demographic characteristics for the 83 subjects in Study M15-340 are summarized in Table 21. Overall, the demographic profile of the subjects enrolled appears consistent with that expected for the enrolled population of patients with active JIA with active polyarthritis with regard to sex (79.5% female), race (92.8% White), and age (mean 9.2 years, range 2 to 17 years). The proportions of subjects ages 2 to < 6 (26.5%) and 12 to < 18 years (30.1%) were similar, but a slightly higher proportion of subjects were age 6 to < 12 (43.4%). The mean body weight was 35.70 kg with 23 subjects (27.7%) 10 to < 20 kg, 17 subjects (20.5%) 20 to < 30 kg, and the remaining 43 subjects (51.8%) 30 kg or more. The mean body mass index (BMI) was 18.429 kg/$m^2$ with the vast majority of subjects (90.4%) being less than 25 kg/$m^2$. Approximately one quarter (22.9%) were Hispanic/Latino.

**Table 21. Demographic Characteristics, Study M15-340, Parts 1-3**

| Demographic Parameters | Age 2 to <6 years N=22 n (%) | Age 6 to <12 years N=36 n (%) | Age 12 to <18 years N=25 n (%) | Total N=83 N (%) |
|---|---|---|---|---|
| **Sex** | | | | |
| Male | 4 (18.2) | 10 (27.8) | 3 (12.0) | 17 (20.5) |
| Female | 18 (81.8) | 26 (72.2) | 22 (88.0) | 66 (79.5) |
| **Age (years)** | | | | |
| Mean (SD) | 3.5 (1.34) | 9.1 (1.62) | 14.4 (1.44) | 9.2 (4.36) |
| Median | 3.0 | 9.0 | 14.0 | 9.0 |
| Min, max | 2, 6 | 6, 12 | 12, 17 | 2, 17 |
| 2 to < 6 | 22 (100) | 0 | 0 | 22 (26.5) |
| 6 to < 12 | 0 | 36 (100) | 0 | 36 (43.4) |
| 12 to < 18 | 0 | 0 | 25 (100) | 25 (30.1) |
| **Race** | | | | |
| White | 22 (100) | 33 (91.7) | 22 (88.0) | 77 (92.8) |
| Black or African American | 0 | 1 (2.8) | 0 | 1 (1.2) |
| Asian | 0 | 2 (5.6) | 2 (8.0) | 4 (4.8) |
| American Indian or Alaska Native | 0 | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 | 0 |
| Other | 0 | 0 | 1 (4.0) | 1 ( 1.2) |

| | | | | |
|---|---|---|---|---|
| **Ethnicity** | | | | |
| Hispanic or Latino | 5 (22.7) | 11 (30.6) | 3 (12.0) | 19 (22.9) |
| Not Hispanic or Latino | 17 (77.3) | 25 (69.4) | 22 (88.0) | 64 (77.1) |
| **Weight (kg)** | | | | |
| Mean (SD) | 14.86 (3.024) | 32.82 (12.005) | 58.19 (18.543) | 35.70 (20.949) |
| Median | 14.05 | 29.75 | 56.80 | 30.20 |
| 10 to < 20 | 21 (95.5) | 2 (5.6) | 0 | 23 (27.7) |
| 20 to < 30 | 1 (4.5) | 16 (44.4) | 0 | 17 (20.5) |
| ≥ 30 | 0 | 18 (50.0) | 25 (100) | 43 (51.8) |
| **Height (cm)** | | | | |
| Mean (SD) | 97.05 (10.130) | 135.84 (12.254) | 160.16 (8.895) | 132.88 (26.243) |
| Median | 93.75 | 135.75 | 160.30 | 137.00 |
| **BMI (kg/m$^2$)** | | | | |
| Mean (SD) | 15.702 (1.3510) | 17.306 (3.3776) | 22.447 (6.0531) | 18.429 (4.8509) |
| Median | 15.366 | 16.578 | 21.705 | 17.059 |
| < 25 | 22 (100) | 34 (94.4) | 19 (76.0) | 75 (90.4) |
| ≥ 25 | 0 | 2 (5.6) | 6 (24.0) | 8 (9.6) |
| **Region** | | | | |
| North America | 6 (27.3) | 9 (25.0) | 5 (20.0) | 20 (24.1) |
| South/Central America | 0 | 0 | 0 | 0 |
| Western Europe | 13 (59.1) | 24 (66.7) | 18 (72.0) | 55 (66.3) |
| Eastern Europe | 3 (13.6) | 1 (2.8) | 0 | 4 (4.8) |
| Asia | 0 | 2 (5.6) | 2 (8.0) | 4 (4.8) |

Source: Adapted from Tables 2.1__1.2 and 2.1__2.2, SUR for Study M15-340

**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

Baseline characteristics, shown in Table 22, were consistent with the intended population of patients with JIA with active polyarthritis with moderate to severe disease activity based on active joint count, joints with limited range of motion, physician's global assessment of disease activity, the parent/parent's assessment of overall well-being, childhood health assessment questionnaire (C-HAQ), and acute phase reactant levels. The majority of patients had polyarticular rheumatoid factor negative JIA (68.7%), generally balanced across age groups (2 to< 6 years: 68.2%, 6 to <12 years: 63.9%, 12 to <18 years: 76.0%). Polyarticular rheumatoid factor positive JIA (15.7%), extended oligoarticular arthritis (13.3%) and systemic JIA without systemic symptoms (2.4%) were far less frequent ILAR JIA subtypes. Polyarticular rheumatoid factor positive JIA was more common in the older age groups (2 to <6 years: 0, 6 to <12 years: 22.2%, 12 to <18 years: 20.0%), whereas extended oligoarticular arthritis was more common in younger age groups (2 to < 6 years: 27.3%, 6 to < 12 years: 13.9%, 12 to < 18 years: 0), but the different proportions reflected small numerical differences. All enrolled subjects had 5 or more active joints regardless of the JIA subtype. The mean duration of disease was 3.113 years.

**Table 22. Baseline Disease Characteristics, Study M15-340, Parts 1-3**

| Demographic Parameters | Age 2 to <6 years N=22 n (%) or mean ±SD (range) | Age 6 to <12 years N=36 n (%) or mean ±SD (range) | Age 12 to <18 years N=25 n (%) or mean ±SD (range) | Total N=83 n (%) or mean ±SD (range) |
|---|---|---|---|---|
| Duration of JIA with active polyarthritis disease symptoms (years) | 1.644 ±1.3089 (0.27, 4.34) | 2.225 ±2.7160 (0.13, 10.15) | 5.625 ±3.3926 (0.70, 13.23) | 3.113 ±3.1430 (0.13, 13.23) |
| ILAR classification | | | | |
| Polyarticular rheumatoid factor-negative | 15 (68.2) | 23 (63.9) | 19 (76.0) | 57 (68.7) |
| Polyarticular rheumatoid factor-positive | 0 | 8 (22.2) | 5 (20.0) | 13 (15.7) |
| Extended oligoarticular | 6 (27.3) | 5 (13.9) | 0 | 11 (13.3) |
| Systemic without systemic symptoms but with polyarticular course | 1 (4.5) | 0 | 1 (4.0) | 2 (2.4) |
| Physician's global assessment of disease activity (VAS 0-10 cm) | 52.9 ±16.71 (28, 83) | 55.7 ±21.97 (11, 100) | 60 ±25.75 (20, 94) | 56.2 ±21.73 (11, 100) |
| Parent/patient assessment of overall well-being (VAS 0-10 cm) | 38.7 ±26.63 (1, 88) | 42.2 ±23.83 (0, 90) | 44.1 ±22.19 (0, 88) | 41.8 ±23.93 (0, 90) |
| Number of active joints | 8.4 ±3.08 (5, 15) | 12.6 ±8.93 (5, 48) | 13.2 ±9.52 (5, 48) | 11.7 ±8.19 (5, 48) |
| Number of joints with limited range of motion | 6.0 ±2.86 (0, 12) | 10.6 ±8.71 (3, 46) | 10.2 ±8.65 (2, 41) | 9.3 ±7.76 (0, 46) |
| Childhood Health Assessment Questionnaire (C-HAQ) | 0.679 ±0.6220 (0.00, 2.00) | 10.6 ±8.71 (0.00, 2.63) | 1.075 ±0.7889 (0.00, 2.88) | 0.986 ±0.7609 (0.00, 2.88) |
| C-reactive protein (CRP) (mg/dL) | 14.68 ± 21.939 (0.2, 83.8) | 8.64 ±17.553 (0.2, 92.3) | 5.04 ±9.211 (0.2, 39.7) | 9.16 ± 17.120 (0.2, 92.3) |
| Erythrocyte sedimentation rate (ESR) | 23.5 ±18.49 (6, 63) | 21.7 ±20.34 (2, 94) | 14.5 ±10.13 (2, 45) | 20.0 ±17.60 (2, 94) |
| Uveitis | 0 | 0 | 0 | 0 |
| Prior Medications | | | | |
| csDMARDs<br>bDMARDs | 11 (50.0)<br>2 (9.1) | 14 (38.9)<br>1 (2.8) | 18 (72.0)<br>12 (48.0) | 43 (51.8)<br>15 (18.1) |
| Baseline Medications | | | | |

| | | | | |
|---|---|---|---|---|
| Oral steroids | 5 (22.7) | 10 (27.8) | 5 (20.0) | 20 (24.1) |
| | 1.28 ±0.701<br>(0.4, 2.0) | 5.43 ±2.566<br>(2.8, 10.0) | 5.95 ±2.928<br>(2.3, 10.0) | 4.52 ±2.960<br>(0.4, 10.0) |
| Methotrexate | 10 (45.5) | 11 (30.6) | 11 (44.0) | 32 (38.6) |
| | 7.750 ±2.1890<br>(5.00, 10.00) | 14.127 ±4.6301<br>(5.00, 20.00) | 17.318 ±6.0178<br>(6.00, 25.00) | 13.231 ±5.9910<br>(5.00, 25.00) |

* Prednisone equivalent dose in mg/day
Source: Adapted from Table 2.3__1.2, SUR for Study M15-340

Prior to the study, 51.8% of subjects had received at least 1 csDMARD, and 18.1% of subjects had received a bDMARD with the highest proportions of subjects for each of these agent classes being in the age group 12 to <18 years, consistent with the enrolled subgroup possibly having more refractory disease. At baseline, 24.1% of subjects were receiving oral corticosteroids, generally balanced across age groups (2 to <6 years: 22.7%, 6 to <12 years: 27.8%, 12 to <18 years: 20.0%). Methotrexate was in use at baseline in 38.6% of subjects with similar proportions in the age groups 2 to <6 and 12 to <18 years (45.5% and 44.0%, respectively) but lower in the age group 6 to <12 years (30.6%) due to small numerical differences.

**Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

Study M15-340 was an open-label study in which all enrolled subjects received active treatment with upadacitinib. To assess compliance, subjects and/or their caregivers were instructed to return all used or unused investigational product bottles at each study visit, and drug accountability was determined by tablet count for upadacitinib tablets and by bottle weight for upadacitinib oral solution. For subjects receiving upadacitinib tablets, compliance was derived as the number of tablets used divided by the number of tablets that should have been used. For subjects receiving upadacitinib oral solution, compliance was derived as the weight or oral solution used divided by the weight of the oral solutions that should have been used. For subjects who switched between oral solutions to tablets, compliance was derived as the weighted average of treatment compliance for each route of administration. Compliance could not be reliably determined for 3 subjects receiving upadacitinib oral solution as a result of data entry errors. The data for these subjects were excluded from the compliance analysis.

Table 23 summarizes treatment compliance as of the data cutoff for the 4-Month SUR. Overall mean compliance was 104.0%. Mean compliance was 97.9% for subjects who received upadacitinib tablets, 111.4% for subjects who received upadacitinib oral solution, and 98.4% for subjects who switched from upadacitinib oral solution to tablet. Compliance was generally consistent across all age groups.

**Table 23. Treatment Compliance, Study M15-340**

| | **Age 2 to <6 years N=22 Mean (SD)** | **Age 6 to <12 years N=33 Mean (SD)** | **Age 12 to <18 years N=25 Mean (SD)** | **Total N=83 Mean (SD)** |
|---|---|---|---|---|
| **Overall** | **109.9 (7.61)** | **104.5 (13.45)** | **98.3 (10.20)** | **104.0 (11.85)** |
| Tablets | 0 | 1 (2.8) | 1 (4.0) | 2 (2.4) |
| Oral Solution | 0 | 1 (2.8) | 1 (4.0) | 2 (2.4) |
| Tablets to Solution | 0 | 3 (8.3) | 3 (12.0) | 6 (7.2) |

Source: Table 2.2__3.2, February 15, 2024 response to clinical information request dated January 29, 2024

Table 24 summarizes the use of concomitant NSAIDs, conventional DMARDs (csDMARDs), corticosteroids, and other immunosuppressant medications. Concomitant use is defined as use after the first dose and before the last dose of study drug. In total, 81.9% of subjects used 1 or more NSAIDs, higher in the 2 to <6 years (68.2%) and 6 to <12 years (83.3%) age groups than in the 12 to <18 years (52.0) age group). Concomitant methotrexate was used by 39.8% of subjects, generally similar across age groups. In addition, 30.1% of subjects received concomitant oral corticosteroids, and 9.6% of subjects used non-oral corticosteroids, both generally similar across age groups. No other csDMARDs, targeted synthetic DMARDs other than study drug, biologic DMARDs, or other immunosuppressants were used through the data cutoff of the 4-Month SUR, consistent with these agents being prohibited per protocol.

**Table 24. Concomitant Medication Use, Study M15-340**

| | Age<br>2 to <6 years<br>N=22<br>n (%) | Age<br>6 to <12 years<br>N=36<br>n (%) | Age<br>12 to <18 years<br>N=25<br>n (%) | Total<br>N=83<br>N (%) |
|---|---|---|---|---|
| NSAIDs | 15 (68.2) | 30 (83.3) | 13 (52.0) | 68 (81.9) |
| Methotrexate | 10 (45.5) | 13 (36.1) | 11 (44.0) | 34 (41.0) |
| Oral Corticosteroids | 6 (27.3) | 13 (36.1) | 6 (24.0) | 25 (30.1) |
| Non-Oral Corticosteroids | 3 (13.6) | 2 (5.6) | 3 (12.0) | 8 (9.6) |

Source: Table 2.2, March 1, 2024 response to clinical information request dated February 26, 2024

Rescue therapy use was not defined or recorded for Study M15-340.

**Efficacy Results – Primary Endpoint**

The primary efficacy endpoints were PK exposure at Day 7 (Part 1) and estimates of the population central values and the empirical Bayesian estimates of the individual values of upadacitinib oral clearance (CL/F) and volume of distribution (V/F) from population PK modeling and simulation (Parts 2 and 3). Refer to Section 6 for full discussion of the PK results.

**Efficacy Results – Secondary and other relevant endpoints**

No primary or secondary efficacy endpoints were defined for this study due to the nature of the single-arm, open-label design. Descriptive efficacy at Weeks 12, 24, 36, and 48 were assessed as other endpoints. As noted in Section 7.2.1 and in Section 8.1.1 Study M15-340 /Statistical Analysis Plan, the descriptive efficacy analyses were performed using data from the 51 subjects in Parts 1 and 2 available through a data cutoff date of September 22, 2022. Data from subjects in Part 3 were not used since enrollment for Part 3 started just shortly before the data cutoff date (June 17, 2022).

JIA ACR Pediatric Responses

ACR 30 Pediatric Responses were noted in all subjects with available data at Week 12 (Table 25). As shown in Figure 11, ACR 70, 90, and 100 Pediatric Response rates increased through Week 24, and the ACR 50 Pediatric Response rate increased through Week 36. All ACR Pediatric Responses were generally maintained through Week 48.

By age group, the younger subjects (2 to <6 years and 6 to <12 years) had similar improvements in ACR Pediatric Responses at Weeks 12, 24, and 48. However, the oldest age group (12 to <18 years) had lower improvement rates for ACR 70, 90, and 100 Pediatric Responses compared to the younger age groups. The lower improvement rates in the older subgroup likely reflect more refractory disease, consistent with the higher rates of prior csDMARD and bDMARD use by older subjects also noted under in Section 8.1.1 Study M15-340/Other Baseline Characteristics.

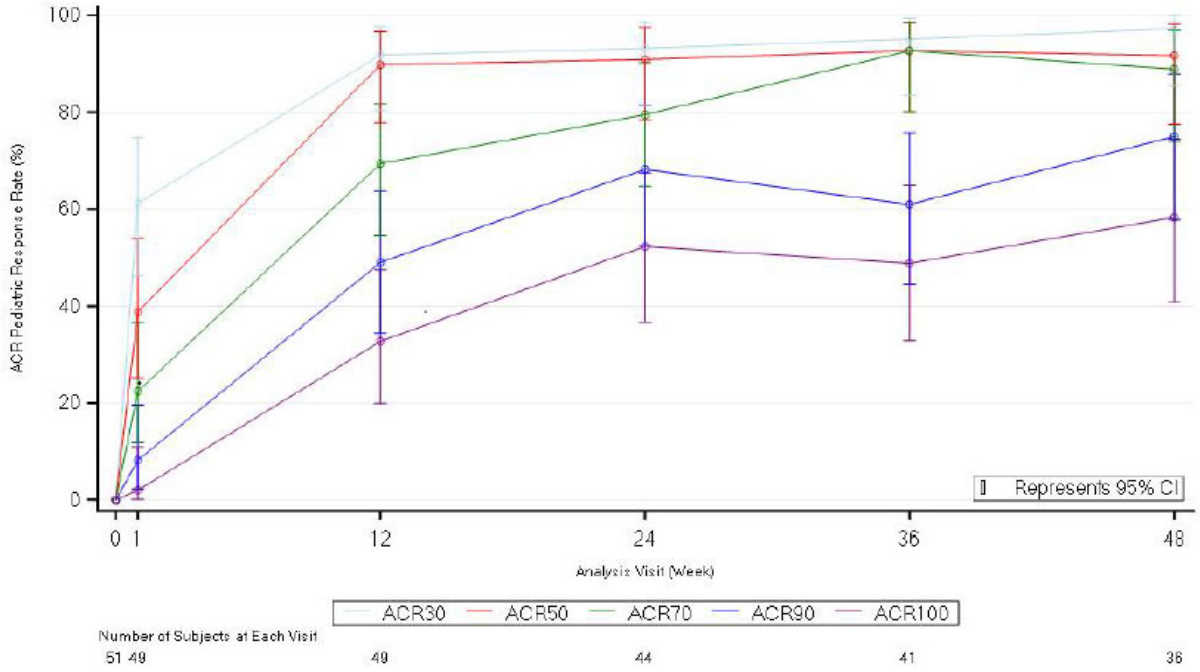
Also consistent with subjects in the 12 to <18 years subgroup having more refractory disease, a higher proportion of subjects 12 to <18 years (31.3%) reported worsening at Week 12 of at least 30% in at least 1 of the 6 ACR Core Set Criteria compared to subjects 6 to <12 years (10.5%) and 2 to <6 years (18.2%). However, at Week 48, these proportions became similar across all age groups (2 to <6 years: 14.3%, 6 to <12 years: 14.3%, 12 to <18 years: 16.7%).

**Table 25. ACR Pediatric 30/50/70/90/100 Responses, Study M15-340, ITT Set, Parts 1 and 2**

| | Age 2 to <6 years n (%) | Age 6 to <12 years n (%) | Age 12 to <18 years n (%) | Total N (%) |
|---|---|---|---|---|
| **Week 12** | | | | |
| ACR 30 | 13 (100) | 19 (100) | 13 (100) | 45 (100) |
| ACR 50 | 12 (92.3) | 19 (100) | 13 (76.5) | 44 (89.8) |
| ACR 70 | 11 (84.6) | 16 (84.2) | 7 (41.2) | 34 (69.4) |
| ACR 90 | 7 (53.8) | 12 (63.2) | 5 (29.4) | 24 (49.0) |
| ACR 100 | 4 (30.8) | 8 (42.1) | 4 (23.5) | 16 (32.7) |
| Proportion of subjects with worsening of ≥30% in ≥1 of the 6 ACR Core Set Criteria | 2 (18.2) | 2 (10.5) | 5 (31.3) | 9 (19.6) |
| **Week 24** | | | | |
| ACR 30 | 8 (100) | 18 (100) | 15 (83.3) | 41 (93.2) |
| ACR 50 | 8 (100) | 18 (100) | 14 (77.8) | 40 (90.9) |
| ACR 70 | 7 (87.5) | 16 (88.9) | 12 (66.7) | 35 (79.5) |
| ACR 90 | 6 (75.0) | 14 (77.8) | 10 (55.6) | 30 (68.2) |
| ACR 100 | 5 (62.5) | 11 (61.1) | 7 (38.9) | 23 (52.3) |
| Proportion of subjects with worsening of ≥30% in ≥1 of the 6 ACR Core Set Criteria | 1 (14.3) | 3 (17.6) | 4 (25.0) | 8 (20.0) |
| **Week 36** | | | | |
| ACR 30 | 6 (85.7) | 18 (100) | 15 (93.8) | 39 (95.1) |
| ACR 50 | 6 (85.7) | 18 (100) | 14 (87.5) | 38 (92.7) |
| ACR 70 | 6 (85.7) | 18 (100) | 14 (87.5) | 38 (92.7) |
| ACR 90 | 5 (71.4) | 12 (66.7) | 8 (50.0) | 25 (61.0) |
| ACR 100 | 4 (57.1) | 11 (61.1) | 5 (31.3) | 20 (48.8) |
| Proportion of subjects with worsening of ≥30% in ≥1 of the 6 ACR Core Set Criteria | 2 (40.0) | 2 (11.8) | 2 (15.4) | 6 (17.1) |
| **Week 48** | | | | |
| ACR 30 | 7 (100) | 14 (100) | 14 (93.3) | 35 (97.2) |
| ACR 50 | 7 (100) | 13 (92.9) | 13 (86.7) | 33 (91.7) |
| ACR 70 | 7 (100) | 13 (92.9) | 12 (80.0) | 32 (88.9) |
| ACR 90 | 6 (85.7) | 12 (85.7) | 9 (60.0) | 27 (75.0) |
| ACR 100 | 5 (71.4) | 8 (57.1) | 8 (53.3) | 21 (58.3) |
| Proportion of subjects with worsening of ≥30% in ≥1 of the 6 ACR Core Set Criteria | 1 (14.3) | 2 (14.3) | 2 (16.7) | 5 (15.2) |

Source: Adapted from Tables 14.2__1.1 to 14.2__1.6, CSR for Study M15-340

**Figure 11. ACR Pediatric Response Rate Over Time, Study M15-350, ITT Set, Parts 1 and 2**




Source: Figure 2, CSR for Study M15-340

Table 27, and Table 28 show the JIA ACR component scores overall and by age group for the number of active joints, number of joints with limited range of motion, and ESR, respectively. Consistent with the mean percent improvement from baseline composite scores seen, these component scores also improved generally overall and across all age groups over 48 weeks. As also shown in Table 29, improvement in CRP over time also paralleled the improvement in ESR. The Patient Reported Outcome (PRO) JIA ACR component scores for C-HAQ, physician's global assessment of disease activity, number of active joints, and patient /parent assessment of overall well-being also improved over 48 weeks. See Section 8.2.1 Study Results/Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints for additional discussion.

**Table 26. Total Number of Active Joints, Study M15-340, ITT Set, Parts 1 and 2**

| | Age 2 to <6 years Mean ±SD | Age 6 to <12 years Mean ±SD | Age 12 to <18 years Mean ±SD | Total Mean ±SD |
|---|---|---|---|---|
| Week 0 | 8.0 ±3.11 | 11.6 ±7.18 | 11.7 ±6.40 | 10.6 ±6.14 |
| Week 1 | 6.9 ±4.42 | 8.2 ±7.92 | 5.2 ±6.47 | 6.8 ±6.59 |
| Week 12 | 1.1 ±1.12 | 1.4 ±2.87 | 1.5 ±2.53 | 1.3 ±2.36 |
| Week 24 | 0.3 ±0.71 | 0.3 ±0.84 | 1.2 ±2.04 | 0.7 ±1.46 |
| Week 36 | 0.9 ±1.21 | 0.7 ±1.60 | 1.1 ±2.49 | 0.9 ±1.91 |
| Week 48 | 0.1 ±0.38 | 1.5 ±3.50 | 1.9 ±4.22 | 1.4 ±3.51 |

Source: Table 14.2__3.1, CSR for Study M15-340

**Table 27. Number of Joints with LOM, Study M15-340, ITT Set, Parts 1 and 2**

| | Age 2 to <6 years Mean ±SD | Age 6 to <12 years Mean ±SD | Age 12 to <18 years Mean ±SD | Total Mean ±SD |
|---|---|---|---|---|
| Week 0 | 5.9 ±3.20 | 9.3 ±6.33 | 8.4 ±4.78 | 8.1 ±5.18 |
| Week 1 | 4.6 ±3.16 | 6.3 ±4.08 | 4.7 ±4.93 | 5.3 ±4.19 |
| Week 12 | 1.4 ±1.45 | 1.9 ±2.51 | 2.3 ±2.43 | 1.9 ±2.24 |
| Week 24 | 0.9 ±1.36 | 1.7 ±2.77 | 2.1 ±3.31 | 1.7 ±2.78 |
| Week 36 | 0.4 ±0.79 | 1.4 ±2.29 | 0.9 ±1.24 | 1.1 ±1.76 |
| Week 48 | 0.1 ±0.38 | 1.7 ±3.63 | 1.6 ±2.53 | 1.4 ±2.79 |

Source: Table 14.2__3.1, CSR for Study M15-340

**Table 28. ESR, M15-340, ITT Set, Parts 1 and 2**

| | Age 2 to <6 years Mean ±SD | Age 6 to <12 years Mean ±SD | Age 12 to <18 years Mean ±SD | Total Mean ±SD |
|---|---|---|---|---|
| Week 0 | 25.8 ±21.19 | 18.8 ±16.42 | 13.6 ±10.65 | 18.8 ±16.50 |
| Week 1 | 22.0 ±16.51 | 12.3 ±9.49 | 8.5 ±9.65 | 13.7 ±12.89 |
| Week 12 | 13.1 ±7.74 | 8.9 ±6.59 | 12.5 ±13.80 | 11.2 ±10.14 |
| Week 24 | 11.9 ±6.53 | 9.5 ±7.09 | 10.3 ±8.31 | 10.3 ±7.41 |
| Week 36 | 21.3 ±22.89 | 10.2 ±7.19 | 15.8 ±29.26 | 13.6 ±20.39 |
| Week 48 | 11.5 ±6.80 | 10.4 ±6.11 | 11.1 ±14.97 | 10.9 ±10.80 |

Source: Table 14.2__7.1, CSR for Study M15-340

**Table 29. CRP, M15-340, ITT Set, Parts 1 and 2**

| | Age 2 to <6 years Mean ±SD | Age 6 to <12 years Mean ±SD | Age 12 to <18 years Mean ±SD | Total Mean ±SD |
|---|---|---|---|---|
| Week 0 | 17.659 ±25.9930 | 4.343 ±5.5250 | 2.777 ±5.5720 | 7.445 ±15.4248 |
| Week 1 | 7.838 ±11.9474 | 0.670 ±0.7050 | 0.766 ±1.4423 | 2.825 ±7.1796 |
| Week 12 | 0.933 ±1.9681 | 1.312 ±3.9165 | 2.981 ±8.5044 | 1.862 ±5.8356 |
| Week 24 | 0.653 ±0.7594 | 1.190 ±2.1152 | 1.486 ±3.1222 | 1.214 ±2.4162 |
| Week 36 | 2.638 ±5.6206 | 0.520 ±0.7859 | 3.628 ±11.3928 | 2.081 ±7.5097 |
| Week 48 | 1.654 ±2.7735 | 1.224 ±3.2758 | 2.628 ±21.27 | 1.913 ±6.0315 |

Source: Table 14.2__8.1, CSR for Study M15-340

Juvenile Arthritis Disease Activity Scores (JADAS)

Table 30 presents the Juvenile Arthritis Disease Activity Scores using a 27-joint count and CRP (JADAS27-CRP) for each age group at Weeks 0, 1, 12, 24, 36, and 48. Mean JADAS27-CRP scores continued to improve overall and in all age groups up to Week 48.

At Week 12, 58% of subjects achieved JADAS27-CRP scores ≤3.8 (cutoff for low disease activity), and 32.0% of subjects with available data achieved JADAS-CRP scores ≤1.0 (cutoff for inactive disease). At Week 48, the proportion of responders increased with 77.8% and 50% of subjects achieving JADAS27-CRP scores ≤3.8 and ≤1.0, respectively.

**Table 30. Juvenile Arthritis Disease Activity Scores (JADAS27-CRP), M15-340, ITT Set, Parts 1 and 2**

| | Age 2 to <6 years Mean ±SD | Age 6 to <12 years Mean ±SD | Age 12 to <18 years Mean ±SD | Total Mean ±SD |
|---|---|---|---|---|
| Week 0 | 16.61 ±3.889 | 19.91 ±7.341 | 20.41 ±8.510 | 19.21 ±7.091 |
| Week 1 | 13.64 ±4.730 | 13.39 ±6.196 | 10.24 ±7.127 | 12.48 ±6.194 |
| Week 12 | 3.42 ±13.849 | 2.83 ±3.764 | 5.48 ±4.813 | 3.94 ±4.285 |
| Week 24 | 1.07 ±1.153 | 1.49 ±1.787 | 4.13 ±3.911 | 2.53 ±3.097 |
| Week 36 | 3.25 ±4.199 | 1.71 ±3.150 | 4.91 ±6.861 | 3.22 ±5.236 |
| Week 48 | 0.62 ±1.141 | 2.44 ±4.895 | 4.47 ±5.641 | 3.00 ±4.953 |

Note: Joints considered: cervical spine, elbows, wrists, metacarpophalangeal joints (from first to third), proximal interphalangeal, joints, hips, knees, and ankles.
Source: Table 14.2__9.2.1, CSR for Study M15-340

**Dose/Dose Response**

Not applicable. Descriptive efficacy outcomes in Study M15-340 were assessed at a single dose level.

**Durability of Response**

ACR Pediatric Responses and JADAS27-CRP continued to improve overall and in all age groups up to Week 48. See the discussion of JIA Pediatric Responses and Juvenile Arthritis Disease Activity Scores above for full details.

**Persistence of Effect**

Not applicable. The study was not designed to evaluate persistence of effect.

**Efficacy Results – Secondary or exploratory COA (PRO) endpoints**

The following PRO measures were used as a part of the descriptive efficacy assessments in this single-arm uncontrolled study.

- Physician Global Assessment of Disease Activity
- Childhood Health Assessment Questionnaire (C-HAQ)
- Patient/Parent Assessment of Overall Well-being

Table 31, Table 32, and Table 33, respectively, present the results for each of these PRO measures overall and by age group up to Week 48. The results appear generally consistent with the JIA ACR response across 48 weeks.

**Table 31. C-HAQ, Study M15-340, ITT Set, Parts 1 and 2**

| Change from baseline | Age 2 to <6 years Mean ±SD | Age 6 to <12 years Mean ±SD | Age 12 to <18 years Mean ±SD | Total Mean ±SD |
|---|---|---|---|---|
| Week 0 | 0.90 ±0.645 | 1.07 ±0.761 | 1.04 ±0.752 | 1.01 ±0.717 |
| Week 1 | 0.82 ±0.552 | 0.85 ±0.679 | 0.83 ±0.660 | 0.83 ±0.626 |
| Week 12 | 0.54 ±0.607 | 0.43 ±0.472 | 0.71 ±0.583 | 0.56 ±0.552 |
| Week 24 | 0.45 ±0.732 | 0.28 ±0.353 | 0.63 ±0.648 | 0.46 ±0.572 |
| Week 36 | 0.34 ±0.746 | 0.19 ±0.301 | 0.48 ±0.570 | 0.33 ±0.511 |
| Week 48 | 0.38 ± 0.688 | 0.18 ±0.301 | 0.40 ±0.575 | 0.31 ±0.508 |

Source: Table 14.2__2.1, CSR for Study M15-340

**Table 32. Physician's Global Assessment of Disease Activity (VAS), M15-340, ITT Set, Parts 1 and 2**

| | Age 2 to <6 years Mean ±SD | Age 6 to <12 years Mean ±SD | Age 12 to <18 years Mean ±SD | Total Mean ±SD |
|---|---|---|---|---|
| Week 0 | 51.5 ±12.39 | 59.3 ±20.91 | 62.4 ±27.34 | 58.0 ±21.26 |
| Week 1 | 38.9 ±17.46 | 38.9 ±17.27 | 27.4 ±22.60 | 35.3 ±19.48 |
| Week 12 | 6.1 ±7.90 | 4.1 ±6.04 | 13.8 ±16.67 | 8.1 ±12.02 |
| Week 24 | 1.1 ±1.64 | 1.7 ±2.80 | 10.4 ±16.47 | 5.2 ±11.41 |
| Week 36 | 5.6 ±9.55 | 4.8 ±11.92 | 10.1 ±17.14 | 7.0 ±13.81 |
| Week 48 | 2.1 ±5.67 | 3.1 ±6.87 | 9.6 ±21.80 | 5.6 ±14.99 |

Source: Table 14.2__5.1, CSR for Study M15-340

**Table 33. Patient/Parent Global Assessment of Disease Activity (VAS), M15-340, ITT Set, Parts 1 and 2**

| | Age 2 to <6 years Mean ±SD | Age 6 to <12 years Mean ±SD | Age 12 to <18 years Mean ±SD | Total Mean ±SD |
|---|---|---|---|---|
| Week 0 | 50.3 ±23.94 | 42.3 ±22.68 | 45.8 ±19.95 | 45.7 ±21.90 |
| Week 1 | 36.4 ±25.04 | 34.6 ±19.90 | 28.9 ±16.27 | 33.3 ±20.27 |
| Week 12 | 15.6 ±25.05 | 13.5 ±15.70 | 26.2 ±19.71 | 18.6 ±20.31 |
| Week 24 | 4.3 ±4.06 | 10.1 ±15.99 | 20.5 ±18.52 | 13.3 ±16.75 |
| Week 36 | 4.4 ±4.86 | 5.6 ±11.56 | 21.9 ±22.08 | 11.8 ±17.62 |
| Week 48 | 1.3 ±2.14 | 6.3 ±8.95 | 20.1 ±21.27 | 11.1 ±16.58 |

Source: Table 14.2__6.1, CSR for Study M15-340

**Additional Analyses Conducted on the Individual Trial**

None.

**Integrated Review of Effectiveness**

Not applicable. Only a single clinical study was conducted.

### 8.1.3. Assessment of Efficacy Across Trials

Not applicable since only a single clinical study was conducted to assess efficacy.

### 8.1.4. Integrated Assessment of Effectiveness

Not applicable since only a single clinical study was conducted to assess efficacy.

## 8.2. Review of Safety

### 8.2.1. Safety Review Approach

NDA 211675/S-021

The primary safety assessment of upadacitinib for JIA with active polyarthritis relies on data from a single clinical study, Study M15-340, conducted as a multiple-dose, open-label, multiple-part study in pediatric subjects with JIA with active polyarthritis ages 2 to less than 18 years of age who received oral upadacitinib for up to 156 weeks. The assessment presented in this review is based on all available safety data from the CSR and 4-Month SUR and their supporting datasets. Data were submitted and reviewed from a total of 83 subjects with JIA with active polyarthritis from Parts 1, 2, and 3.

The safety of oral upadacitinib in JIA with active polyarthritis patients with active polyarthritis as observed in Study M15-340 was also compared to the established safety profile of oral upadacitinib in adult RA patients. However, direct comparisons of safety of treatment with oral upadacitinib in subjects with JIA with active polyarthritis as compared to other indications are limited by differences in study designs, differences in frequencies of some types of events between the JIA with active polyarthritis and RA populations, and the limitations of cross-study comparisons.

Additional supporting safety data were also reviewed from Study M16-049, an open-label PK and safety study in pediatric subjects ages 2 to less than 12 years with AD, and pooled long-term follow up safety data in adolescent subjects with AD ages 12 to less than 18 years from Studies M16-045, M16-047, and M18-089.

NDA 211675/S-022

The safety of oral upadacitinib in pediatric PsA patients is supported by the safety observed in pediatric subjects with JIA with active polyarthritis ages 2 to less than 18 years of age in Study M15-340. As described in Section 2.1, pJIA and pediatric PsA are both forms of JIA and share similar demographic characteristics, certain clinical features (namely, inflammatory arthritis), and concomitant therapy. Thus, the pJIA population, as well as the broader JIA with active polyarthritis population, are relevant to pediatric PsA. The PK exposure is expected to be similar between pJIA and pediatric PsA, supporting the relevance of the safety data from pJIA to the pediatric PsA population.

Additional supportive safety data was provided by cross-reference to the studies in pediatric and adolescent subjects with AD submitted in S-021 (Studies M16-049, M16-045, M16-047, and M18-089).

### 8.2.2. Review of the Safety Database

**Overall Exposure**

Overall exposure of subjects with JIA with active polyarthritis to oral upadacitinib is summarized in Table 34. Eight-three (83) subjects received at least one administration of upadacitinib with a mean cumulative dose of 539.2 mg. Forty-eight (48) subjects (57.8%) completed at least 52 weeks of treatment.

**Table 34. Extent of Exposure, Study M15-340, Safety Analysis Set**

| | Age 2 to <6 years N=22 n (%) | Age 6 to <12 years N=36 n (%) | Age 12 to <18 years N=25 n (%) | Total N=83 N (%) |
|---|---|---|---|---|
| **Duration Interval (Weeks)** | | | | |
| ≥ 1 | 22 (100) | 36 (100) | 25 (100) | 83 (100) |
| ≥ 12 | 18 (81.8) | 32 (88.9) | 24 (96.0) | 74 (89.2) |
| ≥ 26 | 15 (68.2) | 27 (75.0) | 18 (72.0) | 60 (72.3) |
| ≥ 48 | 14 (63.6) | 20 (55.6) | 15 (60.0) | 49 (59.0) |
| ≥ 52 | 13 (59.1) | 20 (55.6) | 15 (60.0) | 48 (57.8) |
| ≥ 104 | 5 (22.7) | 6 (16.7) | 12 (48.0) | 23 (27.7) |
| ≥ 156 | 0 | 3 (8.3) | 9 (36.0) | 12 (14.5) |
| **Duration (Days)** | | | | |
| Mean (SD) | 425.7 (311.20) | 428.3 (346.35) | 726.6 (546.67) | 539.2 (423.39) |
| Median | 382.5 | 496.0 | 655.0 | 489.0 |
| Q1, Q3 | 113, 714 | 193, 641 | 161, 1279 | 139, 783 |
| Min, Max | 34, 1007 | 26, 1303 | 79, 1448 | 26, 1448 |

Source: Table 2.2__1.2, SUR for Study M15-340

**Adequacy of the safety database:**

The safety database for this application relies primarily on the observed safety in Study M15-340 as reported in the CSR and SUR. The safety data from Study M15-340 includes 83 subjects with JIA with active polyarthritis ages 2 to less than 18 years who received treatment with oral upadacitinib for up to 156 weeks. The demographic and disease characteristics of the patients in Study M15-340 are described in Section 8.1.2. In general, the patients in Study M15-340 appear to adequately represent the U.S. population of patients with JIA with active polyarthritis. Additional supportive evidence of safety is provided from Study M16-049, an

ongoing open-label study that has evaluated upadacitinib in33 pediatric subjects ages 2 to less than 12 years with AD, and the pooled long-term follow up safety data in 529 adolescent subjects with AD ages 12 to less than 18 years from Studies M16-045, M16-047, and M18-089. Overall, the safety data provided from Study M15-340 and the supportive safety data from Studies M16-049, M16-045, M16-048, and M18-089 are adequate to inform the safety assessment of upadacitinib in patients with JIA with active polyarthritis, in the context of the established safety profile in adult RA , and in patients with pediatric PsA, in the context of the established safety profile in adult PsA.

### 8.2.3. Adequacy of Applicant's Clinical Safety Assessments

**Issues Regarding Data Integrity and Submission Quality**

No important concerns regarding data integrity and the quality of overall submission were identified to impact the safety review.

**Categorization of Adverse Events**

Adverse events (AEs) and serious adverse events (SAEs) were defined according to standard ICH definitions.

Treatment-emergent adverse events (TEAEs) were defined as AEs with an onset date that is after the first dose of study drug and no more than 30 days after the last dose of study drug. The intensity of AEs was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5. If no guidance was provided by the NCI-CTCAE, the Investigator assessed the severity of AEs based on best medical judgment on the following 5-point scale: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), Grade 5 (death). Causality was assessed by the Investigator based on the following definitions:

- 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.

In the initial CSR, AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 25.0. In the 4-Month SUR, Version 26.0 was used.

Adverse events of special interest (AESIs) were defined based on safety concerns reported for other JAK inhibitors and upadacitinib data from preclinical studies and the RA development program and were identified per standard MedDRA queries (SMQs),customized MedDRA queries (CMQs), or by MedDRA preferred terms (PTs). For Study M15-340, the AESI categories were as follows:

- Serious infections (by CMQ of "Infections" – subset for SAEs)
- Opportunistic infections (by CMQ for "Opportunistic Infection" excluding "Tuberculosis and Herpes Zoster")
- Herpes Zoster (by CMQ for "Herpes Zoster")
- Active Tuberculosis (by CMQ for "Active Tuberculosis)
- Possible malignancy (by SMQ for "Malignancies" )
- Malignancy (all types) (by SMQ for "Malignant tumours" )
- Non-Melanoma Skin Cancer (NMSC) (by SMQ for "Skin malignant tumours" (broad SMQ) removing "Melanoma" CMQ)
- Malignancy excluding NMSC (by SMQ for "Malignant tumours" removing NMSC output)
- Lymphoma (by SMQ for "Malignant lymphomas")
- Adjudicated gastrointestinal perforations
- Anemia (by CMQ for "Non-Hemolytic and Non-Aplastic Anemias")
- Neutropenia (by CMQ for "Hematological Toxicity – Neutropenia")
- Lymphopenia (by CMQ for "Hematological Toxicity – Lymphopenia")
- Renal dysfunction (SMQ for "Acute Renal, Failure")
- Hepatic disorder (SMQ for "Drug Related Hepatic Disorders")
- Elevated CPK (search for the PT of "Blood creatine phosphokinase increased")
- Adjudicated cardiovascular events (e.g., major adverse cardiovascular event [MACE])
- Adjudicated embolic and thrombotic events (non-cardiac, non-central nervous system [CNS])

**Routine Clinical Tests**

Clinical laboratory tests measured during the study included routine hematology, blood chemistry, ESR, and CRP through Week 156 and serum/urine pregnancy testing for females of childbearing potential. Hepatitis A, B and C serologies and rheumatoid factor were assessed at screening. Chest X-Ray and QuantiFERON-TB Gold testing were conducted at Screening and Week 52, and a TB questionnaire was administered at Weeks 48, 96, and 144. Laboratory results were graded according to the CTCAE version 5.0. NCI-CTCAE grades were used in the summary of laboratory data (Grades 1–4).

### 8.2.4. Safety Results

The safety of upadacitinib is well-characterized in numerous clinical studies across various indications, including in adult patients with RA and PsA. In this JIA with active polyarthritis clinical program, no new safety signals were identified in the pediatric patients compared to the known adverse event profile of upadacitinib in adult patients (USPI). The observed safety profile of upadacitinib in children with JIA with active polyarthritis was consistent with the known safety profile of upadacitinib (see Section 8.2.11 Integrated Assessment of Safety).

**Deaths**

No deaths were reported in Study M15-340.

**Serious Adverse Events**

In Study M15-340, 11 subjects (13.3%) experienced 18 treatment-emergent SAEs (TE-SAEs) as summarized in Table 35. TE-SAEs reported in more than one subject included abdominal pain, juvenile idiopathic arthritis, and nausea, each in 2.4% of subjects. All other TE-SAEs were single events by preferred term (PT) in single individuals.

**Table 35. TE-SAEs, Study M15-340, Safety Analysis Set**

| Preferred Term | Age 2 to <6 years N=22 n (%) | Age 6 to <12 years N=36 n (%) | Age 12 to <18 years N=25 n (%) | Total N=83 N (%) |
|---|---|---|---|---|
| **# subjects with ≥1 TE-SAEs** | **2 (9.1)** | **3 (8.3)** | **6 (24.0)** | **11 (13.3)** |
| Abdominal pain | 0 | 0 | 2 (8.0) | 2 (2.4) |
| Juvenile idiopathic arthritis | 1 (4.5) | 0 | 1 (4.0) | 2 (2.4) |
| Nausea | 0 | 0 | 2 (8.0) | 2 (2.4) |
| Adenoidal hypertrophy | 1 (4.5) | 0 | 0 | 1 (1.2) |
| Conversion disorder | 0 | 0 | 1 (4.0) | 1 (1.2) |
| Headache | 0 | 0 | 1 (4.0) | 1 (1.2) |
| Melaena | 0 | 0 | 1 (4.0) | 1 (1.2) |
| Musculoskeletal chest pain | 0 | 0 | 1 (4.0) | 1 (1.2) |
| Ovarian cyst | 0 | 0 | 1 (4.0) | 1 (1.2) |
| Papillitis | 0 | 1 (2.8) | 0 | 1 (1.2) |
| Suicidal ideation | 0 | 0 | 1 (4.0) | 1 (1.2) |
| Tonsillar hypertrophy | 1 (4.5) | 0 | 0 | 1 (1.2) |
| Testicular torsion | 0 | 1 (2.8) | 0 | 1 (1.2) |
| Upper respiratory tract infection | 0 | 0 | 1 (4.0) | 1 (1.2) |
| Urinary tract infection | 0 | 1 (2.8) | 0 | 1 (1.2) |

Source: Table 8, SUR for Study M15-340

A single subject in Part 2 reported Grade 3 suicidal ideation. The subject was a 15-year-old female with a family history of psychiatric disorder in her mother and a prior non-serious event of depression. The subject was hospitalized for an exacerbation of depression and suicidal ideation, which resolved after being treated with mirtazapine, and study drug was not discontinued. Given the multiple risk factors for depression and suicidality and that the subject recovered while continuing on study drug long-term, the TE-SAE of suicidal ideation was unlikely to be related to study treatment.

**Dropouts and/or Discontinuations Due to Adverse Effects**

In Part 1, no subjects reported treatment-emergent adverse events (TEAEs) that led to study drug discontinuation or study withdrawal.

In Parts 2 and 3, 4 subjects reported 5 TEAEs that led to study drug discontinuation. Two of the subjects were in the Age Group 12 to <18 years. A 14-year-old female in Part 2 discontinued for a Grade 2 event of juvenile idiopathic arthritis on Study Day 92 (Day 85 of Part 2). A 13-year-old female also in Part 2 discontinued for a Grade 1 TEAE of nasopharyngitis on Study Day 206 (Day 199 of Part 2). The 2 other subjects who discontinued study drug because of TEAEs were in the Age Group 6 to <12 years. An 11-year-old female in Part 2 discontinued for a Grade 2 flare of JIA

on Study Day 1067 (Day 1060 of Part 2). Another 11-year-old female in Part 3 discontinued for abdominal pain and nausea on Study Day 30.

Although small numbers of subjects discontinued upadacitinib for TEAEs, the overall small numbers limit the conclusions that can be made. The types of events were consistent with the known safety profile of upadacitinib. No new safety signals were identified.

**Significant Adverse Events**

Protocol-specified AESIs for Study M15-340 are as described in Section 8.2.3 Adequacy of Applicant's Clinical Safety Assessments/Categorization of Adverse Events.

AESIs that occurred in at least 1 subject are summarized in Table 36. Hepatic disorders and CPK elevation were the most commonly reported AESIs, occurring in 7.2% subjects each. Hepatic disorders occurred in 1 subject in the Age Group 2 to <6 years (4.5%), 3 subjects in the Age Groups 6 to <12 years (8.3%), and 2 subjects in the Age Group 12 to <18 years (8.0%). CPK elevation occurred in 3 subjects each in the Age Groups 6 to <12 years (8.3%) and 12 to <18 years (12.0%), respectively. Anemia was the next most commonly reported AESI, occurring in 2 subjects each in the Age Groups 2 to <6 years (9.0%) and 6 to <12 years (5.6%). AESIs of neutropenia occurred in 3 subjects, all in the Group 6 to <12 years (8.4%). Serious infection, opportunistic infection excluding tuberculosis and herpes zoster, and lymphopenia were each reported in 2 subjects. No AESIs of malignancy, non-melanoma skin cancer (NMSC), malignancy excluding NMSC, lymphoma, adjudicated gastrointestinal perforations, herpes zoster, renal dysfunction, active tuberculosis, adjudicated cardiovascular events, and adjudicated thrombotic events were reported for any subjects.

**Table 36. AESIs, Study M15-340, Safety Analysis Set**

| AESI | Age 2 to <6 years N=22 n (%) | Age 6 to <12 years N=36 n (%) | Age 12 to <18 years N=25 n (%) | Total N=83 N (%) |
|---|---|---|---|---|
| **# subjects with ≥1 treatment-emergent event** | **3 (13.6)** | **13 (36.1)** | **8 (32.0)** | **24 (28.9)** |
| Serious infections | 0 | 1 (2.8) | 1 (4.0) | 2 (2.4) |
| Opportunistic infections (excluding tuberculosis and herpes zoster) | 0 | 1 (2.8) | 1 (4.0) | 2 (2.4) |
| Hepatic disorder | 1 (4.5) | 3 (8.3) | 2(8.0) | 6 (7.2) |
| Anemia | 2 (9.0) | 2 (5.6) | 0 | 4 (4.8) |
| Neutropenia | 0 | 3 (8.3) | 0 | 3 (3.6) |
| Lymphopenia | 0 | 0 | 2 (8.0) | 2 (2.4) |
| Creatine phosphokinase (CPK) elevation | 0 | 3 (8.3) | 3 (12.0) | 6 (7.2) |

Source: Table 9, SUR for Study M15-340
Reviewer's analysis

Serious Infections

Two AESIs of serious infection were reported in 2 subjects, both in Part 2. A 16-year-old female subject had a Grade 2 TEAE of upper respiratory tract infection that led to hospitalization. The other subject was a 10-year-old female who had a Grade 2 TEAE of urinary tract infection that also led to hospitalization. Both events are also discussed under Section 8.2.4 Safety Results/Serious Adverse Events. Neither event led to study drug discontinuation.

Opportunistic Infections

Two (2) AESI of opportunistic infection (excluding tuberculosis zoster and herpes), respectively, were reported in 2 subjects, both in Part 2. A 15-year-old female subject experienced a Grade 2 TEAE of esophageal candidiasis that led to hospitalization. A 10-year-old female experienced a non-serious Grade 1 TEAE of esophageal candidiasis. Neither event led to study drug discontinuation.

Hepatic Disorder

Eight (8) AESIs of hepatic disorder were reported in 6 subjects, all in Part 2. Three of these AESIs were related to Grade 3 TEAEs, including an event of increased alanine aminotransferase (ALT) occurred in an 8-year-old male subject on Study Day 253, an event of transaminasemia in a 15-year old female on Study Day 359, and a 16-year-old female on Study Day 905, concurrent with an AESI of lymphopenia (see discussion of Lymphopenia below) approximately a month after discontinuing study drug and withdrawing consent. The 8-year-old male and the 15-year-old female had Grade 3 ALT elevations in the context of concomitant methotrexate use, and, in

both cases, ALT values normalized with interruption of study drug.

AESIs associated with mild or moderate TEAEs occurred in 3 subjects, including Grade 1 events of hypertransaminasemia in a 10-year-old female on Study Day 427 and a 2-year-old female on Study Day 331. A Grade 2 TEAE of hepatosplenomegaly occurred in an 11-year-old female but without an association with elevated liver enzymes.

The final AESI of hepatic disorder was associated with TEAEs of ALT increased and aspartate aminotransferase (AST) increased reported in a 15-year-old female subject concurrently with an AESI of blood creatinine phosphokinase increased. The co-occurrence with the TEAE of blood creatinine phosphokinase increased suggested a muscle rather than actual hepatic etiology. Both TEAEs were Grade 1 in severity and resolved after approximately 1 month. This AESI was classified as having no reasonable possibility of being related to study drug.

No AESIs of hepatic disorder led to study drug discontinuation.

Anemia

Six (6) AESIs of anemia were reported in 4 subjects, all in the Age Groups 2 to <6 or 6 to <12. In Part 2, a 3-year-old female subject reported a Grade 2 TEAE of iron deficiency anemia on Study Day 203. This event was classified as having no reasonable possibility of being related to study drug. In Part 3, a 2-year-old female had a TEAE of hemoglobin decreased on Study Day 85, an 8-year-old female had coincident Grade 1 TEAEs of hematocrit decreased and hemoglobin decreased on Study Day 85, and an 11-year-old female also had coincident Grade 1 TEAEs of hematocrit decreased and hemoglobin decreased on Study Day 168. None of these TEAEs were considered serious. No AESIs of anemia led to study drug interruption or discontinuation.

Neutropenia

Eight (8) AESIs of neutropenia were reported in 3 subjects. In Part 2, an 11 year-old female reported coincident Grade 1 TEAEs of neutrophil count decreased and neutrophil percentage decreased on Study Day 761 and again on Study Day 1015. In Part 3, an 11 year-old female experienced TEAEs of neutrophil percentage decreased on Study Days 13, 55, and 252, and an 8 year-old male had a Grade 1 TEAEs of neutrophil percentage decreased on Study Day 57. All TEAEs were either Grade 1 or 2, and none of these TEAEs led to study drug discontinuation.

Lymphopenia

Two AESIs of lymphopenia were reported in 2 subjects, both in Part 2. A 14-year-old female experienced a Grade 1 event on Study Day 89. The event did not lead to study drug discontinuation. The second AESI was associated with a Grade 2 TEAE in the 16-year-old female who also had an AESI of hepatic disorder due to TEAE of transaminasemia on Study 905 after discontinuing study drug and withdrawing consent (see also Hepatic Disorders discussion).

CPK elevation

The 6 AESIs of creatine phosphokinase (CPK) elevation were Grade 1 TEAEs of blood CPK increased in 6 subjects, 3 subjects each from the Age Groups 12 to <18 years and 6 to <12 years. Three of the CPK elevations were attributed to exercise and/or increased physical activity, including basketball training for >2 hours and intense hiking activity, and were classified as having no reasonable possibility of being related to study drug. All 6 events of CPK elevation were Grade 1 in severity. None of the events led to study drug discontinuation.

Other Adverse Events of Interest

A 15-year-old female subject in Part 3 experienced a Grade 3 TE-SAE of suicidal ideation as discussed in Section 8.2.4 Safety Results/Serious Adverse Events. As already noted, given multiple risk factors depression and suicidality pre-dating study treatment, the event was classified as having no reasonable possibility of relation to study drug, and study drug was not discontinued.

Summary

Overall, AESIs of hepatic disorders, CPK elevation, cytopenias, and serious and opportunistic infections were reported in small numbers of patients. The small numbers of events limit the conclusions that can be made, and these event types reflect known risks and are consistent with the known safety profile for upadacitinib. No new safety signals were identified.

**Treatment Emergent Adverse Events and Adverse Reactions**

In Study M15-340, 76 subjects (91.6%) treated with upadacitinib experienced at least 1 TEAE. TEAEs occurring in at least 2 subjects are presented in Table **37**. The most frequently reported TEAEs were in the SOCs of Infections and Infestations (75.9%), Gastrointestinal Disorders (39.8%), and General Disorders and Administration Site Conditions (28.9%).

In the Infections and Infestations SOC, the most common TEAEs by PT (>2 subjects) were upper respiratory tract infection (43.4%), COVID-19 (33.7%), nasopharyngitis (27.7%), gastroenteritis (20.5%), gastrointestinal infection (7.2%), pharyngitis streptococcal (6.0%), urinary tract infection (6.0%), otitis externa (4.8%), tonsillitis (4.8%) and bronchitis (3.6%). Greater proportions of subjects in the Age Group 2 to <6 years reported upper respiratory tract infections (2 to <6 years: 59.0%, 6 to <12 years: 33.3%, 12 to <18 years: 44.5%), gastroenteritis (2 to <6 years: 31.8%, 6 to <12 years: 16.7%, 12 to <18 years: 16.0%), and pharyngitis streptococcal (2 to <6 years: 18.2%, 6 to <12 years: 2.8%, 12 to <18 years: 0). Urinary tract infection was also reported in a higher proportion of subjects in the Age Group 6 to <12 years (2 to <6 years: 4.5%, 6 to <12 years: 11.1%, 12 to <18 years: 0). These differences were due to small numerical differences in subjects between age groups.

In the Gastrointestinal Disorders SOC, the most common TEAEs by PT were abdominal pain (15.7%) nausea (13.3%), abdominal pain upper (6.0%), and gastritis (4.8%). Abdominal pain (2 to <6 years: 9.1%, 6 to <12 years: 16.7%, 12 to <18 years: 48%), nausea (2 to <6 years: 4.5%, 6 to <12 years: 11.1%, 12 to <18 years: 24.0%), and abdominal pain upper (2 to <6 years: 0%, 6 to <12 years: 8.3%, 12 to <18 years: 8.0%) were more frequently reported in older subjects. The differences were due to small numerical differences in subjects between age groups.

In the General Disorders and Administration Site Conditions SOC, pyrexia and influenza-like illness were the most commonly reported TEAEs by PT, occurring in 16.9% of subjects each. Both were most commonly reported in subjects Ages 2 to <6 years. Influenza-like illness was reported in 31.8% of subjects 2 to <6 years compared to 13.9% of subjects 6 to <12 years and 8.0% of subjects 12 to <18 years. Pyrexia was reported in 22.7% of subjects 2 to <6 years compared to 19.4% of subjects 6 to <12 years and 8.0% of subjects 12 to <18 years. Again, the differences were due to small numerical differences in subjects between age groups.

**Table 37. TEAEs Reported in >2 Subjects by Decreasing Frequency, Study M15-340, Safety Analysis Set**

| System Organ Class<br>Preferred Term | Age<br>2 to <6 years<br>N=22<br>n (%) | Age<br>6 to <12 years<br>N=36<br>n (%) | Age<br>12 to <18 years<br>N=25<br>n (%) | Total<br>N=83<br>N (%) |
|---|---|---|---|---|
| **# subjects with ≥1 TEAEs** | **20 (90.9)** | **33 (91.7)** | **23 (92.0)** | **76 (91.6)** |
| Upper respiratory tract infection | 13 (59.1) | 12 (33.3) | 11 (44.5) | 36 (43.4) |
| COVID-19 | 7 (31.8) | 13 (36.1) | 8 (32.0) | 28 (33.7) |
| Nasopharyngitis | 3 (13.6) | 12 (33.3) | 8 (32.0) | 23 (27.7) |
| Gastroenteritis | 7 (31.8) | 6 (16.7) | 4 (16.0) | 17 (20.5) |
| Influenza like illness | 7 (31.8) | 5 (13.9) | 2 (8.0) | 14 (16.9) |
| Pyrexia | 5 (22.7) | 7 (19.4) | 2 (8.0) | 14 (16.9) |
| Abdominal pain | 2 (9.1) | 6 (16.7) | 5 (20.0) | 13 (15.6) |
| Headache | 0 | 6 (16.7) | 5 (20.0) | 11 (13.3) |
| Nausea | 1 (4.5) | 4 (11.1) | 6 (24.0) | 11 (13.3) |
| Arthralgia | 0 | 3 (8.3) | 5 (20.0) | 8 (9.6) |
| Blood creatine phosphokinase increased | 0 | 3 (8.3) | 3 (8.3) | 6 (7.2) |
| Gastrointestinal infection | 0 | 5 (13.9) | 1 (4.0) | 6 (7.2) |
| Abdominal pain upper | 0 | 3 (8.3) | 2 (8.0) | 5 (6.0) |
| Pharyngitis streptococcal | 4 (18.2) | 1 (2.8) | 0 | 5 (6.0) |
| Urinary tract infection | 1 (4.5) | 4 (11.1) | 0 | 5 (6.0) |
| Blood triglycerides increased | 0 | 4 (11.1) | 0 | 4 (4.8) |
| Gastritis | 0 | 3 (8.3) | 1 (4.0) | 4 (4.8) |
| Lymphocyte percentage increased | 1 (4.5) | 3 (8.3) | 0 | 4 (4.8) |
| Monocyte count decreased | 1 (4.5) | 3 (8.3) | 0 | 4 (4.8) |
| Otitis externa | 0 | 4 11.1) | 0 | 4 (4.8) |
| Tonsillitis | 0 | 1 (2.8) | 3 (12.0) | 4 (4.8) |
| Bronchitis | 3 (13.6) | 0 | 0 | 3 (3.6) |
| Neutrophil percentage decreased | 0 | 3 (8.3) | 0 | 3 (3.6) |
| Reticulocyte count decreased | 0 | 3 (8.3) | 0 | 3 (3.6) |

Source: Table 2.4__1.2, SUR for Study M15-340
Reviewer's analysis

Most TEAEs were mild or moderate in intensity (i.e., Grade 1 or 2). Grade 3 TEAEs were reported by 11 subjects (13.3%). In subjects 2 to <6 years, there were single Grade 3 events of adenoidal hypertrophy and tonsillar hypertrophy. In subjects 6 to <12 years, there were single Grade 3 events of alanine aminotransferase increased, aspartate aminotransferase increased, testicular torsion, and papillitis. In subjects 12 to <18 years, there were 2 Grade 3 events of abdominal pain and single Grade 3 events of melaena, hypertransaminasemia, upper respiratory tract infection, musculoskeletal chest pain, headache, ovarian cyst, conversion disorder, and suicidal ideation. The Grade 3 events of alanine aminotransferase increased,

aspartate aminotransferase increased, hypertransaminasemia and upper respiratory tract infection were also classified as an AESI (see Significant Adverse Events for additional discussion). The Grade 3 events of testicular torsion and suicidal ideation were also classified as SAEs (see Section 8.2.4 Safety Results/Serious Adverse Events for additional discussion). There were no Grade 4 or 5 events.

**Laboratory Findings**

Hematology

As of the data cutoff for the 4-Month SUR, there were no Grade 4 or higher post-baseline changes in hematology parameters by maximum CTCAE grade. Neutropenia, lymphopenia, and anemia are labeled risks for upadacitinib. TEAEs for these types of events are discussed as AESIs under Section 8.2.4 Safety Results/Significant Adverse Events.

Eighteen (18) subjects (21.7%) had decreased platelets from baseline. A single subject in the 2 to < 6 years age group experienced a Grade 3 event of decreased neutrophils, also classified as an AESI, and discussed in detail under Safety Results/Significant Adverse Events. Grade 2 neutrophil decreases were reported in 12 (6.4%) subjects, and Grade 1 neutrophil decreases were reported in 5 (6.0%) subjects. The Grade 2 neutrophil decreases were generally balanced across each groups, occurring in 4 subjects in the 2 to < 6 years, 5 subjects in the 6 to <12 years, and 3 subjects in the 12 to <18 years age groups. The Grade 1 neutrophil decreases were seen in 1 subject in the 6 to <12 years and 4 subjects in the 12 to <18 years age groups.

Twenty-seven (27) (33.8%) subjects reported leukocyte changes from baseline, all Grade 1 in severity. These changes were also generally balanced by age group with 7 subjects in the 2 to <6 years and 10 subjects each in the 6 to <12 years and 12 to <18 years age groups.

Nine (9) subjects (9.22%) had low lymphocyte changes from baseline. However, none had Grade 3 or higher changes. Seven subjects (8.4%) had worsening from Grade 0 to Grade 1, and 2 subjects (2.4%) had worsening from Grade 1 to Grade 2. Among subjects with Grade 0 to Grade 1 changes, 2 were in the 2 to <6 years, 4 were in 6 to <12 years, and 1 was in the 12 <18 years age groups. The 2 subjects with Grade 1 to Grade 2 were both in the 12 to <18 years age groups.

Nineteen (19) subjects (22.9%) had worsened decreased hemoglobin from baseline, though none were Grade 3 or higher changes. Seventeen (17) subjects (20.5%) had worsening from Grade 0 to Grade 1, and 2 subjects (2.4%) had worsening from Grade 1 to Grade 2. Among subjects with Grade 0 to Grade 1 changes, 6 were in the 2 to <6 years, 8 were in 6 to <12 years, and 3 were in the 12 to <18 years age groups. The 2 subjects with Grade 1 to Grade 2 worsening included 1 subject each in the 2 to <6 and 12 to <18 years age groups.

Five (5) subjects (6.0%) had decreased platelets, all mild or moderate in severity. All were Grade 2 platelet decreases, with 4 of the Grade 2 events occurring in subjects in the 6 to <12 years age group and the remaining single Grade 2 event occurring in a subject in the 12 to <18 years age group.

The observed differences between age groups in numbers of subjects with lymphocyte changes, decreased hemoglobin, and platelets reflect small numerical differences of low grade events.

Chemistries other than lipids and CPK

Liver enzyme elevations are a labeled risk for upadacitinib reflected in the current USPI under Warnings and Precautions.

From baseline, 15 subjects (18.1%) had ALT elevations, 16 subjects (19.3%) had AST elevations, and 13 subjects (15.7%) had alkaline phosphatase elevations. Four (4) subjects (4.8%) with ALT elevations had increases 3x the upper limit of normal (ULN) or higher, and 3 subjects had increases 5x ULN higher. Three subjects (3.6%) had Grade 3 ALT elevations, including 1 subject in the 6 to <12 years age group and 2 subjects in the 12 to <18 years age group. All other reported ALT elevations were either Grade 1 or 2 in severity. The Grade 3 ALT elevations were associated with AESIs of hepatic disorder and are discussed in additional detail under Section 8.2.4 Safety Results/Significant Adverse Events.

No subjects with AST elevations had increases meeting Hy's Law Criteria, and all subjects with AST elevations had only Grade 1 events (4 subjects 2 to <6 years, 8 subjects 6 to <12 years, and 4 subjects 12 to <18 years). Alkaline phosphatase elevations 1.5x ULN or higher were reported in 3 subjects (3.6%), all in the 12 to <18 years age group, and all alkaline phosphatase elevations were Grade 1 events.

For all other LFTs and chemistries including electrolytes, creatinine, and glucose, there were no Grade 3 or higher abnormalities reported. Small numbers of mild or moderate abnormalities were observed with no apparent or clinically meaningful trends over time.

Lipids

Increases in lipid parameters are a labeled risk for upadacitinib reflected in the current USPI under Warnings and Precautions.

Fourteen subjects (16.9%) had total cholesterol elevations from baseline, though all but 1 subject had only mild (i.e., Grade 1) elevations. Among the 13 subjects with Grade 1 elevations, 1 was in the 2 to <6 years age group, 4 were in the 6 to <12 years age group, and 8 were in the 12 to <18 years age group. The 1 other subject with a total cholesterol elevation had a Grade 2 elevation and was in the 12 to <18 years age group.

Fourteen (14) subjects (16.9%) had total cholesterol elevations from baseline, though all but 1 subject had only mild (i.e., Grade 1) elevations. Among the 13 subjects with Grade 1 elevations, 1 was in the 2 <6 years age group, 4 were in the 6 to <12 years age group, and 8 were in the 12 to <18 years age group. The 1 other subject with a total cholesterol elevation had a Grade 2 elevation and was in the 12 to <18 years age group.

Twenty (20) subjects (24.1%) had triglyceride elevations from baseline, all Grade 1 or Grade 2 in maximum severity. Among the 18 subjects with Grade 1 elevations, 6 were in the 2 <6 years age group, 9 were in the 6 to <12 years age group, and 3 were in the 12 to <18 years age group. Two (2) subjects had Grade 0 to Grade 2 elevations with 1 subject each in the 6 to <12 years and 12 to <18 years age groups, respectively. A single subject had a Grade 1 to Grade 2 elevation in the 2 to <6 years age group.

CPK

CPK elevations are a labeled risk for upadacitinib reflected in the current USPI under Warnings and Precautions. Thirty-five subjects (42.2%) had CPK elevations, including 2 subjects (2.4%) with single Grade 4 abnormalities and 3 subjects (3.6%) with single Grade 3 abnormalities. Both subjects with Grade 4 events were in the 12 to 18 years age group. Among subjects with Grade 3 events, 1 was in the 6 to <12 years age group, and 2 were in the 12 to <18 years age group. Because all of these Grade 3 and Grade 4 values normalized upon retest, none of these subjects had TEAEs reported for their CPK elevations. The vast majority of subjects with CPK elevations (n=29, 34.9%) had worsening from Grade 0 to Grade 1. Seven (7) of these subjects were 2 to <6 years of age, 10 were 6 to <12 years of age, and 5 were 12 to <18 years of age. The 1 other subject with a CPK elevation from baseline had worsening Grade 1 to Grade 2 and was in the 6 to <12 years age group.

Abnormalities reported as TEAEs and associated with AESIs of CPK elevation are discussed under Section 8.2.4 Safety Results/Significant Adverse Events.

**Vital Signs**

Vital signs were assessed at all study visits. Subjects with potentially clinically significant blood pressure changes included 3 subjects each (3.6%) with low and high sitting systolic blood pressure, respectively (3 with low values in the 6 to <12 years age group and 3 with high values in the 12 to <18 years age groups), 11 subjects (13.3%) with low diastolic sitting blood pressure (4 subjects aged 2 to <6 years, 5 subjects aged 6 to <12 years, and 2 subjects aged 12 to <18 years), and 3 subjects with high diastolic sitting blood pressure (2 subjects aged 2 to <6 years and 1 subject aged 6 to <12 years). The other potentially clinically significant vital sign abnormality reported was low body weight in 4 subjects, including 1 subject in the 2 to <6 years

age group and 3 subjects in the 12 to <18 years age group. However, no clinically meaningful trends in vital sign parameters were observed over time.

**Electrocardiograms (ECGs)**

Not assessed

**QT**

Not assessed

**Immunogenicity**

Not assessed

### 8.2.5. Analysis of Submission-Specific Safety Issues

**Adverse Events of Special Interest**

Refer to Section 8.2.4 Safety Results/Significant Adverse Events.

**Effects on Growth**

Given that nonclinical studies of JAK inhibitors have identified adverse effects on bone growth and development, height, weight, and Body Mass Index (BMI) were assessed during study visits throughout subject participation in Study M15-340. Height and BMI were compared with data from standard growth charts and summarized by Z-scores standards using the World Health Organization clinical growth charts (WHO, 2023). Z-scores are standard deviation scores used to compare the height or BMI of subjects with JIA with active polyarthritis to that of healthy children of the same age. A Z-score <0 for height indicates a shorter stature compared to a healthy child of the same age, and a Z-score <0 for BMI indicates a lower BMI compared to a healthy child of the same age. Growth profiles were assessed via evaluation of the mean height and BMI Z-scores over time.

The data from the upadacitinib program to inform treatment-related impacts on growth are limited. As of the data cutoff for the 4-Month SUR, height and weight data were available for 50 out of 83 total subjects (60.2%) with JIA with active polyarthritis through at least Week 48. However, the conclusions that can be drawn from these data are limited given the small number of subjects (overall and within age groups) with available long-term data. Other factors,

including chronic inflammatory disease and corticosteroid use, also confound the treatment-related assessment of growth in the JIA population that can be attributed to upadacitinib. In addition, Study M15-340 was not designed to evaluate the effect of upadacitinib on bone growth and development.

Mean height consistently increased over time in all age groups. At Week 48, larger mean increases from baseline were observed in the 2 younger age groups than in the oldest age group (mean change from baseline [cm] ± standard deviation [n]: 2 to< 6 years [n=14], 8.33 ±4.660; 6 to <12 years [n=20], 4.31 ±1.844; 12 to <18 years [n=16], 2.39 ±2.869). However, mean height Z-scores remained consistently between -0.20 and 0.40 across all age groups up to Week 48, consistent with no clinically meaningful changes or trends over time.

Mean weight increased over time in all age groups. At Week 48, the greatest mean increase in weight was observed in the age group 6 to < 12 years (mean change from baseline [kg] ±standard deviation [n]: 2 to <6 years, 2.98 ±0.760; 6 to <12 years, 6.60 ±4.920; 12 to <18 years, 3.59 ±4.017). Mean z-scores for BMI remained between 0.10 and 0.79 in all age groups up to Week 48, consistent with no clinically meaningful changes or trends in weight, in the context of height, over time.

Four (4) (4.8%) of the 83 total subjects in Study M15-340 experienced a potentially clinically significant decrease in weight, defined as a decrease >7% from baseline. However, all of these subjects had other factors potentially contributing directly or indirectly to their weight loss. A 14-year-old female who had a potentially clinically significant weight decrease documented at Days 57 and 83 reported a Grade 1 TEAE of weight decreased and concurrent TEAEs of loss of appetite, polymenorrhoea, and upper respiratory tract infection. This subject discontinued from the study due to worsening of her JIA. The other 3 subjects with a potentially clinically significant weight decrease included a 3-year-old female at Day 15, a 16-year-old female at Day 682, and a 15-year-old female at Days 589, 673, 757, and 841. Although none of the 3 subjects reported a TEAE of weight decreased, each subject reported other TEAEs that may have contributed directly and/or indirectly to their weight loss: streptococcal pharyngitis in the 3-year-old female, gastroenteritis in the 16 year-old female, and nausea and abdominal pain in the 15-year old female.

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

Not applicable

### 8.2.7. Safety Analyses by Demographic Subgroups

While the number of AESI were small, no meaningful differences were observed across the age groups studied.

### 8.2.8. Specific Safety Studies/Clinical Trials

Not applicable

### 8.2.9. Additional Safety Explorations

**Human Carcinogenicity or Tumor Development**

As described in the boxed warning and the Warnings and Precautions in the approved USPI for upadacitinib, malignancies have been reported in patients treated with upadacitinib, and higher rates of lymphomas and lung cancers have been seen with other JAK inhibitors versus TNF blockers in RA patients. No events of malignancy were observed in Study M15-340. See also Section 8.2.4 Safety Results/Significant Adverse Events for additional details.

**Human Reproduction and Pregnancy**

There were no reports of pregnancy in Study M15-340. No new information on human reproduction and pregnancy was submitted or required for NDA 211675/S-021 or NDA 211675/S-022.

**Pediatrics and Assessment of Effects on Growth**

The Applicant did not conduct dedicated studies to assess the impact of upadacitinib on growth in the JIA with active polyarthritis and pediatric PsA populations. Specific bone monitoring (such as imaging via MRI or X-ray) to evaluate the impact on growth plates was not conducted in the upadacitinib JIA with active polyarthritis and pediatric PsA clinical programs.

As discussed in Section 8.2.5, height, weight, and BMI were assessed in subjects with active JIA with active polyarthritis during study visits throughout participation in Study M15-340, and the data were compared with standard growth charts and summarized using Z-scores. No clinically meaningful changes from baseline were observed over time in JIA with active polyarthritis subjects continuously evaluated for at least 48 weeks. However, the low number of subjects followed over time limit the conclusions that can be drawn. See Section 8.3.5 Analysis of Submission-Specific Safety Issues/Effects on Growth for full details.

**Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

No new information regarding overdose, drug abuse potential, withdrawal and rebound was submitted in this supplement.

### 8.2.10. Safety in the Postmarket Setting

**Safety Concerns Identified Through Postmarket Experience**

There are no post-marketing data for upadacitinib submitted with either NDA 211675/S-021 or NDA 211675/S-022.

**Expectations on Safety in the Postmarket Setting**

The observed safety profile for upadacitinib in JIA with active polyarthritis in Study M15-340 is generally similar to the observed safety profile of upadacitinib in approved adult indications including RA and PsA as well as the known safety profile of another approved JAK inhibitor in JIA with active polyarthritis. Therefore, the safety profile of upadacitinib in the postmarket setting is expected to be consistent with the known risks associated with JAK inhibitors in JIA with active polyarthritis and other indications. There are no new safety issues that would raise concern when considering how the drug may be used in the postmarket setting. To further assess the long-term safety of upadacitinib in pJIA and pediatric PsA, the Agency and Applicant have agreed to a postmarketing requirement (PMR) (see Section 13 for discussion).

### 8.2.11. Integrated Assessment of Safety

Study M15-340 was the single study conducted to evaluate the PK, safety, and efficacy of upadacitinib in subjects with JIA with active polyarthritis. No integration of safety is presented.

Additional supportive safety data for upadacitinib in pediatric populations were provided from Study M16-049, an ongoing open-label PK and safety study in pediatric subjects ages 2 to less than 12 years with AD, and pooled long-term follow up safety data in adolescent subjects with AD ages 12 to less than 18 years from Studies M16-045, M16-047, and M18-089.

Study M16-049 is a multiple-dose, open-label, two-part study in pediatric subjects with AD ages 2 to less than 12 years of age. Part 1 evaluated PK as well as safety and tolerability and is now completed. In Part 2, an ongoing long-term safety extension, subjects who completed Part 1 are receiving up to an additional 104 weeks of open-label treatment with upadacitinib. Interim safety data from Study M16-049 were available from 35 subjects, including 33 subjects in Part 2.

Among these 33 subjects, 17 subjects were ages 2 to <6 years, and 16 subjects were ages 6 to <12 years. Twenty (20) subjects were exposed to upadacitinib for at least 52 weeks, including 8 subjects 2 to <6 years and 12 subjects 6 to <12 years. There were no deaths in the study. SAEs were reported in 3 subjects (9.1%), including single events of COVID-19, ophthalmic zoster, and major depression. Four (4) subjects discontinued study treatment for TEAEs, including 1 subject for coincident neutropenia and thrombocytopenia, another subject for coincident anxiety and major depression, and single unique subjects for events of ophthalmic zoster and eczema. The Grade 3 TEAE of ophthalmic zoster was classified as an AESI of serious infection. There were also single TEAEs of Grade 3 CPK elevation and Grade 1 neutropenia, also classified as AESI. Common TEAEs (occurring in >2 subjects) included upper respiratory tract infection (15.2%), COVID-19 (12.1%), abdominal discomfort (9.1%), vomiting (9.1%), headache (9.1%), cough (9.1%), dermatitis atopic (9.1%), neutropenia (6.1%), impetigo (6.1%), influenza (6.1%), molloscum contagiosum (6.1%), oropharyngeal pain (6.1%), and asthma (5.7%). While leveraging the observed safety in subjects with AD to support the safety in subjects with JIA with active polyarthritis is limited by differences in the underlying disease populations, the observed safety profile of upadacitinib in this younger age group (ages 2 to <12 years) was generally similar to the known safety profile in adolescent/adult AD and other approved indications. No new safety signals were identified.

Pooled long-term follow up safety data in adolescent subjects with AD ages 12 to less than 18 years from Studies M16-045, M16-047, and M18-089 were available for 529 subjects exposed to upadacitinib, including 264 subjects exposed to 15 mg daily and 265 subjects exposed to 30 mg daily. Two hundred twenty (220) subjects exposed to 15 mg daily and 236 subjects exposed to 30 mg daily received at least 52 weeks of treatment. There were no deaths. Similar proportions of SAEs were reported between treatment groups (15 mg daily: 9.8%, 30 mg daily: 10.9%). The proportions of subjects with TEAEs that led to study drug discontinuation were also similar between treatment groups (15 mg daily: 9.1%, 30 mg daily: 7.2%). The types of SAEs, TEAEs, AESI, and TEAEs leading to study drug discontinuation in this long-term safety database of adolescent subjects were also generally consistent with the known safety profile of upadacitinib. No new safety signals were identified. However, differences in study designs, study populations, and the limitations of cross-study comparisons limit the definitive conclusions that can be drawn with respect to the population of JIA with active polyarthritis patients.

## 8.3. **Statistical Issues**

Study M15-340 was a multiple-dose, open-label, multiple-part study in pediatric subjects with JIA with active polyarthritis ages 2 to less than 18 years of age. The primary objective of Study M15-340 was to assess the PK following oral upadacitinib in patients with active JIA with active polyarthritis. Efficacy in JIA with active polyarthritis was assessed as a supportive endpoint.

The substantial evidence of efficacy to support the pJIA and pediatric PsA indications relies on the extrapolation of efficacy of oral upadacitinib established in adults with RA and PsA, respectively, based on a PK-matching approach. The descriptive efficacy assessments observed in active JIA with active polyarthritis from Study M15-340 provide additional supportive efficacy data. No statistical issues were identified from review of the open-label efficacy data provided by Study M15-340 that impact the overall conclusions on safety and efficacy.

## 8.4. Conclusions and Recommendations

### 8.4.1. NDA 211675/S-021

The Applicant submitted Study M15-340 to support upadacitinib for the treatment of active pJIA in patients ages 2 years and older and to fulfill a PREA PMR (PMR 3680-1) required at the time of the approval for the RA indication to conduct a multiple-dose pharmacokinetic study in children from 2 to less than 18 years of age with JIA. The study was designed and conducted as an open-label, multiple-dose, multicenter, multipart, PK, safety, and tolerability study in pediatric subjects ages 2 to less than 18 years old with JIA with active polyarthritis. The primary objectives were to evaluate the PK, safety, and tolerability of multiple doses of upadacitinib in pediatric subjects with JIA with active polyarthritis. Evaluation of the descriptive efficacy of upadacitinib in JIA with active polyarthritis was a secondary objective.

The efficacy of upadacitinib in pJIA is based on matching systemic exposure and extrapolation of established efficacy of upadacitinib in adult RA. As discussed in 6.2.1, the Clinical Pharmacology review team has determined that the exposures in patients with JIA with active polyarthritis treated with upadacitinib in Study M15-340 were within the range of exposures seen in the pivotal studies in adult RA patients treated with upadacitinib (Studies M13-549, M13-542, M14-465, M13-545, and M15-555). Therefore, the Applicant has provided an adequate PK bridge for upadacitinib to support the extrapolation of efficacy in the adult RA population to the pJIA population. In addition, supportive numerical trends of improvement from baseline were observed for the descriptive efficacy endpoints in Study M15-340 in subjects with JIA with active polyarthritis, providing additional support of the efficacy of upadacitinib in pJIA.

The safety assessment of upadacitinib for the proposed pJIA indication is primarily based on the safety data from 83 subjects with active polyarthritis treated with weight-tiered dosing for upadacitinib in Study M15-340. There were no deaths. The most common TE-SAEs included abdominal pain and nausea, and the most common TEAEs included infections, abdominal pain, and nausea, consistent with the known safety profile of upadacitinib. The safety data are further supported by safety from Study M16-049, an ongoing PK and safety study in pediatric

subjects with AD ages 2 to less than 12 years old, and the pooled long-term follow up safety data in adolescent subjects with AD ages 12 to less than 18 years from Studies M16-045, M16-047, and M18-089. The overall safety profile was similar to that previously known safety profile in adult RA patients treated with upadacitinib and other indications. No new safety signals were identified.

Overall, the efficacy and safety evidence provided in this submission support a favorable benefit/risk profile of upadacitinib for the treatment of pJIA patients ages 2 to less than 18 years following the proposed weight-tiered dosing with either oral upadacitinib extended-release tablets or upadacitinib oral immediate-release solution. The safety of upadacitinib in pJIA was consistent with the known safety of upadacitinib and offers an acceptable risk for the therapeutic benefits. Approval of upadacitinib will provide an additional treatment option in the United States and the second JAK inhibitor treatment available for pJIA in the United States. Therefore, we recommend approval of upadacitinib for active pJIA in pediatric patients 2 years of age and older.

Study M15-340 was designed and conducted consistent with the post-marketing requirement under PMR 3680-1. We recommend that PMR 3680-1 be considered fulfilled based on the results of Study M15-340. In addition, the Applicant has adequately addressed the efficacy and safety of upadacitinib in subjects with JIA with active polyarthritis with a PK-based extrapolation approach. We recommend that the Applicant should be released from the requirements of the other PMR issued with the approval of upadacitinib for RA (PMR 3680-2), which required the conduct of a randomized withdrawal, double-blind, placebo-controlled study to evaluate the efficacy and safety of upadacitinib in the pediatric population. See Section 10.1 Pediatrics/ NDA 211675/S-021 for additional discussion.

### 8.4.2. NDA 211675/S-022

There were no new clinical studies conducted or submitted with S-022.

The efficacy of upadacitinib in pediatric patients ages 2 to less than 18 years old with active PsA was assessed via a full efficacy extrapolation approach from existing efficacy and PK/PD data in adults with PsA, adults with RA, and pediatric patients with JIA with active polyarthritis treated with upadacitinib. The efficacy of upadacitinib in adults with active PsA was demonstrated in the pivotal studies in adult PsA patients treated with upadacitinib (Studies M15-554 and M15-572). To support a PK bridge between adults and children with PsA, PK data from adults with RA and PsA were compared, and PK data from S-021 for pediatric subjects with JIA with active polyarthritis in Study M15-340 were compared with PK data from adults with PsA. Systemic exposures were matched between adults with PsA, adults with RA, and children/adolescents with JIA with active polyarthritis, supporting the similarity of exposures in

adults and pediatric patients with PsA. The systemic exposure with the proposed weight-tiered dosing, either with upadacitinib extended-release tablets or upadacitinib 1 mg/mL oral immediate-release solution, in pediatric subjects 2 to less than 18 years of age with active PsA is expected to be comparable to the systemic exposure with the approved dosing in adults with active PsA. Therefore, the Applicant has provided an adequate PK bridge for upadacitinib to support the extrapolation of efficacy in adult PsA population to the pediatric PsA population.

The safety assessment of upadacitinib in pediatric patients with PsA is primarily supported by the safety data submitted in S-021 to support the safety of upadacitinib for pJIA. The safety of upadacitinib in pJIA is relevant to the expected safety in pediatric patients with PsA, given that pJIA and pediatric PsA are both forms of JIA and that the PK exposure of upadacitinib is expected to be similar in pediatric patients with pJIA and PsA. The safety of upadacitinib in pJIA was consistent with the known safety of upadacitinib in both adult PsA and RA as well as other indications. There were no new safety signals identified.

Therefore, we recommend approval of upadacitinib for active PsA in pediatric patients 2 years of age and older. Approval of upadacitinib will provide an additional treatment option in the United States and the first JAK inhibitor treatment available for pediatric patients with PsA in the United States.

We also recommend that PMR 4201-1 issued at the time of approval for PsA to provide PK and safety information to support the pediatric assessment of upadacitinib in PsA be considered fulfilled based on the information submitted in S-022. See Section 10.2 Pediatrics/ NDA 211675/S-022 for additional discussion.

### 8.4.3. NDA 218347

There was no clinical information submitted with NDA 218347. Based on the cross-referenced clinical information in NDA 211647/S-021 and S-022, we recommend approval of upadacitinib 1 mg/mL oral immediate-release solution to allow for administration to patients weighing less than 30 kg or unable to swallow solid dosage forms.

# 9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was convened for NDA 2116745/S-021, NDA 211675/S-022, or NDA 218347. No issues were identified warranting advisory committee input.

# 10 Pediatrics

## 10.1. NDA 211675/S-021

On August 16, 2019, upadacitinib was approved for the treatment of adults with moderately to severely active RA who had have an inadequate response or intolerance to methotrexate. Upadacitinib was considered to have a new active ingredient, and, therefore, PREA applied. The Agency agreed to waive the pediatric study requirement for birth to less than 2 years of age because necessary studies are impossible or highly impracticable. PREA-required pediatric assessments in patients 2 years and older were deferred. S-021 has been submitted to address the following PREA PMRs issued with the original approval:

**Table 38: PREA PMRs for RA**

| PMR # | PMR Details | Final Report Due Date |
|---|---|---|
| 3680-1 | Conduct a multiple-dose pharmacokinetic study in children from 2 to less than 18 years of age with juvenile idiopathic arthritis (JIA) | February 2021 (original date)<br><br>Extended to March 2023 (deferral extension granted on September 10, 2021) |
| 3680-2 | Conduct a randomized withdrawal, double-blind, placebo-controlled study to evaluate the efficacy and safety of upadacitinib in children from 2 to less than 18 years of age with polyarticular-course JIA (pcJIA) | October 2026 |

For PMR 3680-1, the Division determined that the PK information provided from Study M15-340 adequately fulfills the requirements of the PMR as issued with the original NDA approval. For PMR 3680-2, the Division has since reconsidered the approach to the pediatric assessment for pcJIA or JIA with active polyarthritis, as discussed in Section 3, and considers that efficacy information could be provided based on available PK in pediatric subjects to support extrapolation of efficacy from the adult RA population. The Division determined that the Applicant has adequately addressed the efficacy and safety of upadacitinib for pJIA with the extrapolation of efficacy from RA as discussed in Section 6 and the assessment of safety in subjects with JIA with active polyarthritis as discussed in Section 8. Thus, the Applicant should be released from the requirements of PMR 3680-2. S-021 was reviewed at the PeRC meeting on March 19, 2024. PeRC agreed with the Division's assessments and recommendations for both PMR 3680-1 and PMR 3680-2.

## 10.2. NDA 211675/S-022

On December 14, 2021, upadacitinib was approved for the treatment of adults with active psoriatic arthritis who have had an inadequate response or intolerance to one or more TNF blockers. PREA was considered applicable because of the new indication. The Agency agreed to waive the pediatric study requirement for birth to less than 5 years of age because necessary studies are impossible or highly impracticable given the rarity of the diagnosis of pediatric PsA in this age group. A PREA-required pediatric assessment in patients 5 years and older was deferred. S-022 has been submitted to address the following PREA PMR issued with the original approval:

**Table 39: PREA PMRs for PsA**

| PMR # | PMR Details | Final Report Due Date |
|---|---|---|
| 4201-1 | Provide PK and safety information to support the pediatric assessment of upadacitinib for the treatment of juvenile psoriatic arthritis (jPsA) in children 5 to 17 years of age. | October 2026 |

The Division determined that the cross-referenced PK and safety information from S-021 for the relevant pediatric study population of JIA with active polyarthritis adequately fulfilled the requirements of PMR 4201-1 as issued. The Applicant provided adequate data and information to inform the benefit-risk assessment of upadacitinib for the treatment of pediatric patients 2 years of age and older with active PsA. During the review of S-022 at the FDA PeRC meeting on March 19, 2024, PeRC agreed with the Division's assessment and recommendation that the provided information fulfills the intent of PMR 4201-1.

## 10.3. NDA 218347

In NDA 218347, the Applicant submitted information to support a new 1 mg/mL oral immediate-release solution to allow for administration to pediatric patients with pJIA and pediatric PsA weighing less than 30 kg or unable to swallow solid dosage forms. The Division has determined that use of the new oral solution for these pediatric patients is supported by the efficacy and safety information submitted in NDA 211675/S-021 and cross-referenced in S-022. Because upadacitinib has been granted Orphan Drug Designation of pediatric JIA categories excluding systemic JIA (see Section 3.2), PREA does not apply for the proposed pediatric formulation. Therefore, no review by the FDA PeRC was required for this application.

# 11 Labeling Recommendations

## 11.1. Prescription Drug Labeling

*Prescribing information*

Table 40 presents a high-level summary of the labeling proposal and subsequent key interactions between the Applicant and the Agency. Labeling revisions for NDA 211675 S-021 and S-022 and for NDA 218347 were reviewed concurrently.

**Table 40. Summary of Labeling Updates for Upadacitinib**

| Section | Labeling Changes |
|---|---|
| Section 1 Indications and Usage | • Indication added of "Treatment of patients 2 years and older with active polyarticular juvenile idiopathic arthritis who have had an inadequate response or intolerance to one or more TNF blockers"<br>○ The Applicant initially proposed an indication of "Treatment of patients 2 years of age and older with active polyarticular (b) (4) juvenile idiopathic arthritis who have had an inadequate response or intolerance to one or more TNF blockers." "Polyarticular (b) (4) juvenile arthritis" was replaced with "polyarticular juvenile idiopathic arthritis" because efficacy is supported by extrapolation of efficacy from adult RA, and pJIA is the pediatric disease most similar to adult RA. Aligning revisions to references to the pJIA indication were also implemented throughout the updated labeling.<br>• Expansion of indication for adult PsA as follows: "Treatment of adults and pediatric patients 2 years of age and older with active psoriatic arthritis who have had an inadequate response or intolerance to one or more TNF blockers"<br>○ The Applicant initially proposed a separate indication of "Treatment of "pediatric patients 2 years of age and older with active (b) (4) psoriatic arthritis." The indication was revised as an expansion of the indication for adult PsA to accurately reflect the disease similarity between the pediatric population and the adult population from which efficacy was extrapolated. Aligning revisions to references to the PsA indication were also implemented throughout the updated labeling.<br>○ During the review, the Agency confirmed that Orphan exclusivity would apply for this pediatric subgroup under orphan-drug designation (#15-4854). |
| Section 2 Dosage and Administration | • Addition of the following statements to Section 2.2:<br>○ Rinvoq LQ oral solution is not substitutable with Rinvoq extended-release tablets.<br>○ Changes between Rinvoq LQ oral solution and Rinvoq extended-release-tablets should be made by the health care provider.<br>○ Rinvoq LQ should be administered using the provided press-in bottle |

<table>
<tr><td></td><td>
adapter and oral dosing syringe.<br>
○ Rinvoq LQ is dosed twice daily.<br>
• Inclusion of dosing instructions for Rinvoq and Rinvoq LQ for pediatric patients with PsA in Section 2.4
<table>
<tr><th>Patient Weight</th><th>Rinvoq LQ</th><th>Rinvoq</th></tr>
<tr><td>10 kg to less than 20 kg</td><td>3 mg (3 mL oral solution) twice daily</td><td>Not recommended</td></tr>
<tr><td>20 kg to less than 30 kg</td><td>4 mg (4 mL oral solution) twice daily</td><td>Not recommended</td></tr>
<tr><td>30 kg and greater</td><td>6 mg (6 mL oral solution) twice daily</td><td>15 mg (one 15 mg tablet) once daily</td></tr>
</table>
• Addition of Section 2.10 to provide dosing instructions for Rinvoq and Rinvoq LQ for pediatric patients with pJIA (as above)<br>
• Addition of pJIA and PsA and pediatric patients 2 years and older to the indications in Section 2.11 for which dose adjustments for renal or hepatic impairment are not required<br>
• Addition of pJIA and PsA and pediatric patients 2 years and older to the indications in Section 2.12 for which dose adjustments are not required if concomitantly receiving strong CYP3A4 inhibitors
</td></tr>
<tr><td>Section 3<br>Dosage Forms and Strengths</td><td>• Addition of information for Rinvoq LQ</td></tr>
<tr><td>Section 5 Warnings and Precautions</td><td>• Edits throughout to indicate the warnings and precautions for Rinvoq extended-release tablets also apply for Rinvoq LQ</td></tr>
<tr><td>Section 6.1 Clinical Trials Experience</td><td>• Description added of Study M15-340 in pediatric patients 2 years and older with JIA with active polyarthritis with statement that adverse reactions observed were consistent with the established safety profile of Rinvoq.<br>
○ The study population for Study M15-340 was initially described throughout the labeling as “pediatric patients 2 years and older with active polyarticular (b) (4) juvenile idiopathic arthritis (b) (4) “Polyarticular (b) (4) juvenile idiopathic arthritis” was replaced with “JIA with active polyarthritis” to more accurately describe the enrolled study population. Study M15-340 also enrolled JIA ILAR subtypes other than pJIA, (b) (4) . Aligning revisions to descriptions of the study population for Study M15-340 were implemented throughout the updated labeling.</td></tr>
<tr><td>Section 8.4 Pediatric Use</td><td>• Revisions to statements describing pediatric populations in which safety and efficacy information are available<br>
• Addition of description of data supporting use of Rinvoq extended-release tablets</td></tr>
</table>

| | |
|---|---|
| | and Rinvoq LQ in indicated pediatric populations:<br>○ Data from adequate and well-controlled studies in adults with RA and PsA<br>○ PK data from adults with RA and PsA and pediatric patients with pJIA<br>○ Safety data from Study M15-340 in patients 2 to less than 18 years of age with JIA with active polyarthritis<br>• Statement regarding comparable PK between adults with RA and PsA and pediatric patients with pJIA and expectation of comparable PK exposure between adults PsA and pediatric patients with PsA<br>• Updates to statements of populations in which the safety and effectiveness of Rinvoq have not been established in pediatric patients (i.e., AS, nr-axSpA, UC, and CD)<br>• Addition of a statement where the safety and effectiveness of Rinvoq LQ has not been established in pediatric/adolescent patients (i.e., AD) |
| Section 11<br>Description | • Description of Rinvoq LQ added |
| Section 12.3<br>Pharmacokinetics, Pediatrics | • Addition of PK information for Rinvoq LQ<br>• Description of observed PK for pediatric patients for Rinvoq extended-release tablets and Rinvoq LQ in Study M15-340 |
| Section 14<br>Clinical Studies | • Addition of Section 14.8 describing the observed safety and efficacy of Rinvoq extended-release tablets and Rinvoq LQ in pediatric patients 2 years and older with JIA with active polyarthritis in Study M15-340 |
| Section 16<br>How Supplied/ Storage and Handling | • Storage and handling information added for Rinvoq LQ |

*Other Prescription Drug Labeling*

Revisions to patient labeling were made to align with the revised prescribing information, including the addition of the pJIA indication, expansion of the PsA indication to pediatric patients, and updates to the statement describing the pediatric populations for which safety and effectiveness are not known.

Labeling consultants, including the Division of Medication Error Prevention I (DMEPA), the Office of Prescription Drug Promotion (OPDP), and the Division of Medical Policy Programs (DMPP), have reviewed the submitted labeling and their recommendations which pertain primarily to internal consistency and improving readability and clarity of the labeling have been considered and conveyed to the Applicant.

All labeling changes were agreed upon with the Applicant.

# 12 Risk Evaluation and Mitigation Strategies (REMS)

No new risk management plans are submitted in NDA 211675/S-021, NDA 211675/S-022, or NDA 218347. As no new safety signals have been identified, a Risk Evaluation and Management Strategy (REMS) is not recommended.

# 13 Postmarketing Requirements and Commitment

**Clinical postmarketing requirement (PMR)**

In considering whether a postmarketing requirement for safety should be enacted, the review team considered the following factors:

- The Applicant provided limited data on the long-term safety of upadacitinib in patients with JIA with active polyarthritis.
- There are a number of effective therapeutic options for this patient population that have physiological functions in immune system development.
- Recent evidence from non-clinical studies with other JAK inhibitors suggests effects on skeletal system and bone ossification.

Therefore, to ensure the long-term benefit-risk profile of upadacitinib in pJIA and pediatric patients with PsA remains favorable, the review team concluded that safety should be further assessed by a long-term safety study in pJIA and pediatric PsA with inclusion of control groups for each disease population, to evaluate for malignancies, serious and opportunistic infections, thromboses, and effects on growth. The Office of Surveillance and Epidemiology (OSE) review team determined that these potential toxicities cannot be adequately assessed using the Active Risk Identification Analysis (ARIA). For additional details, see the OSE ARIA sufficiency review by Dr. Margie Goulding dated April 19, 2024.

Consequently, the safety PMR is the following:

> Conduct a long-term registry study in pediatric patients 2 to less than 18 years of age with polyarticular Juvenile Idiopathic Arthritis (pJIA) or Psoriatic Arthritis (PsA) treated with upadacitinib to characterize the risk of malignancies, serious infections (including opportunistic infections), thrombosis, and effects on growth. The registry should enroll upadacitinib-exposed patients and control groups of pediatric pJIA and PsA patients treated with standard-of-care. The applicant should adjudicate the study outcomes. Patients should be followed for 5 years.
>
> Draft Protocol Submission: January 2025
> Final Protocol Submission: September 2025
> Trial Completion: February 2035
> Final Report Submission: February 2036

# 14 Division Director (Clinical)/Signatory Comments

I agree with the review team's assessment of the data submitted, the benefit-risk assessment, and the conclusions regarding the data supporting the recommended regulatory actions.

The regulatory action for NDA 211675/S-021 and S-022 and for NDA 218347 is Approval with labeling changes agreed upon with the Applicant.

The data provided in NDA 211675/S-021 fulfills the PREA PMR 3680-1 listed under NDA 211675 (included in the August 16, 2019 approval letter). Additionally, given that that the Applicant has adequately addressed the efficacy and safety of upadacitinib subjects with JIA with active polyarthritis, the Applicant will be released from the requirements of the other PREA PMR issued with the approval of upadacitinib for RA (PMR 3680-2) listed under NDA 211675.

In addition, the information provided in NDA 211675/S-022 fulfills the PREA PMR 4201-1 also listed under NDA 211675 (included in the December 14, 2021 approval letter).

To further assess the long-term safety of upadacitinib, including the potential to adversely impact bone development and growth, a PMR will be issued requiring a long-term registry study in pediatric patients 2 to less than 18 years of age with pJIA or PsA treated with upadacitinib to characterize the risk of malignancies, serious infections (including opportunistic infections), thrombosis, and effects on growth.

# 15 Appendices

## 15.1. References

Brunello F, Tirelli F, Pegoraro L, Dell'Apa F, et al., 2022, New insights on juvenile psoriatic arthritis. *Front Pediatr*, 10:884727.

Carvalho AL and Hedrich CM, 2021, The molecular pathophysiology of psoriatic arthritis-the complexity interplay between genetic predisposition, epigenetic factors, and the microbiome, *Front Mol Biosci.* 8:662047.

Chan Kwong AHP, Calvier EAM, Fabre D, et al., 2020, Prior information for population pharmacokinetic and pharmacokinetic/pharmacodynamic analysis: overview and guidance with a focus on the NONMEM PRIOR subroutine. *J Pharmacokinet Pharmacodyn*. 47(5):431-46.

Espinosa M and Gottlieb BS, 2012, Juvenile Idiopathic Arthritis, *Pediatrics in Review*, 33:303-313.

Feger DM, Longson M, Dodanwala H, et al., 2019, Comparison of adults with polyarticular juvenile idiopathic arthritis to adults With rheumatoid arthritis, *J Clin Rheumatol*, 25: 163-70.

Macaubas C, Nguyen K, Milojevic D, et al, 2009, Oligoarticular and polyarticular JIA: epidemiology and pathogenesis, *Nat Rev Rheumatol*, 5(11):616-26.

Nigrovic P. Psoriatic juvenile idiopathic arthritis: pathogenesis, clinical manifestations, and diagnosis. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA (Accessed on January 26, 2024).

Oberle EJ, Harris JG, Verbsky JW, 2014, Polyarticular juvenile idiopathic arthritis – epidemiology and management approaches, Clin Epidemiol, 24:6:379-93.

Petty RE, Southwood TR, Manners P, et al., 2001, International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, *J Rheumatol*, 31(2):390–392.

Ravelli A and Martini A, 2007, Juvenile idiopathic arthritis. *Lancet*, 369(9563):767-78.

Ringold S, Angeles-Han ST, Beukelman T, et al. 2019, 2019 American College of Rheumatology/ Arthritis Foundation Guidelines for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis, *Arthritis Care & Res*, 71:717-734.

Schanberg LE, Mulugeta LY, Akinlade B, et al., 2023, Therapeutic development in polyarticular course juvenile idiopathic arthritis: extrapolation, dose selection, and clinical trial design, *Arthritis and Rheumatology*, 75(10): 1856-66.

Southwood TR, Petty RE, Malleson PN, 1989, Psoriatic arthritis in children. *Arthritis Rheum*, 32:1007–1013.

Stoll ML and Mellins ED, 2020, Psoriatic arthritis in childhood. A commentary on the controversy. *Clin Immunol*, 2149(1): 108395.

Stoll ML, Zurakowski D, Nigrovic LE, Nichols DP, et al., 2006, Patients with juvenile psoriatic arthritis comprise two distinct populations, *Arthritis and Rheumatism*, (54):3564-3372.

US-Rinvoq United States Prescribing Information (USPI), last revised November, 2023. Available online at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/211675s019lbl.pdf

World Health Organization. Child growth standards. Geneva, Switzerland: WHO; 2023 [cited 2023 Dec 19]. Available from: https://www.who.int/tools/child-growthstandards/ Standards

World Health Organization. Growth reference data for 5-19 year. Geneva, Switzerland: WHO; 2023 [cited 2023 Dec 19]. Available from: https://www.who.int/tools/growth-reference-data-for-5to19-years/indicators/.

Zisman D, Gladman D, Stoll M, et al., 2017, The juvenile psoriatic arthritis cohort in the CARRA Registry: Clinical characteristics, classification, and outcomes, *J Rheum*, 44(3)342-351.

## 15.2. Financial Disclosure

**Covered Clinical Study: M15-340**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 70 | | |
| 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): 1 | | |
| 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)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: 1<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in Sponsor of covered study: _____ | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☒ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☒ | 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) |

## 15.3. OCP Appendices (Technical documents supporting OCP recommendations)

### 15.3.1 Individual study review: Study M15-340

**Title:** An Open-Label Multiple-Dose Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Upadacitinib in Pediatric Subjects with Polyarticular Course Juvenile Idiopathic Arthritis

**Study period:**
- First Subject First Visit: 24 June 2019
- Last Subject Last Visit: not yet occurred, data cutoff for this interim report was 22 September 2022

**Objectives:**
- Part 1:
  - To evaluate the PK, safety, and tolerability of multiple doses of upadacitinib in pcJIA, referred to this review as "JIA with active polyarthritis" as discussed in Sections 1.2 and 2.1.
  - To evaluate the palatability of upadacitinib oral solution in pediatric subjects.
- Part 2:
  - To evaluate the long-term safety and tolerability of upadacitinib in JIA with active polyarthritis who completed Part 1
- Part 3 (Additional Safety Cohort):
  - To evaluate the long-term safety and tolerability of upadacitinib in JIA with active polyarthritis
- For Parts 1, 2, and 3:
  - To evaluate descriptive efficacy of upadacitinib in JIA with active polyarthritis

**Study design**
This is a phase 1, multiple-dose, open-label study consisting of three parts in pediatric subjects ages 2 to less than 18 years with JIA with active polyarthritis (Figure 1). Approximately 124 pediatric male and female subjects with JIA with active polyarthritis are planned to be enrolled in the study.

In Part 1, subjects received open-label upadacitinib for 7 days at two dose levels (Low Dose and High Dose levels). The Low Dose and High Dose levels were designed to provide comparable plasma exposures within each body weight category to 15 mg QD and 30 mg QD of the upadacitinib tablet in adults with RA, respectively. These two dose levels were planned to be evaluated sequentially in Age Group 1 (12 to <18 years), Age Group 2 (6 to <12 years), and Age Group 3 (2 to <6 years). The High Dose level was only evaluated for Age Group 1 (Cohort 2)

were then removed since the Applicant was no longer pursing the development of the adult dose of 30 mg QD for RA. The Low Dose levels were evaluated for Age Group 1 (Cohort 1), Age Group 2 (Cohort 3), and Age Group 3 (Cohort 5).

In Part 1, upadacitinib dose was administered based on body weight. A dosing scheme with four body weight categories (Table 5) was initially proposed, which was revised based on preliminary PK analysis of the data collected from 23 subjects who completed Part 1 (Table 6). Subjects received multiple doses (QD or BID) of upadacitinib administered for 7 consecutive days prior to enrollment in Part 2. Subjects were asked to take the doses at the same time every day starting with Day 1. On the morning of Day 7, subjects were administered the study drug approximately 30 minutes after a meal and stayed at the site for 12 hours for observation and PK blood sample collections. The PK sampling schedule in Part 1 is:

- Part 1 Day 7 (QD tablet regimens): predose and 0.5, 1, 2, 3, 4, 6, 9, 12, and 24 hours postdose
- Part 1 Day 7 (BID oral solution regimens): predose and 0.25, 0.5, 1, 2, 4, 8, and 12 hours postdose

**Test drug product**

Three oral solution formulations were used in this study. The 1 mg/mL (pH (b) (4)) solution was initially used in the study. The 0.5 mg/mL (pH (b) (4)) solution was later developed (b) (4) the 1 mg/mL (pH (b) (4)) solution was developed (b) (4) The 1 mg/mL (pH (b) (4)) oral solution formulation prototype is proposed as the commercial oral solution formulation for pediatric use.

Three tablet strengths were originally used in the study (7.5, 15, and 30 mg). The 7.5 mg tablet was no longer used in the study after the body weight categories and dose levels were adjusted in Protocol Version 8.0, and the 30 mg tablet was no longer used after the High Dose levels were removed for the younger age groups.

**Table 41. Identity of Investigational Product in Study M15-340**

| Study Drug | Dosage Form | Strength | MMID | Bulk Product Lot Number |
|---|---|---|---|---|
| Upadacitinib | Solution (immediate-release) | 0.5 mg/mL (pH (b) (4))[a] | 20061437 | 1000346293 |
| | | | | 1000346840 |
| | | | | 1000346841 |
| | | | | 1000346842 |
| | | 1 mg/mL (pH (b) (4)) | 20025801 | 1000260709 |
| | | | | 1000295805 |
| | | 1 mg/mL (pH (b) (4)) | 20066801 | 1000424657 |
| | | | | 1000424660 |
| | | | | 1000424661 |
| | | | | 1000437813 |
| | | | | 1000480600 |
| | Tablet (extended-release) | 7.5 mg[b] | 20014312 | 1000240717 |
| | | | | 1000295704 |
| | | | | 1000312651 |
| | | 15 mg | 20014313 | 1000248912 |
| | | | | 1000251197 |
| | | | | 1000258477 |
| | | | | 1000344248 |
| | | | | 1000452216 |
| | | 30 mg[c] | 20014314 | 1000250965 |
| | | | | 1000264163 |
| | | | | 1000344256 |

a. Used in Protocol Version 6.0 to Protocol Version 8.0.
b. Used in Protocol Version 1.0 to Protocol Version 7.0.
c. Used in Protocol Version 1.0 to Protocol Version 8.0.

Source: Table 4, CSR for Study M15-340

**Results**

As of September 22, 2022, 57 subjects with JIA with active polyarthritis were enrolled in this study and received study drug, including 51 subjects who completed Part 1, Part 2 (N = 41) and Part 3 (N = 6) are still ongoing (Table 42 and Table 43). Upadacitinib PK parameters following the initial and revised dosing regimens are shown in Table 7.

**Table 42. Demographic Summary for All Subjects (Study M15-340)**

| | Cohort 1 (N = 9) | Cohort 2 (N = 9) | Cohort 3 (N = 19) | Cohort 5 (N = 14) | Additional Safety Cohort (N = 6) | All Subjects (N = 57) |
|---|---|---|---|---|---|---|
| **Age (years)** | | | | | | |
| Mean ± SD | 14.9 ± 1.5 | 13.9 ± 1.2 | 9.5 ± 1.6 | 3.6 ± 1.5 | 9.2 ±3.3 | 9.5 ± 4.4 |
| (Range) | (13 – 17) | (12 – 16) | (6 – 12) | (2 – 6) | (6 – 15) | (2 – 17) |
| **Weight (kg)** | | | | | | |
| Mean ± SD | 61.3 ± 14.6 | 51.7 ± 13.0 | 37.8 ± 14.4 | 15.1 ± 3.2 | 37.1 ± 22.0 | 38.1 ± 20.4 |
| (Range) | (42.0 – 92.9) | (32.5 – 71.5) | (19.7 ± 72.1) | (11.0 ± 22.5) | (25.4 ± 81.1) | (11.0 – 92.9) |
| **BMI (kg/m$^2$)** | | | | | | |
| Mean ± SD | 23.5 ± 4.98 | 19.8 ± 3.42 | 18.3 ± 4.05 | 15.7 ± 1.57 | 19.1 ± 5.89 | 18.8 ± 4.52 |
| (Range) | (16.0 – 33.7) | (14.6, 25.5) | (12.1, 28.3) | (13.9, 18.3) | (15.9, 31.0) | (12.1, 33.7) |
| **Sex** | | | | | | |
| Male, n (%) | 2 (22.2) | 1 (11.1) | 4 (21.1) | 3 (21.4) | 2 (33.3) | 12 (21.1) |
| Female, n (%) | 7 (77.8) | 8 (88.9) | 15 (78.9) | 11 (78.6) | 4 (66.7) | 45 (78.9) |
| **Race** | | | | | | |
| White, n (%) | 8 (88.9) | 9 (100) | 18 (94.7) | 14 (100) | 6 (100) | 55 (96.5) |
| Black, n (%) | 0 | 0 | 1 (5.3) | 0 | 0 | 1 (1.8), |
| Multi-Race, n (%) | 1 (11.1) | 0 | 0 | 0 | 0 | 1 (1.8) |

Cohort 1: Age 12 to < 18 years; Low Dose from Day 1
Cohort 2: Age 12 to < 18 years; High Dose from Day 1 to Day 7 and Low Dose from Day 8
Cohort 3: Age 6 to < 12 years; Low Dose from Day 1
Cohort 5: Age 2 to < 6 years; Low Dose from Day 1
Additional Safety Cohort: Age 2 to < 18 years; Low Dose from Day 1
Note: Percentages may not add up to 100 due to rounding.
Cross reference: Table 14.1__1.3

Source: Table 7, CSR for Study M15-340

**Table 43. Number of Subjects Enrolled Before and After Dosing Scheme Update by Cohort and Regimen (Part 1)**

| Number of Subjects Enrolled Under: | Cohort 1 Low Dose QD (N = 9) | Cohort 2 High Dose QD (N = 9) | Cohort 3 Low Dose | | | Cohort 5 Low Dose BID (N = 14) |
|---|---|---|---|---|---|---|
| | | | QD (N = 12) | BID (N = 7) | Total[c] (N = 19) | |
| Protocol Version 1.0 to 7.0[a] | 9 | 9 | 6[d] | 1 | 7 | 2 |
| Protocol Version 8.0 or Later[b] | 0 | 0 | 6[d] | 6 | 12 | 12 |

a. Subjects were dosed according to the original dosing scheme in Table 2.
b. Subjects were dosed according to the updated dosing scheme in Table 3.
c. QD and BID regimens summarized together.
d. One subject was enrolled under Protocol Version 9.0, which was mis-captured as Protocol Version 6.0 in the current interim database lock. All statistical analyses were conducted assuming this subject was enrolled under Protocol Version 6.0. This error will be corrected in the next database version.

(Source: Table 13, CSR for Study M15-340

**Conclusions**

- In subjects with JIA with active polyarthritis, upadacitinib Tmax was approximately 3 hours and 1 hour following the administration of the extended-release tablet formulation and the immediate-release oral solution, respectively.
- Upadacitinib apparent oral clearance increased with increasing body weight in subjects with JIA with active polyarthritis.

### 15.3.2 Bioanalytical assay

A high-performance liquid chromatography with tandem mass spectrometry (LC-MS/MS) method (R&D/12/654) has been developed and fully validated for the quantitative determination of upadacitinib in human K2EDTA plasma samples from Study M15-340. This method validation has been reviewed in the original NDA submission for RA (Refer to NDA211675 Clinical Pharmacology Review by Dr. Lei He dated May 17, 2019). All samples from Study M15-340 were stored at -20°C and analyzed within 796 days, which is within the demonstrated long-term stability duration (1615 days at -20°C).

The Office of Study Integrity and Surveillance (OSIS) conducted a remote regulatory assessment of the bioanalytical portion of Study M15-340 and concluded that the data from the audited study is reliable. Refer to the OSIS review by Dr. Makini Cobourne-Duval dated (b) (4), for more details.

### 15.3.3 Population Pharmacokinetic Analyses

**Executive Summary:**

- Upadacitinib pharmacokinetics in pediatrics was characterized through population analysis of data collected from pediatric subjects with JIA with active polyarthritis and AD and leveraging prior information from adults (healthy subjects and subjects with RA, PsA, or AD) through a Bayesian approach. The PopPK model parameter estimations were verified by the reviewer, and the results are consistent with the findings reported by the Sponsor. Upadacitinib PopPK models developed for the target populations using prior information improved model stability and reduced variability of parameter estimation.
- The model-predicted upadacitinib plasma exposures in pediatric subjects with pJIA and pediatric PsA from the proposed pediatric dosing regimens were compared to the target model-predicted exposures in adults with RA and PsA. The proposed weight-based pediatric dosing regimen, along with the specified body weight categories, is anticipated to yield upadacitinib plasma exposures in pediatric patients that are comparable to the targeted plasma exposure observed in adult patients with RA and PsA.

- The PopPK modeling and simulation supports the proposed weight-tiered dosing regimen in pediatric subjects with pJIA and PsA.

**15.3.3.1 PopPK model**

**Objectives:**

The primary objectives of the PopPK analysis were to characterize the population pharmacokinetics of upadacitinib in pediatric subjects and to compare the model-predicted plasma exposures from the current pediatric dosing scheme with adult exposures.

**Model Development:**

**Data:**

To develop a PopPK model for upadacitinib in pediatric patients, an adult model (referred to as Model 1) was constructed. This adult model was based on data from adult and adolescent subjects with atopic dermatitis (AD). The dataset for Model 1 comprised information from a phase 2 study in AD (Study M16-048, encompassing individuals aged 18 to 75 years) and four global phase 3 AD studies (Studies M16-045, M16-047, M17-377, and M18-891, each including participants aged 12 to 75 years).

For the pediatric PopPK model (referred to as Model 2), data were sourced from a phase 1 study involving subjects with JIA with active polyarthritis (Study M15-340, aged 2 to <18 years), and another phase 1 study involving pediatric patients with AD (Study M16-049, aged 2 to <12 years).

The analysis included a total of 84 subjects diagnosed with JIA with active polyarthritis and AD (Table 44), drawn from Studies M16-049 and M15-340, who received upadacitinib and had at least one plasma concentration measurement above the lower limit of quantification (LLOQ). Of these, 51 subjects were from Study M15-340, and 33 subjects were from Study M16-049. The LLOQ for plasma sample assay in the pediatric studies (i.e., Studies M15-340 and M16-049) was 0.0505 ng/mL. Notably, no records fell below the LLOQ, and no outliers were excluded from the analysis.

**Table 44. Demographic and Baseline Characteristics of Subjects with JIA with active polyarthritis and AD from Studies M16-049 and M15-340 by Age Group**

| Characteristic | 2 to <6 years (N = 28) | 6 to <12 years (N = 36) | 12 to <18 years (N = 20) | All Subjects (N = 84) |
|---|---|---|---|---|
| Age (year) | | | | |
| Mean (SD) | 3.36 (1.06) | 8.53 (1.66) | 14.2 (1.53) | 8.14 (4.31) |
| Median | 3.00 | 9.00 | 14.0 | 8.00 |
| Min, Max | 2.00, 5.00 | 6.00, 11.0 | 12.0, 17.0 | 2.00, 17.0 |
| Body Weight (kg) | | | | |
| Mean (SD) | 15.5 (2.56) | 33.1 (12.2) | 56.4 (14.6) | 32.8 (18.7) |
| Median | 15.6 | 30.3 | 57.0 | 26.1 |
| Min, Max | 11.0, 20.9 | 18.1, 70.0 | 32.5, 92.9 | 11.0, 92.9 |
| Creatinine Clearance (mL/min) | | | | |
| Mean (SD) | 180 (38.9) | 163 (26.0) | 138 (25.6) | 162 (34.2) |
| Median | 172 | 159 | 137 | 157 |
| Min, Max | 125, 271 | 119, 225 | 99.1, 208 | 99.1, 271 |
| Sex, n (%) | | | | |
| Male | 13 (46%) | 9 (25%) | 3 (15%) | 25 (30%) |
| Female | 15 (54%) | 27 (75%) | 17 (85%) | 59 (70%) |
| Formulation, n (%) | | | | |
| ER | 0 (0%) | 19 (53%) | 20 (100%) | 39 (46%) |
| Oral-IR solution | 28 (100%) | 17 (47%) | 0 (0%) | 45 (54%) |
| Study, n (%) | | | | |
| M15-340 | 12 (43%) | 19 (53%) | 20 (100%) | 51 (61%) |
| M16-049 | 16 (57%) | 17 (47%) | 0 (0%) | 33 (39%) |

Source: Table 4, Upadacitinib (ABT-494) Population Pharmacokinetic Report, R&D/22/1451

**Methodology:**

Model 1 (adult model) was developed based on data from adult and adolescent subjects with atopic dermatitis (AD) by leveraging the previously developed upadacitinib PopPK model in healthy subjects and subjects with RA and PsA (R&D/19/1199) as prior to inform the analysis through a Bayesian analysis approach. In this previous analysis, upadacitinib pharmacokinetics were described by a two-compartment model with mixed zero- and first-order absorption with lag time for upadacitinib extended-release formulation and linear elimination. The model

included the following covariates: subject population (RA or PsA versus healthy) on CL/F, creatinine clearance on CL/F, and baseline body weight on CL/F and Vc/F.

The structural, statistical (inter- and intra-individual variability) and covariate components of the prior model were maintained in this model. All pharmacokinetic parameter estimates, the variance-covariance matrix of the fixed effects, and the estimates for the random effects were strongly informed by the prior model via the $PRIOR NWPRI function.

Model 2 (pediatric model) was developed using data from pediatric subjects with JIA with active polyarthritis and AD and leveraging prior information from Model 1 through a Bayesian analysis approach. Similarly, the structural, statistical (inter and intra-individual variability), and covariate components of the prior model were maintained in this pediatric model. The pharmacokinetic parameter estimates, the variance-covariance matrix of the fixed effects, and the estimates for the random effects (inter- and intra-individual variability) from Model 1 were used as priors following the same approach as in Model 1.

In order to properly inform the estimates describing the effects of body weight in pediatrics, weak adult priors for these coefficients were applied in the model (by increasing the associated variances by ten-fold). Accordingly, all other pharmacokinetic parameters in the model were strongly informed by prior data in adults. The bioavailability of upadacitinib immediate-release solution relative to immediate-release capsule formulation was fixed to 1.17. This value was based on the observation in a relative bioavailability study (Study M16-552) where administration of two 6 mg doses of a upadacitinib oral solution 12 hours apart resulted in 17% higher upadacitinib AUC relative to administration of a single 15 mg upadacitinib extended-release tablet (R&D/18/0171).

Simulations were conducted based on the developed models to compare exposures between pediatric and adult subjects.

The final model was evaluated based on goodness-of-fit plots, visual predictive checks, and nonparametric bootstrap. The non-linear mixed-effects modeling software NONMEM was used for all data analyses and simulation-based model evaluations.

**Results:**

Model 1:

Model 1 was developed using the previously developed upadacitinib PopPK model in healthy subjects and subjects with RA and PsA (R&D/19/1199) as a prior. Further assessment was conducted for the effect of disease population (subjects with AD versus RA/PsA) on upadacitinib CL/F. The additional coefficient for AD was not found to be significant. This indicated that upadacitinib pharmacokinetics were similar between subjects with RA, PsA, and AD. All covariate effects which were previously included in the prior model were confirmed to be statistically significant in the final adult model.

The goodness-of-fit plots (

Figure **12**) showed a random distribution of observed versus individual or population model-predicted upadacitinib concentrations along the line of unity, the distributions of CWRES showed no trends when plotted against time or population predicted upadacitinib concentrations. Prediction-corrected VPCs for the upadacitinib concentrations in adult and adolescent subjects with AD (Figure 13) demonstrated that the model adequately captured the observed upadacitinib concentration time-course and variability of the observed data.

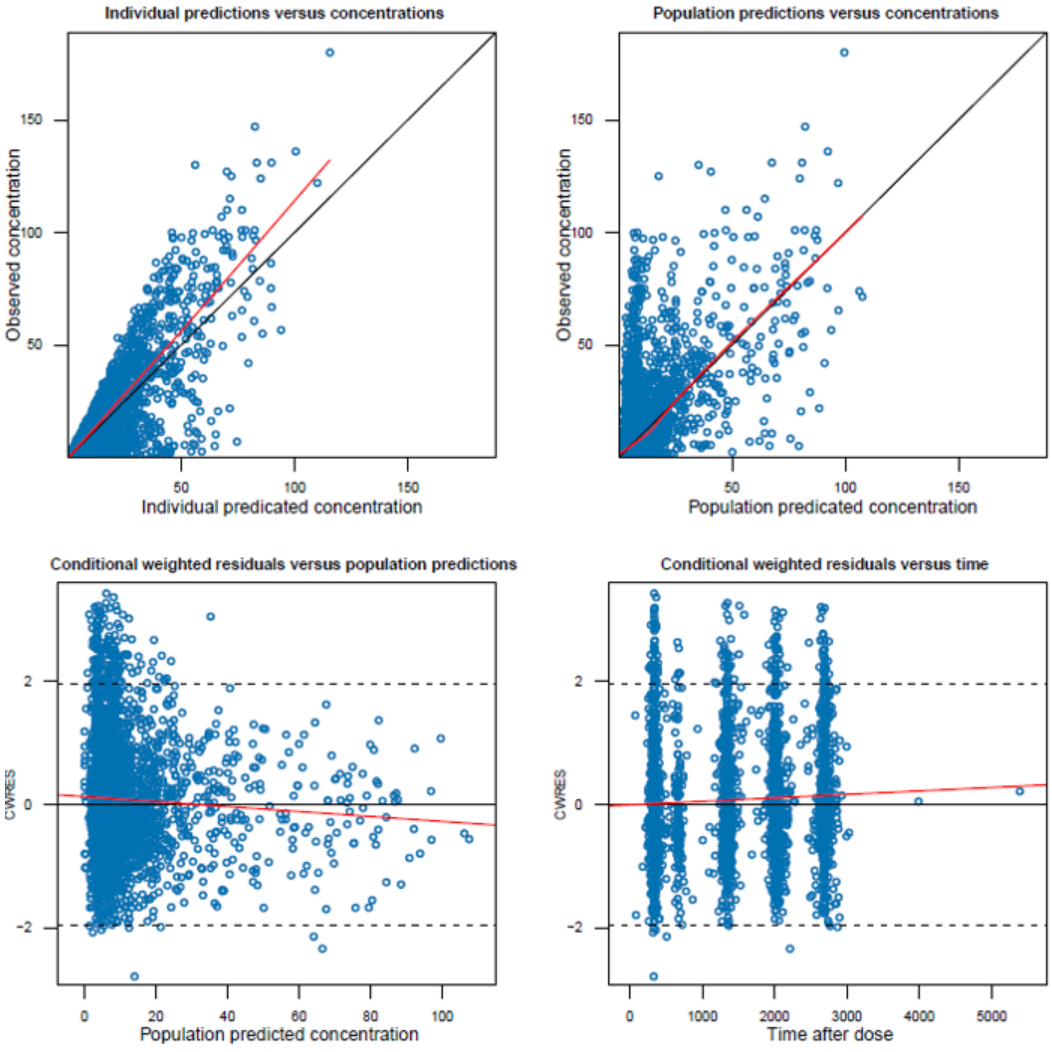
**Table 45. Final Parameter Estimates of Upadacitinib Pharmacokinetics in Model 1**

| **Parameter** | **Estimate** | **%SE** |
|---|---|---|
| CL/F (L/h) | 41.7 | 1.54 |
| Vc/F (L) | 157.6 | 1.61 |
| Extended-Release Ka (1/h) | 0.055 | 4.5 |
| Extended-Release Absorption Lag Time (h) | 0.153 | 7.37 |
| Fraction of Extended-Release Dose | 0.716 | 5.95 |
| Absorbed through Zero-Order Process<br>Zero-Order Absorption Duration (h) | 3.32 | 1.61 |
| Immediate-Release Ka (1/h) | 2.75 | Fixed |
| Immediate-Release Absorption Lag Time (h) | 0.2 | Fixed |
| Bioavailability of the Extended-Release Formulation Relative to the Immediate-Release Formulation | 0.756 | 1.35 |
| Q/F (L/h) | 3.18 | 5.55 |
| Vp/F (L) | 68 | 6.69 |
| Ratio of CL/F in Subjects with RA, PsA, or AD relative to Healthy Subjects | 0.757 | 1.72 |
| Covariate Exponent Creatinine Clearance on CL/F | 0.248 | 8.71 |
| Covariate Exponent of Body Weight on Vc/F | 0.834 | 7.10 |
| Covariate Exponent of Body Weight on CL/F | 0.132 | 24.3 |
| | | |
| IIV on CL/F (%CV) | 0.205 | 81.6 |
| IIV on Vc/F (%CV) | 0.242 | 81.6 |
| IIV on Extended-Release Ka (%CV) | 0.602 | 8.9 |
| Proportional Error Phase 1 | 0.345 | Fixed |

| | | |
|---|---|---|
| Additive Error, SD | 0.0245 | Fixed |
| Proportional Error Phase 2/3 | 0.544 | 3.38 |

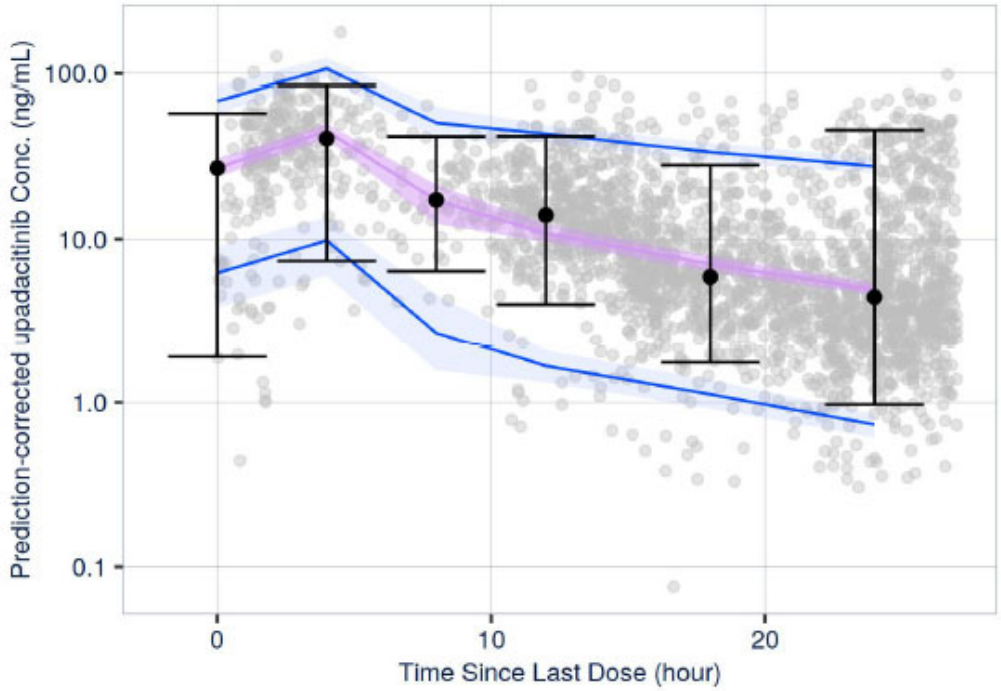
Source: Reviewer's analysis

**Figure 12. Goodness of fit of Upadacitinib Pharmacokinetics in Model 1**




Source: Reviewer's analysis

**Figure 13. Prediction-Corrected Visual Predictive Checks of Upadacitinib in Model 1**




The blue lines represent the 90% PI of the model, the shaded blue areas are the associated 90% CIs of the 5th and 95th percentiles of simulated concentrations. The purple line represents the predicted median and the purple shaded area is its 90% CI. The black points and error bars represent the median and 90% inter-percentile range (5th to 95th percentile) of the observed data, respectively. Grey circles denote observed concentrations.

Source: Figure 1, Upadacitinib (ABT-494) Population Pharmacokinetic Report, R&D/22/1451

Model 2:

The final upadacitinib adult model (Model 1) was used as a prior for the analysis of pediatric data (Model 2). Model 2 was a two-compartment model with mixed zero- and first-order absorption with lag time for the extended-release formulation and linear elimination (Table 46).

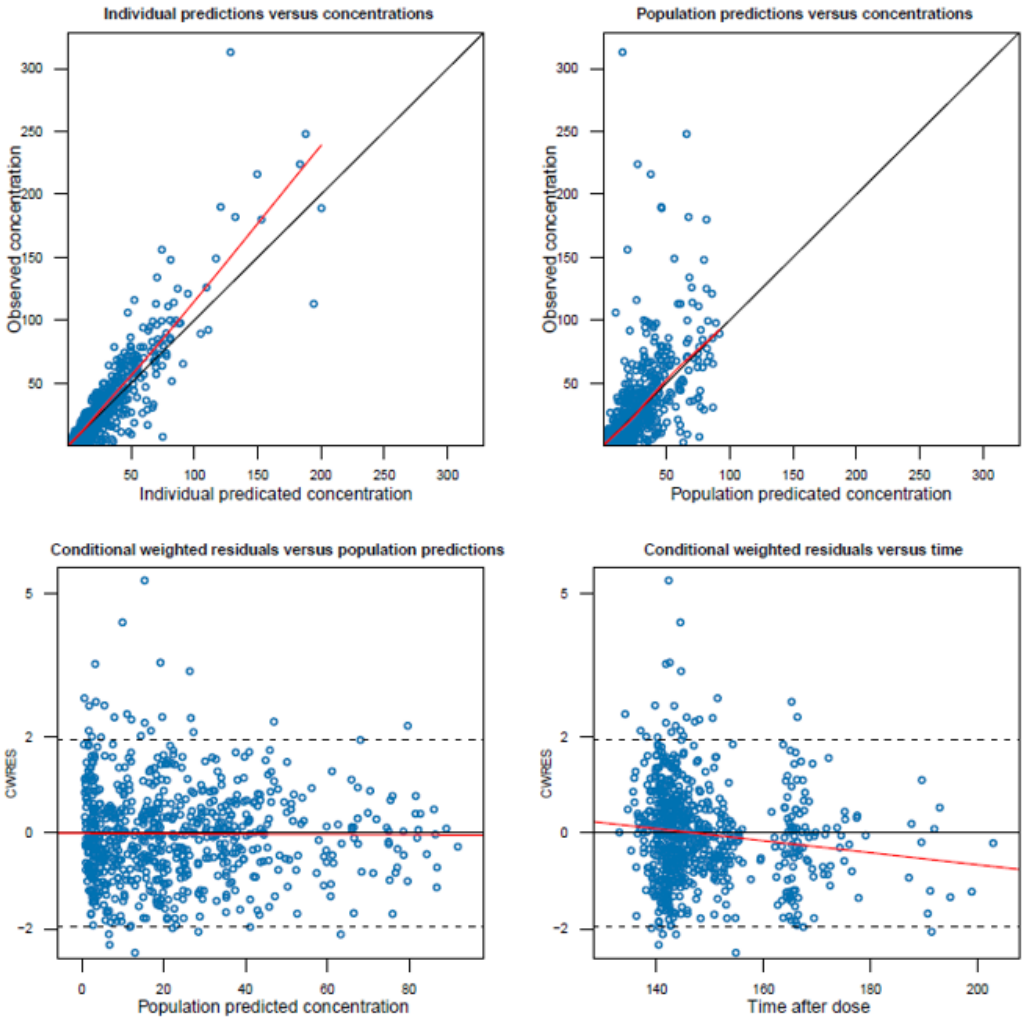
The goodness-of-fit plots showed a random distribution of observed versus individual or population model-predicted upadacitinib concentrations along the line of unity (Figure 14). Additionally, there was no systematic model misspecifications. Prediction-corrected VPCs for the upadacitinib concentrations in pediatric subjects with JIA with active polyarthritis and AD demonstrated that the model adequately captured the observed upadacitinib concentration time-course and variability of the observed data for both the extended-release tablet and immediate-release solution formulations (Figure 15).

**Table 46. Final Parameter Estimates of Upadacitinib Pharmacokinetics in Model 2**

| Parameter | Estimate | %SE |
|---|---|---|
| CL/F (L/h) | 41.7 | 1.52 |
| Vc/F (L) | 157.6 | 1.61 |
| Extended-Release Ka (1/h) | 0.057 | 4.62 |
| Extended-Release Absorption Lag Time (h) | 0.151 | 7.07 |
| Fraction of Extended-Release Dose Absorbed through Zero-Order Process | 0.72 | 6.03 |
| Zero-Order Absorption Duration (h) | 3.32 | 1.54 |
| Bioavailability of the Extended-Release Formulation Relative to the Immediate-Release Formulation | 1.17 | Fixed |
| Q/F (L/h) | 3.29 | 5.47 |
| Vp/F (L) | 68.7 | 6.68 |
| Covariate Exponent of Body Weight on Vc/F | 0.538 | 6.31 |
| Covariate Exponent of Body Weight on CL/F | 0.388 | 4.4 |
| Immediate-Release Ka (1/h) | 2.23 | 17 |
| Immediate-Release Absorption Lag Time (h) | 0.079 | 7.05 |
| | | |
| IIV on CL/F (%CV) | 0.382 | 17.7 |
| IIV on Vc/F (%CV) | 0.574 | 19.6 |
| IIV on Extended-Release Ka (%CV) | 0.62 | 9.11 |
| Proportional Error Phase 1 | 0.454 | Fixed |
| Additive Error, SD | 0.024 | 7.03 |

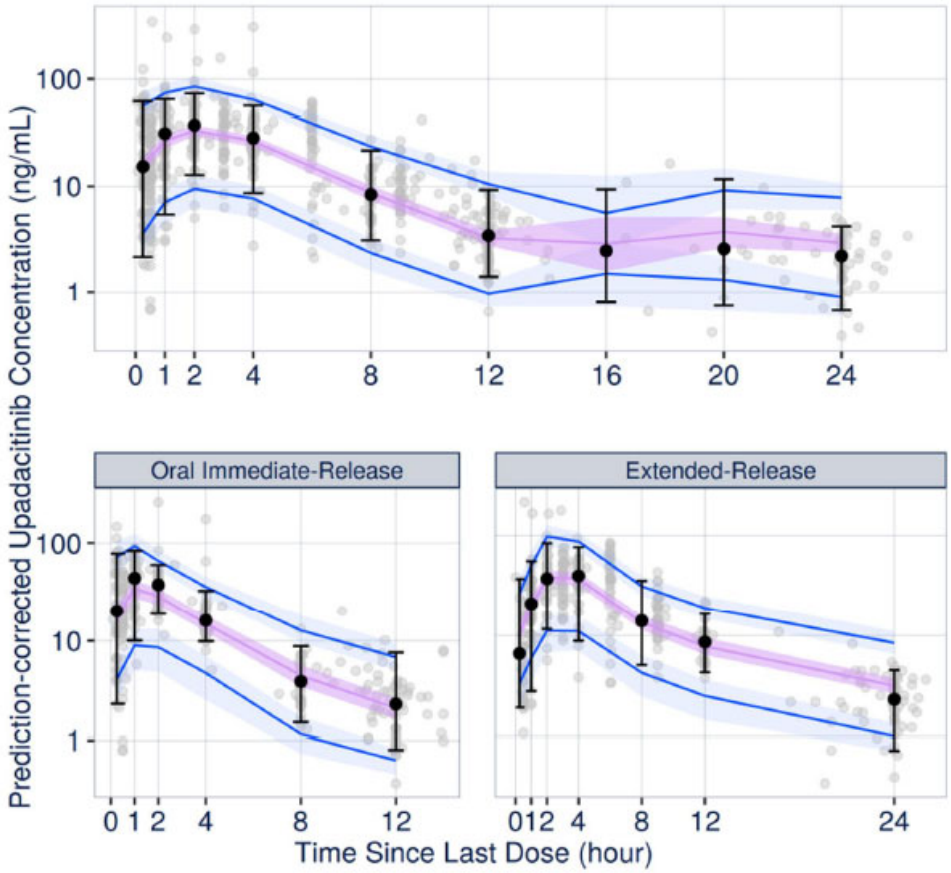
Source: Reviewer's analysis

**Figure 14. Goodness of fit of Upadacitinib Pharmacokinetics in Model 2**




Source: Reviewer's analysis

**Figure 15. Prediction-Corrected VPCs of Upadacitinib Concentration in Model 2 in the Overall Population and by Formulation**




Source: Figure 3, Upadacitinib (ABT-494) Population Pharmacokinetic Report, R&D/22/1451

***Reviewer's Comments:***

- *The PopPK model parameter estimations conducted by the reviewer for Model 1 and Model 2 are consistent with the findings reported by the Sponsor.*
- *Notably, the original upadacitinib PopPK model, which was developed based on data from 4170 subjects (96% subjects with RA and 4% healthy subjects), was initially submitted for the adult RA indication during the original approval. This model appeared to be sophisticated and encountered convergence challenge within the FDA computing system. Refer to the original review for further details ( https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211675Orig1s000ClinPharmR.pdf).*

- *Given the comparable observed binned plasma concentration versus time profiles of upadacitinib between subjects with RA and subjects with PsA, a Bayesian pharmacokinetic modeling approach was implemented using prior information (with $PRIOR NWPRI statement) from the original upadacitinib PopPK model to construct the PopPK model for PsA subjects (Reference: R&D/19/1261).*
- *In the present submission, both Model 1 (adult model) and Model 2 (pediatric model) employed Bayesian PRIOR subroutine for building the upadacitinib PopPK models, which allowed the specification of prior parameters distributions. Parameters incorporated with priors exhibited consistent similarities across respective previous and new populations. According to investigations conducted by the reviewer, upadacitinib PopPK models developed for the target populations using prior information improved model stability and reduced variability of parameter estimation.*

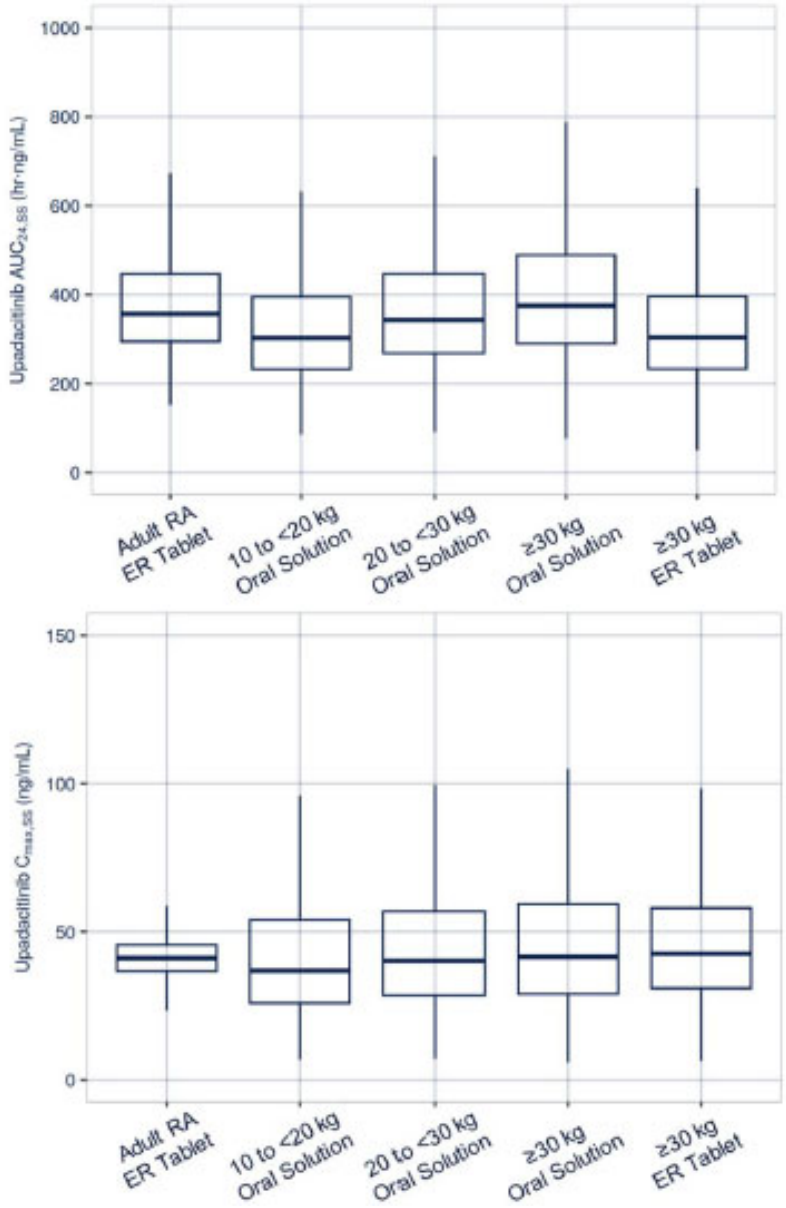
**15.3.3.2 PopPK Model Based Simulation**

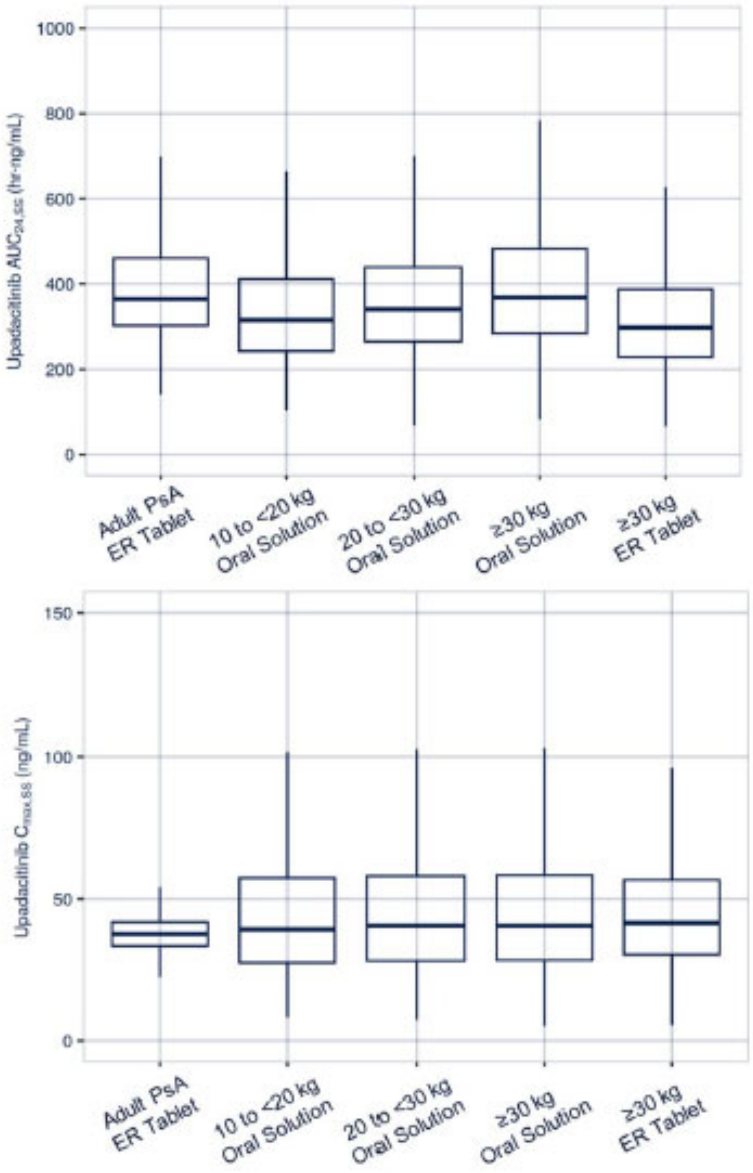
**15.4.3.2.1 Comparison of Model-Predicted Upadacitinib Exposures between Adults and Pediatrics**

Upadacitinib population pharmacokinetic model in pediatrics (Model 2 in R&D/22/1451) was used to simulate the plasma concentration-time profiles from the QD and BID regimens in pediatric subjects weighing ≥30 kg (eligible for receiving either BID oral solution or QD tablets). The proposed pediatric dosing regimen of 6 mg BID for oral solution and 15 mg QD for tablets was assumed in the simulation. The simulated profiles were overlayed in Figure 4 and the daily steady-state Cmax, AUC0-24, and Ctrough are summarized in Table 47. These simulations demonstrate that 15 mg QD using the ER formulation and 6 mg BID using the IR oral solution have similar upadacitinib daily plasma exposures. Additionally, a comparison of the distribution of model-predicted upadacitinib AUC24,ss and Cmax,ss for the investigated dose groups in pediatric subjects and adult subjects with RA and PsA (with respective doses 15 mg QD) was estimated and presented in Table 10, Table 12 **,** and Figure 16.

.

**Figure 16. Distribution of Model-Predicted Upadacitinib Exposures in Pediatric Subjects by Body Weight Compared to Adult Subjects with RA and PsA**






Source: Figure 1, Response to information requested dated December 4, 2023

**Table 47. Summary Statistics of Model-Predicted Upadacitinib Exposures after Administration of QD and BID Regimens in Pediatric Subjects**

| | Oral Solution 6 mg BID | ER Tablet 15 mg QD |
|---|---|---|
| **AUC0-24(ng*hr/mL)** | | |
| Mean (SD) | 399 (162) | 322 (132) |
| Median [Min, Max] | 370 [75.6, 1630] | 298 [57.0, 1200] |
| Gmean (GCV) | 369 (40.9) | 298 (41.2) |
| **Cmax (ng/mL)** | | |
| Mean (SD) | 46.2 (27.3) | 43.3 (21.1) |
| Median [Min, Max] | 39.8 [4.26, 287] | 39.3 [4.29, 182] |
| Gmean (GCV) | 39.8 (58.5) | 38.7 (51.0) |
| **Cavg (ng/mL)** | | |
| Mean (SD) | 16.6 (6.73) | 13.4 (5.51) |
| Median [Min, Max] | 15.4 [3.15, 67.9] | 12.4 [2.38, 49.8] |
| Gmean (GCV) | 15.4 (40.9) | 12.4 (41.2) |

Source: Reviewer's analysis

***Reviewer's Comments:***

- *Upadacitinib pharmacokinetics in pediatrics was characterized through population analysis of data collected from pediatric subjects with JIA with active polyarthritis and AD and leveraging prior information from adults (healthy subjects and subjects with RA, PsA, or AD) through a Bayesian approach.*
- *The model-predicted upadacitinib plasma exposures in pediatric subjects with pJIA and pediatric PsA from the proposed pediatric dosing regimens were compared to the target model-predicted exposures in adults with RA and PsA. The proposed weight-tiered pediatric dosing regimen, along with the specified body weight categories, is anticipated to yield upadacitinib plasma exposures in pediatric patients that are comparable to the targeted plasma exposure observed in adult patients with RA and PsA.*

**15.3.3.3 Upadacitinib Efficacy Simulation Analyses in Pediatrics Patients with pJIA and PsA**

**Executive Summary**

For pediatric patients with PsA or pJIA, the model-predicted efficacy of upadacitinib was similar across all age groups (2 to <6 years, 6 to <12 years, and 12 to <18 years). Overall, the simulation analyses support utilization of the proposed pediatric regimen (using either immediate-release oral solution or extended-release tablet) in pediatric subjects with PsA or pJIA across the studied age groups.

**Efficacy Simulation in pJIA:**

Analysis Objective: The objective of this analysis was to simulate the efficacy of upadacitinib in pediatric patients with pJIA.

Data: Records for 766 virtual subjects were generated from an external database for pediatric patients with JIA with active polyarthritis (Optum database).

Methodology: The final upadacitinib population pharmacokinetic model in pediatrics developed in R&D/22/1451 was used to generate upadacitinib plasma exposures (in the virtual subjects with JIA with active polyarthritis after receiving the proposed pediatric doses. The efficacy simulations were conducted using the generated plasma exposures in subjects with JIA with active polyarthritis and utilizing the previously developed exposure-response models for adults with rheumatoid arthritis (RA) (R&D/18/0628). A total of 200 replicates for a study in a sample size of 300 subjects with JIA with active polyarthritis were simulated. Previously developed continuous-time Markov Chain models in adults with RA were used to simulate efficacy in pediatrics compared to the model-predicted efficacy for these endpoints in adults with RA (R&D/18/0628).

Results: Exposure-response simulations were conducted to predict the efficacy of upadacitinib following the administration of proposed pediatric doses to subjects with pJIA using the established time-continuous Markov models for upadacitinib efficacy (ACR20/50/70 through Week 12 and LDA/CR through Week 12) in adult subjects with RA. The simulation results demonstrated similar and non-inferior efficacy in pediatric subjects with JIA with active polyarthritis relative to that in adult subjects with RA (Figure 6). The model-predicted efficacy of the proposed upadacitinib pediatric regimen was similar across all age groups (2 to <6 years, 6 to <12 years, and 12 to <18 years). Overall, the simulation analyses support utilization of the proposed pediatric regimen (using either immediate-release oral solution or extended-release tablet) in pediatric patients with pJIA.

**Efficacy Simulation in PsA:**

Analysis Objective: The objective of this analysis was to simulate the efficacy of upadacitinib in pediatric subjects with PsA.

Data: Records for 900 virtual subjects were generated from an external database for pediatric patients with JIA with active polyarthritis (Optum database).

Methodology: The final upadacitinib population pharmacokinetic model in pediatrics developed in R&D/22/1451 was used to generate upadacitinib plasma exposures (in the virtual subjects with JPsA after receiving the proposed pediatric doses. The efficacy simulations were conducted using the generated plasma exposures in pediatric subjects with PsA and utilizing the previously developed exposure-response models for adults with PsA (R&D/19/1199). A total of 300 replicates for a study in a sample size of 270 pediatric subjects with PsA were simulated. Efficacy was summarized as the percentage of pediatric subjects with PsA who are predicted to achieve Week 12 American College of Rheumatology 50% improvement criteria (ACR50), Week 12 American College of Rheumatology 70% improvement criteria (ACR70), Week 16 static Investigator Global Assessment of Psoriasis (sIGA) 0/1, and Week 24 sIGA 0/1, and were compared to the model-predicted efficacy for these endpoints in adults with PsA (R&D/19/1199).

Results: Exposure-response simulations were conducted to predict efficacy of upadacitinib following the administration of the proposed pediatric doses to subjects with PsA using the established exposure-response models for upadacitinib efficacy (ACR50 and ACR70 at Week 12, sIGA 0/1 at Week 16 and Week 24) in adult subjects with PsA. The simulation results demonstrate that upadacitinib is predicted to have similar and non-inferior efficacy in pediatric subjects with PsA relative to that in adults with PsA (Figure 9). The model-predicted efficacy of upadacitinib in pediatric subjects was similar across all age groups (2 to <6 years, 6 to <12 years, and 12 to <18 years). Overall, the simulation analyses support utilization of the proposed pediatric regimen (using either immediate-release oral solution or extended-release tablet) in pediatric subjects with PsA across the studied age groups.

***Reviewer's Comments:***

- *Based on the cumulative experience with drug development in JIA, as discussed at the FDA/M-CERSI (University of Maryland Center of Excellence in Regulatory Science and Innovation) public workshop on October 02, 2019, titled "Accelerating Drug Development for Polyarticular Juvenile Idiopathic Arthritis (pJIA)", the Agency has reevaluated its approach to pediatric assessment for pJIA and pediatric PsA. Specifically, the Agency has taken into consideration the high degree of similarity between adults with RA and PsA and pediatric patients with JIA and PsA, respectively, to support a scientific rationale for a pediatric extrapolation of efficacy, meaning that efficacy established in adequate and well-controlled*

*studies in adults with RA and PsA could be extrapolated to pediatric patients with RA and PsA, respectively, based on matching of the PK exposures between the two populations. This extrapolation of efficacy is based on appropriate scientific justification and robust data to support the expectation of similarity in exposure-response between the two populations which could be product-specific.*

- *Within the exposure-response analyses detailed in the preceding PsA submission dossier (Reference: R&D/19/1199, NDA 211675/S-002, eCTD Seq. 0043), a significant correlation was observed between upadacitinib average plasma concentration (Cavg) and the key efficacy endpoints. Given the equivalent upadacitinib drug exposure provided by BID IR regimens and the QD ER regimens (as evidenced by comparable AUC0-24, Cmax, and Cavg), it is anticipated that the efficacy of upadacitinib will manifest similarly across the proposed BID and QD regimens in both adult and pediatric populations with PsA.*

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