23 July 2026
EMADOC-1700519818-3390189
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rinvoq

International non-proprietary name: upadacitinib

Procedure No. EMA/X/0000304823

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Contents

List of abbreviations

ACR	American College of Rheumatology
AD	atopic dermatitis
ADME	absorption, distribution, metabolism, and excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event(s) of special interest
ALT	alanine aminotransferase
aRMM	additional risk minimization measures
AST	aspartate aminotransferase
AUC24,ss	area under the plasma concentration-time curve from time 0 to 24 hours at
BCRP	breast cancer resistance protein
bDMARD	biologic disease-modifying anti-rheumatic drug
bDMARD-IR	bDMARD inadequate response
BID	twice daily
BK virus	Human polyomavirus 1
BMI	body mass index
CARRA	Childhood Arthritis and Rheumatology Research Alliance
CD	Crohn's disease
CDC	U.S. Centers for disease control and prevention
C-HAQ	Childhood Health Assessment Questionnaire
CI	confidence interval
Cmax,ss	maximum plasma concentration at steady state
COVID-19	coronavirus disease 2019
CPK	creatine phosphokinase
CRP	C-reactive protein
csDMARD	conventional synthetic disease-modifying anti-rheumatic drug
CSE	Clinical Summary of Efficacy
CSR	clinical study report
CSS	Clinical Summary of Safety
CTLA4-IG	cytotoxic T lymphocyte-associated antigen-4-immunoglobulin
CV	cardiovascular
CYP	cytochrome P450
E	event
EAER	exposure-adjusted event rate
EAIR	exposure-adjusted incidence rate
EMA	European Medicines Agency
ERA	enthesitis-related arthritis
ER	extended-release
EU	European Union
GC	glucocorticoid
GCP	Good Clinical Practice
GI	gastrointestinal
HAQ-DI	Health Assessment Questionnaire – Disability Index
HDL-C	high-density lipoprotein cholesterol
HLA	human leukocyte antigen
IB	Investigator's Brochure

ICH	International Council for Harmonisation of Technical Requirements for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IL	interleukin
ILAR	International League of Associations for Rheumatology
JADAS	Juvenile Arthritis Disease Activity Score
JAK	Janus kinase
JIA	juvenile idiopathic arthritis
LDA	low disease activity
LDL-C	low-density lipoprotein cholesterol
MAA	Marketing Authorisation Application
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MPA	Swedish Medical Products Agency
MTX	methotrexate
NMSC	nonmelanoma skin cancer
NSAID	non-steroidal anti-inflammatory drug
pcJIA	polyarticular course juvenile idiopathic arthritis
PDCO	Paediatric Committee
P-gp	P-glycoprotein
PIP	paediatric investigation plan
pcJIA	polyarticular juvenile idiopathic arthritis
PK	Pharmacokinetic(s)
PsA	psoriatic arthritis
PSP	pediatric study plan
PT	preferred term
PY	patient-years
PCI	potentially clinically important
QD	once daily
QoL	quality of life
RA	rheumatoid arthritis
RF	rheumatoid factor
RMP	risk management plan
SAE	serious adverse event
SAP	statistical analysis plan
sJIA	systemic juvenile idiopathic arthritis
SmPC	Summary of Product Characteristics
SOC	system organ class
TB	tuberculosis
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
UC	ulcerative colitis
UPA	upadacitinib
URTI	upper respiratory tract infection
US	United States
UTI	urinary tract infection
VTE	venous thromboembolic event

1. Administrative/regulatory information and recommendations on the procedure

1.1. Submission of the dossier

On 13 October 2025, Abbvie Deutschland GmbH & Co. KG submitted a group of variation(s) consisting of an extension of the marketing authorisation and the following variation:

Variation(s) requested		Type
C.I.6.a	C.I.6 Change(s) to therapeutic indication(s) - C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension application to introduce a new pharmaceutical form associated with a new strength (1 mg/ml oral solution) and change of pharmacokinetics grouped with an extension of indication (C.I.6.a) to include the treatment of active polyarticular course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older. Rinvoq may be used as monotherapy or in combination with methotrexate. This is based on clinical results from a phase 1 clinical study (study M15-340). As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly. Version 17 of the RMP has also been submitted. In addition, the MAH took the opportunity to update Annex II.

1.2. Legal basis and dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point(s) (b) (c) (d) - Extensions of marketing authorisations.

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. Scientific advice and protocol assistance

Not applicable.

1.4. Information on paediatrics

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) PIP P/0354/2024 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0354/2024 was not yet completed as some measures were deferred.

The PDCO issued on 19 September 2025 a positive partial compliance check for PIP P/0354/2024, in relation to:

Agreed studies/measures (study identifier)	Description
Study 1	Development of age-appropriate oral solid dosage form (dispersible tablet or multi-particulate granules) or age- appropriate oral liquid dosage form
Study 4	Open-label, multiple dose study to evaluate the pharmacokinetics, safety, and tolerability and to confirm the dosing regimen of ABT-494 in children with active polyarticular course JIA

1.5. Information on orphan market exclusivity

1.5.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur:	Kristina Dunder

The application was received by the EMA on	13 October 2025
The procedure started on	30 October 2025
The CHMP Rapporteur's first Assessment Report was received on	19 January 2026
The PRAC Rapporteur's first Assessment Report was added to the Rapporteurs' report and circulated to all PRAC and CHMP members on	27 January 2026
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 February 2026
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	26 February 2026
The MAH submitted the responses to the CHMP consolidated List of Questions on	22 May 2026
The CHMP Rapporteur circulated the Rapporteur's Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	23 June 2026
The PRAC Rapporteur circulated the Rapporteur's Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	29 June 2026
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	09 July 2026
The CHMP Rapporteur circulated the Rapporteur's updated Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	17 July 2026

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Rinvoq on	23 July 2026

1.7. CHMP outcome

1.7.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 1.3. of this report.

In this procedure, the CHMP reviewed the available data from the studies conducted in accordance with the agreed PIP P/0354/2024, namely study 1 and study 4. The results of this study are reflected in sections 4.8, 5.1, 5.2 of the Summary of Product Characteristics (SmPC) for both the tablet forms and the new oral formulation and, as appropriate, the Package Leaflet. Further, these results were pivotal in supporting this application.

In addition, in this procedure, the CHMP assessed the quality measure required under the agreed PIP P/0354/2024 to develop an age-appropriate paediatric formulation.

1.7.2. Opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of a new pharmaceutical form associated with a new strength (1mg/ml0 of Rinvoq is favourable in the following indications:

Polyarticular juvenile idiopathic arthritis

Rinvoq is indicated for the treatment of active polyarticular juvenile idiopathic arthritis (polyarticular rheumatoid factor positive [RF+] or negative [RF-], extended oligoarticular), in patients 2 years of age and older who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). Rinvoq may be used as monotherapy or in combination with methotrexate.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Rinvoq, subject to the conditions described in the following sections.

In addition, the CHMP does recommend the variation to the terms of the marketing authorisation concerning the following changes:

Variation(s) requested		Type
C.I.6.a	C.I.6 Change(s) to therapeutic indication(s) - C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension application to introduce a new pharmaceutical form associated with a new strength (1 mg/ml oral solution) and change of pharmacokinetics grouped with an extension of indication (C.I.6.a) to include the treatment of active polyarticular course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older. Rinvoq may be used as monotherapy or in combination with methotrexate. This is based on clinical results from a phase 1 clinical study (study M15-340). As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC for Rinvoq 15mg, 30mg and 45mg tablets

have been updated. The Package Leaflet has been updated accordingly. Version 21 of the RMP has also been submitted. In addition, the MAH took the opportunity to update Annex II.

1.7.3. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

1.7.4. Other conditions and requirements of the marketing authorisation

1.7.4.1. Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

1.7.5. Conditions or restrictions with regard to the safe and effective use of the medicinal product

1.7.5.1. Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

1.7.5.2. Additional risk minimisation measures

Prior to launch of Rinvoq in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The objective of the programme is to increase awareness of HCPs and patients on the risks of serious and opportunistic infections including TB, herpes zoster, foetal malformation (pregnancy risk), MACE, VTE, malignancy, and GI perforation and how to manage these risks.

The MAH shall ensure that in each Member State where Rinvoq is marketed, all healthcare professionals and patients/carers who are expected to prescribe, dispense or use Rinvoq have access to/are provided with the following educational package:

The physician educational material should contain:

- Guide for healthcare professionals
- Patient card

The Guide for healthcare professionals shall contain the following key elements:

- General introductory language that the HCP measure contains important information to assist the discussion with patients when prescribing upadacitinib. The brochure also informs on steps which can be taken to reduce a patient's risk for key safety aspects of upadacitinib.
- Indication and posology statements provided to reinforce in whom upadacitinib should be used
- Use in patients 65 years of age and older
    - Language to reinforce risks in these patients and use of the 15 mg dose
- Language for HCPs to inform patients of the importance of the patient card
- Risk of serious and opportunistic infections including TB
    - Language on the risk of infections during treatment with upadacitinib
    - Language on increased risk of serious infections in patients 65 years of age and older
    - Details on how to reduce the risk of infection with specific clinical measures (what laboratory parameters should be used to initiate upadacitinib, screening for tuberculosis (TB), and getting patients immunised as per local guidelines, and interruption of upadacitinib if an infection develops)
    - Language on contraindication in patients with active TB and on consideration of anti-TB therapy in patients with latent TB
    - Language on avoidance of live vaccines (i.e., Zostavax) prior to and during upadacitinib treatment
    - Details to advise patients on signs/symptoms of infection to be aware of, so that patients can seek medical attention quickly.
- Risk of herpes zoster
    - Language on the risk of herpes zoster during treatment with upadacitinib
    - Details to advise patients on signs/symptoms of infection to be aware of, so that patients can seek medical attention quickly.
- Risk of foetal malformation
    - Language on teratogenicity of upadacitinib in animals
    - Details on how to reduce the risk of exposure during pregnancy for female patients of childbearing potential based on the following: upadacitinib is contraindicated during pregnancy, female patients of childbearing potential should be advised to use effective contraception both during treatment and for 4 weeks after the final dose of upadacitinib treatment, and to advise patients to inform their HCP immediately if they think they could be pregnant or if pregnancy is confirmed.
- Risk of MACE

    - Reminder that in patients at high risk for MACE upadacitinib should only be used if no suitable treatment alternatives are available, with examples of who may be at high risk.
    - Language on the risk of hyperlipidaemia during upadacitinib therapy
    - Details on monitoring of lipid levels and management of elevated lipid levels per clinical guidelines
- Risk of VTE
    - Examples of the risk factors which may put a patient at higher risk for venous thromboembolic event (VTE) and in whom caution is needed when using upadacitinib.
    - Use of caution in patients at high risk during treatment with upadacitinib
    - Language that patients should be periodically reevaluated for changes in VTE risk
    - Language on need for discontinuation of upadacitinib, evaluation, and appropriate treatment for VTE if clinical features of deep venous thrombosis or pulmonary embolism develop
- Risk of Malignancy
    - In patients at high risk for malignancy upadacitinib should only be used if no suitable treatment alternatives are available, with examples of who may be at high risk.
    - Reminder about the need for periodic skin examination for patients.
    - Risk of gastrointestinal perforation
    - Upadacitinib should be used with caution in patients at risk for gastrointestinal perforation with examples of those who may be at risk.
    - Reminder that patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of diverticulitis or gastrointestinal perforation.

Information for upadacitinib use in moderate to severe AD

- Language on dose-dependent increase in serious infections and herpes zoster with upadacitinib.
- Language on dose-dependent increase in NMSC and malignancy
- Language on dose-dependent increase in plasma lipids with upadacitinib.
- Language that the 30 mg dose is not recommended in certain populations (patients with severe renal impairment and patients taking strong CYP3A4 inhibitors).
- Language to reinforce that the lowest effective dose of upadacitinib should be used for treatment.

Information for upadacitinib use in moderate to severe ulcerative colitis (UC) or Crohn's disease (CD)

- Reminder to review induction and maintenance dosing in product labeling.
- Language on dose-dependent increase in serious infections and herpes zoster with upadacitinib

- Language on dose-dependent increase in NMSC and malignancy
- Reminder about induction and maintenance dose in certain populations (patients taking strong CYP3A4 inhibitors and severe renal impairment).
- Language to reinforce that the lowest effective dose of upadacitinib should be used for maintenance treatment

Upadacitinib use in paediatric patients (children from 2 years and adolescents)

- Reminder that live, attenuated vaccines (ie. varicella, MMR, BCG) which depending on local guidelines may be considered in paediatric patients. Language not to administer these vaccines immediately prior to or during upadacitinib treatment.
- Language to remind paediatric patients of the potential pregnancy risks and on the appropriate use of effective contraception.
- Language that if their paediatric patient has not experienced menarche, to inform their paediatric patient or caregiver to let them know when they do.

Instructions on where to report AEs will be included.
Instructions for how to access digital HCP information will be included, if applicable.

The patient information pack should contain:

- Package leaflet
- A patient card

- **The patient card** shall contain the following key messages:
  - Contact details of the upadacitinib prescriber
  - Language that the patient card should be carried by the patient at any time and to share it with HCPs involved in their care (i.e., non-upadacitinib prescribers, emergency room HCPs, etc.)
  - Description of signs/symptoms of infections the patient needs to be aware of, so that they can seek attention from their HCP:
    - Language to advise patients and their HCPs about the risk of live vaccinations when given during upadacitinib therapy. Examples of live vaccines are provided.
    - Language to advise patients to tell their HCP if they have history or have been in contact with TB.
  - Description of targeted risks for awareness by the patient and for HCPs involved in their care including:
    - Risk of heart disease - Description of signs/symptoms of heart disease that the patient needs to be aware of, so that they can seek attention from their HCP
    - Reminder to use contraception, that upadacitinib is contraindicated during pregnancy, and to notify their HCPs if they become pregnant while taking upadacitinib
  - Reminder to inform their HCP if a child has her first menstrual period while taking upadacitinib
  - Description of signs/symptoms of deep venous thrombosis or pulmonary embolism which the patient needs to be aware of, so that they can seek attention from an HCP

- Reminder of the risk of cancer. Regarding skin cancer reminder to let their doctor know if they notice any new growth on the skin.
- Risk of a hole in the bowel – description of signs/symptoms which the patient needs to be aware of, so that they can seek attention from an HCP

1.7.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

2. Introduction

Therapeutic Context

JIA is a chronic, severe disease with a global incidence estimated of 7.8/100,000 and a prevalence of 20.5/100,000 for children under 16 years of age.

The current ILAR classification identifies 7 disease types: systemic arthritis, oligoarthritis, polyarthritis/RF negative, polyarthritis/RF positive, JPsA, ERA, and undifferentiated arthritis. The classification is based on the number of joints affected, the presence of specific serologic findings, and systemic manifestations of disease in the first 6 months of diagnosis, supported by distinct genetic risk factors and pathogenesis. pcJIA is defined as arthritis of unknown aetiology that begins before 16 years of age, persists for at least 6 weeks, and affects 5 or more joints during the course of the disease. pcJIA accounts for about 30% of all JIA cases. Substantial functional impairment, risk of growth disturbances, joint deformity, and long-term disability are seen across JIA subtypes, including pcJIA. Typical symptoms include limping, stiffness when awakening, reluctance to use limbs, reduced activity level, joint swelling, and difficulty with fine motor activities.

Currently, there is no cure for JIA. The primary target for treatment of patients with JIA is clinical remission, with LDA as an alternative target, particularly in patients with long-standing disease. Per current treatment guidelines, MTX is recommended as the first-line treatment for pcJIA, with NSAIDs and intra-articular GCs recommended as adjunctive therapies. Long-term oral GCs are not recommended due to adverse effects, including growth suppression in children. Adverse effects of MTX, particularly GI intolerance, are limiting for some children. In patients who continue to have active disease despite MTX therapy, the addition of a bDMARD is recommended.

The introduction of biological therapies (TNFα inhibitors, CTLA4-IG, IL-6 receptor inhibitors) has represented a significant advance in therapy for pcJIA. Efficacy of TNFα inhibitors for pcJIA has been demonstrated for multiple agents in the class, including adalimumab, infliximab, golimumab, and etanercept, with ACR Paediatric 30 response rates ranging between 64 to 89% at 12 to 16 weeks. IL-6 receptor blockade, a mechanism relevant to the mechanism of action of upadacitinib, is also effective in children with pcJIA and in adults with RA. Another IL-6 inhibitor, sarilumab, was recently approved for pcJIA in the US and EU. Among JAK inhibitors, tofacitinib was approved by the EMA in 2021 for the treatment of children and adolescents 2 years of age and older with pcJIA. The approval was based on one Phase 3 randomised, double-blind withdrawal study in subjects aged 2 to < 18 years with pcJIA, JPsA, or ERA. Efficacy was demonstrated for tofacitinib treatment in 184 subjects with pcJIA; 77% of subjects achieved ACR Paediatric 30 response at Week 18 during the open-label run-in phase and were eligible for randomized withdrawal. During the randomised withdrawal phase up to Week 44, 29% of subjects experienced a JIA flare on tofacitinib versus 53% on placebo. At Week 44, 18% of subjects who received tofacitinib achieved inactive disease. Safety events observed with tofacitinib treatment during this study were similar to those observed in adults with RA. Another JAK inhibitor, baricitinib, was evaluated in a Phase 3 randomised, double-blind withdrawal study in subjects 2 to < 18 years with extended oligo-JIA or polyarticular JIA, ERA, or JPsA. The study demonstrated ACR Paediatric 30 response rates of 76.3% at Week 12 of the open-label lead-in period across JIA subtypes. During the 34-week randomised withdrawal period, significantly reduced time to and frequency of flares in the baricitinib group versus placebo were observed (incidence of flares was 17.1% versus 50.6%). In addition, 23% of subjects receiving baricitinib demonstrated inactive disease. Safety findings were consistent with the known safety profile of baricitinib in adult RA. The study supported the approval of baricitinib in the EU in 2023. Despite the availability of effective treatments, many patients still do not achieve clinical remission or low disease activity (LDA) and some develop intolerance or lose response

over time. In an analysis of long-term studies, less than half (11 to 47%) of patients were in clinical remission off medication in adulthood. While there has been significant progress in therapy for JIA, there is still an unmet need for additional effective and well-tolerated therapy options to treat JIA, including oral formulations, which is the preferred route of administration in the paediatric population.

2.1. Aspects of development

With this application, the applicant is seeking to extend the clinical indications for Rinvoq to include polyarticular course juvenile idiopathic arthritis (pcJIA) and to register a new oral solution providing upadacitinib 1 mg/mL.

The clinical development plan for the pcJIA indication follows the upadacitinib PIP for the condition of chronic idiopathic arthritis (P/0354/2024). In July 2021, the EMA PDCO agreed to a modification that removed a Phase 3 study from the PIP and included an additional safety cohort to PIP Study 4 (Study M15-340), an open-label, multiple-dose study to evaluate the PK, safety, and tolerability of upadacitinib in paediatric subjects with pcJIA. The EMA PDCO agreed that extrapolation of efficacy from adult RA studies to pcJIA in lieu of the Phase 3 study, was appropriate given that safety would be further supported by the additional safety cohort in Study M15-340 and the upadacitinib paediatric AD clinical development programme.

Hence, this application includes an efficacy extrapolation approach combined with PK and safety data from Study M15-340 and additional safety data from AD studies. The efficacy extrapolation approach, in lieu of a Phase 3 clinical study in pcJIA is based on the 3 key criteria: 1) similarity of disease progression between children with pcJIA and adults with RA; 2) similar response to treatment intervention; and 3) a similar exposure-response or concentration-response relationship that is predictive of the clinical response.

2.2. Description of the product

Upadacitinib (Rinvoq) is a selective and reversible inhibitor of JAK. Since its initial approval for the treatment of adults with RA in 2019, upadacitinib has been approved for the treatment of adults with active AS, nr-axSpA, PsA, UC, CD, GCA and adults and adolescents with AD in the EU. Rinvoq was approved by the US FDA in 2024 for the treatment of patients 2 years of age and older with pcJIA (limited to RF-negative polyarticular and RF-positive polyarticular JIA).

With this application, the applicant souhgt to extend the clinical indications for Rinvoq to include polyarticular course juvenile idiopathic arthritis (pcJIA) and to register a new oral solution providing upadacitinib 1 mg/mL.

The initially proposed indication was as follows: *Rinvoq is indicated for the treatment of active polyarticular course juvenile idiopathic arthritis in patients 2 years of age and older. Rinvoq may be used as monotherapy or in combination with methotrexate.*

The proposed posology was weight based, as follows:

Patient weight	**Dosing regimen**
10 to < 20 kg	3 mg (3 ml oral solution) twice daily
20 to < 30 kg	4 mg (4 ml oral solution) twice daily
≥ 30 kg	6 mg (6 ml oral solution) twice daily or 15 mg (one 15 mg tablet) once daily

3. Quality aspects

Introduction

Upadacitinib is currently available as prolonged-release tablets in three strengths (15 mg, 30 mg, 45 mg). The oral solution has been developed for paediatric use, for patients who are unable to swallow tablets and to allow dose flexibility based on body weight.

The finished product is presented as an oral solution containing upadacitinib hemihydrate, equivalent to 1 mg/ml of anhydrous upadacitinib, as active substance.

Other ingredients are citric acid, sodium benzoate, sodium citrate dihydrate, sucralose and purified water.

The product is available in high density polyethylene (HDPE) bottles with child-resistant polypropylene caps with polyethylene foam liner.

A low-density polyethylene (LDPE) press-in bottle adapter and a 10 ml polypropylene/HPDE graduated oral dosing syringe is co-packaged in an outer carton.

3.1. Active substance

No new information is provided by the applicant for this line extension application. Upadacitinib hemihydrate is a known active substance (AS). It is confirmed by the applicant that there are no differences in the Module 3 active substance documentation for the new pharmaceutical form compared to that used for the current strengths of the Rinvoq prolonged release tablets. This is acceptable.

3.2. Finished medicinal product

3.2.1. Description of the product and pharmaceutical development

3.2.1.1. Description of the product

The finished product (FP) is a multidose oral solution containing upadacitinib 1 mg/ml as free base

(equivalent to 1.02 mg upadacitinib hemihydrate). The solution appears as clear, colourless to light yellow solution, with a pH of 3.0 - 3.8.

The FP is supplied in 200 ml high density polyethylene (HDPE) bottles with child-resistant polypropylene caps with foam liner and tamper-evident rings.

A low density polyethylene (LDPE) press-in bottle adapter and a 10 ml polypropylene/HPDE graduated oral dosing syringe is co-packaged in a carton. The carton is closed with a tamper-evident seal.

The bottle is filled with sufficient amount of content (200 ml) to ensure that the labelled amount of 180 ml oral solution can be withdrawn.

3.2.1.2. Pharmaceutical development

Upadacitinib is currently available as prolonged-release tablets in three strengths (15 mg, 30 mg, 45 mg). An oral solution has been developed for paediatric use in patients 2 years of age and older. The excipients used are known and well-established for use in oral solutions. The choice and quantity of excipients have been discussed and justified.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The need to preserve a paediatric preparation and the choice of the preservative system at the lowest concentration feasible has been justified in terms of benefit-risk balance. The appropriateness of the sodium benzoate as preservative for the target age group(s) has been discussed. It is also well known that there may be an interaction between sodium benzoate and HDPE leading to its uptake (adsorption) into the container wall. The decrease of sodium benzoate during shelf-life is thus due to absorption and not degradation leading to the need to add more sodium benzoate to the formulation to compensate for this loss. The acceptable daily intake (ADI) of benzoic acid and its salts is up to 5 mg/kg for adults and children over 4 weeks old (Committee for Human Medicinal Products (CHMP), Benzyl alcohol and benzoic acid group used as excipients, EMA/CHMP/272866/2013, 2017). Considering the ADI of sodium benzoate, the proposed level to be used in the formulation is judged acceptable. The highest potential exposure of sodium benzoate from upadacitinib oral solution is 0.54 mg/kg.

The rationale for the use of a sweetening agent in a paediatric preparation has been described and justified. A sweetening agent is required in the formulation to mask the inherently bitter taste of the AS, thereby improving palatability and compliance, particularly within paediatric populations who are more sensitive to taste. The European Food Safety Authority (EFSA) has established an Acceptable Daily Intake (ADI) of 15 mg/kg body weight per day for sucralose, as reaffirmed in the EFSA re-evaluation published on 16 February 2026. Calculations across recommended dosing regimens and paediatric body weights confirm that daily exposure is well below the established ADI thresholds, with a margin of safety maintained (e.g., safety factor of 2.8 for the worst-case scenario for a 10 kg patient group).

The bioavailability of upadacitinib immediate release oral solution relative to the 15 mg extended-release formulation was compared in healthy adult subjects in study M16-552. Based on this study, the bioavailability of upadacitinib extended-release tablet formulation is estimated to be 68% relative to the oral immediate release oral formulation.

The differences in the amount of individual excipients between all four immediate-release oral solution formulations (F0, F1, S1, and the proposed commercial F2) are minor relative to the total content in the formulation and none of the excipients are expected to affect gastrointestinal motility or absorption of upadacitinib from the gastrointestinal tract. Upadacitinib is already dissolved in the oral solution formulations and has high solubility and high permeability at clinically relevant doses. The applicant's justification that the four oral solution formulations can be considered bioequivalent to one another is endorsed.

The development of the manufacturing process is brief but acceptable. Relevant parameters for the pharmaceutical form were investigated and there is previous in-house experience with oral solution dosage form. Due to its high solubility at the proposed pH range, upadacitinib readily goes into solution.

The following quality attributes were identified as the focal points for development: (1) upadacitinib assay, (2) sodium benzoate assay, (3) degradation products, (4) microbial quality, (5) appearance, (6) pH, and (7) deliverable volume; no objections are raised on the choice or rationale for selecting them.

No design space is proposed.

No concerns are identified with respect to the information on the container closure system provided in P.2.4. See P.7 and P.8 for further details on packaging as well as stability and storage. Compatibility of the product with the co-packed press in bottle adaptor (PIBA) and oral dosing syringe has been evaluated.

The microbial purity acceptance criteria and test methods applied during release and stability testing are in accordance with Ph. Eur. 5.1.4 for an oral solution dosage form.

Preservative efficacy testing has been performed and from a microbiological point of view the preservative system has been justified.

3.2.2. Manufacture of the product and process controls

3.2.2.1. Manufacture

The manufacturing and batch release sites of the FP are presented in the dossier. Satisfactory evidence of GMP compliance has been provided for all sites involved in the manufacture, control and batch release of the finished product. The manufacturing process for upadacitinib oral solution can be divided into three separate steps. These are: (1) mixing I, (2) mixing II, and (3) packaging. The process is described in a narrative, including where in process controls are performed, and further illustrated in a flow-diagram.The bulk solution may be held for a maximum of 6 days prior to primary packaging (filling into bottles). The hold time was established based on appropriate studies on batches manufactured at commercial scale.

The development of the manufacturing process is adequately described, including scale-up investigations and process optimisation and robustness demonstration.

Process controls

The in-process controls defined in P.3.4 and the holding time of the bulk solution corresponds to those described in P.3.3 and the discussion of the manufacturing process development in P.2.

No enhanced manufacturing approaches are requested.

No concerns have been identified with respect to the control strategy.

Process validation / verification

The manufacturing process is considered a standard process for an immediate-release oral solution dosage form. The manufacturing process of three consecutive commercial batches has been validated and results from validation has been presented during the procedure. The validation demonstrates the process capability of consistently manufacturing the FP in compliance with the predefined acceptance criteria.

3.2.3. Product specification

3.2.3.1. Specifications

The finished product specifications are proposed for release and stability and include appropriate tests for this kind of dosage form including: appearance (visual), clarity and colour (Ph. Eur.), identification of upadacitinib (HPLC, UV), assay (HPLC), assay of sodium benzoate (HPLC), degradation products (HPLC), pH (Ph. Eur.), microbial quality (Ph. Eur.) and deliverable volume.

The proposed analytical procedures and corresponding specification limits are adequate for routine control of the finished product at release and shelf life. They are in line with ICH guidelines and Ph. Eur., and batch release data and stability data.

The justifications for description, pH, identity (upadacitinib and sodium benzoate), deliverable volume and microbiological examination are accepted without additional comments.

There is no meaningful trend in decrease of assay values during the long term or accelerated stability studies of the primary stability batches. Hence, the initially proposed widening of the assay limit during shelf-life was not considered acceptably justified. The applicant has agreed to keep the 95.0 to 105.0% assay release limit throughout the shelf-life.

For degradation products the proposed limits are in line with ICH Q3B, considering a maximum daily dose of 45 mg, the ICH Q3B impurity thresholds are as follows: Report: 0.1 %; identify 0.2 %; qualify 0.44 %. Limits in line with ICH Q3B are acceptable.

The release and shelf-life acceptance criteria for sodium benzoate are based on antimicrobial effectiveness testing (AET) that has been assessed in section P.2 Pharmaceutical development.

During pharmaceutical development dose accuracy using the proposed oral dosing syringe was tested per EP 2.9.27, and the results met the acceptance criteria. The omission of a test in the finished product specification is judged acceptable.

An elemental impurities risk assessment has conducted. It is concluded that no additional elemental impurity controls beyond the proposed specifications and quality standards are necessary to ensure the PDEs are not exceeded.

Since this application concern a new dosage form and hence a new type of manufacturing process and different excipients, a new nitrosamine risk assessment concerning the potential presence of nitrosamine impurities in the finished product was performed according to the applicable guidance.

The formation of two potential nitrosamine impurities has been identified. ”Stage 5 nitrosamine” and NDMA. For doses up to 36 mg/day, the risk assessment did not identify any risk of nitrosamine introduction or formation of the Stage 5 Nitrosamine above the 2.43 µg/day AI or the introduction or formation of NDMA above the 0.096 µg/day AI.
Confirmatory testing using validated methods was performed for Stage 5 Nitrosamine and NDMA on three primary stability batches stored at 30 °C/35% RH for 36 months. The results demonstrate that the nitrosamine impurities were not detected, which is below 10% of the respective acceptable intake limits of 2.43 and 0.096 µg/day, respectively. Based on the information provided, there is no risk of nitrosamine impurities in the finished product. Therefore, no specific control measures are deemed necessary.Analytical procedures and reference standards

The analytical procedures used to control the drug product have been described in sufficient detail. No issues raised with respect to analytical procedure validations. The reference standards and materials are accepted as currently described.

No real time release testing is proposed.

Batch analysis

Batch analysis data for 11 batches manufactured using the commercial formulation at the proposed site of commercial manufacture. One of the batches was packaged in amber glass bottles. The remaining ten were packaged in 200 ml HDPE bottles as proposed for commercial packaging. All batches were manufactured at the manufacturing site proposed for commercial manufacture.
All batches met the proposed commercial specification. The results indicate acceptable consistency between batches.

Container closure

The primary container-closure system for Rinvoq Oral Solution is a 200 ml white high-density polyethylene (HDPE) bottle with a child-resistant polypropylene cap and tamper evident ring with a polyethylene foam liner.

Specifications were provided, together with drawings. The specifications are adequately drawn up; It is stated that the container-closure is child-protective; supplier statement confirm that the caps comply with ISO 8317 for re-closable packaging and 16 CFR 1700.20 for child resistance.

The FP is co-packaged in a secondary carton with one 10 ml oral dosing syringe and one low-density polyethylene press-in bottle adapter (PIBA).

The Declaration of Conformity for the PIBA (self-certification as compliant with Regulation (EU) 2017/745) and the EU MDR certification for the oral dosing syringe are provided in 3.2.R Regional Information.

Dose accuracy testing as per EP 2.9.27, using the oral dosing syringe with Upadacitinib oral solution, has been performed during pharmaceutical development and the results met the acceptance criteria.

3.2.4. Stability of the product

A shelf-life of 3 years without temperature restrictions is proposed and judged acceptable. The bottle should be kept in the outer carton to protect from light. In-use stability for up to 60 days has been confirmed.

The proposed shelf-life is based on long-term stability data for three primary stability batches stored at 5 °C ± 3 °C and 30 °C/35% RH for up to 36-months and accelerated stability data at 40 °C/20% RH for up to 6-months. The finished product is an aqueous product packaged in a semi-permeable packaging. As described in Guideline on Stability Testing: Stability testing of existing active substances and related finished products, EMA/CVMP/QWP/709423/2022,Corr.1**, 13 July 2023, the long term and accelerated stability study has been carried out under conditions of low relative humidity to confirm that the finished product can withstand low relative humidity environments.

Except for the sodium benzoate assay, no significant changes in any results, including upadacitinib assay, appearance, colour, clarity, and pH, were observed at the long-term storage conditions at 5 °C and at 30 °C/ 35%RH. Although a slight decrease in sodium benzoate was observed, the result is within the specification and the sodium benzoate assay level is expected to remain within specification throughout the proposed shelf-life. Upadacitinib oral solution also has demonstrated stability at 40 °C/ 20%RH for 6-months. All results from these batches have met the acceptance criteria for all tests performed at the available time points.

A decrease in sodium benzoate assay has been observed for samples stored at 5 °C, 30 °C/35% RH, and 40 °C/ 20% RH. The observed change has been attributed to adsorption into the HDPE bottle and not to degradation. AET testing has demonstrated the minimum concentration of sodium benzoate required to ensure microbial quality.

The data from the temperature excursion studies support temperature excursions up to 50 °C for 0.5 months and at 20 °C for up to 2 weeks. In addition, an in-use period of 60 days after first opening of the bottle is supported by available data. The data from the in-use stability studies simulating the dose administration based on the Instruction for Use (IFU) over 60 days after opening the bottle demonstrated no meaningful changes in drug product quality attributes (appearance, assay, degradation products, pH, and microbial quality) after 12, 24 and 36 months storage at 30°C/ 35%RH. The FP remained stable for at least 60 days at 30 °C/ 35%RH after opening of the bottle and daily dose removal per the IFU for product stored at 30 °C/ 35%RH for 36 months.

In the pharmaceutical development section data from an in-use stability study in the syringe demonstrated that the product is stable for 24 hours at ambient conditions.

Overall, the stability results justify the proposed shelf life of 3 years without special storage conditions, and keeping the bottle in the outer carton in order to protect from light, and also the in-use shelf life of 60 days after first opening as stated in the SmPC (sections 6.3 and 6.4).

3.2.5. Post-approval change management protocol(s)

Not applicable.

3.2.6. Adventitious agents

There are no excipients of human or animal origin used in the manufacture of the drug product.

3.3. Discussion and conclusions on chemical, pharmaceutical and biological aspects

No new information has been provided for the new active substance. It was confirmed that there are no differences for the new pharmaceutical form compared to that used for the already authorised product. Information on development, manufacture and control of the finished product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

3.4. Recommendation(s) for future quality development

Not applicable.

4. Non-clinical aspects

Introduction

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP. A brief summary from the EPAR for Rinvoq is given below.

4.1. Pharmacology

4.1.1. Pharmacodynamics

4.1.1.1. Primary pharmacodynamics

The primary pharmacodynamics programme of upadacitinib included *in vitro* cell free (biochemical) and cellular assays and *in vivo* studies in two rodent models of arthritis to determine potency and selectivity of upadacitinib. Specificity has been determined by evaluating upadacitinib against a panel of other kinases, ion channels, transporters and cell surface receptors. Janus Kinases (JAKs) are intracellular enzymes that transmit cytokine or growth factor signals involved in a broad range of cellular processes including inflammatory responses, hematopoiesis and immune surveillance. The JAK family of enzymes contains four members, JAK1, JAK2, JAK3 and TYK2 which work in pairs to phosphorylate and activate signal transducers and activators of transcription (STATs). This phosphorylation, in turn, modulates gene expression and cellular function. JAK1 is important in inflammatory cytokine signals while JAK2 is important for red blood cell maturation and JAK3 signals play a role in immune surveillance and lymphocyte function. Upadacitinib is a selective and reversible JAK inhibitor. In human cellular assays, upadacitinib preferentially inhibits signalling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2.

4.1.1.2. *Secondary pharmacodynamics*

Binding selectivity of upadacitinib against a panel of over 70 human protein kinases was investigated in a broad kinome selectivity screen. Of the kinases in the panel, six non-JAK kinases showed an IC_{50} below 5 µM, and two non-JAK kinases had IC50s equal to or below 1 µM (Rock1 at 1 µM and Rock2 at 0.42 µM). Thus, upadacitinib appears to be selective against a number of different non-JAK kinases and upadacitinib seems unlikely to interact with the tested kinases at clinically relevant exposures (C_{max} = 105 nM). Upadacitinib was profiled for its off-target activity against a broad panel of 79 different receptors, ion channels, enzymes and transporters. Upadacitinib (10 µM) did not affect control specific binding by greater than 50% at any of the different receptors, ion channels or transporters tested. The results indicate a low risk for off target activity with upadacitinib at therapeutic plasma concentrations (clinical Cmax = 105 nM).

4.1.1.3. *Safety Pharmacology*

Upadacitinib was assessed in a series of GLP compliant safety pharmacology studies *in vitro* and *in vivo*. Decrease in locomotor activity was observed in rats at highest dose of 100 mg/kg (C_{max} = 13.5 µg/mL). No respiratory effects were observed in rats at an exposure margin of 95-fold above clinical C_{max} (105 ng/mL). A thorough QT study has not been conducted in clinical trials. However, an exposure-response analysis stated that no QT interval prolongation at therapeutic or supratherapeutic

plasma exposures was observed in healthy subjects. From a non-clinical perspective, no further action was considered necessary with respect to safety pharmacology.

4.1.2. Pharmacokinetics

4.1.2.1. Absorption

Upadacitinib displays rapid absorption after a single oral dose, with T_{max} in plasma ranging from 1 to 2 h in rats, dogs and monkeys. The pharmacokinetics was further characterized by high to moderate plasma clearance in rat and dog, respectively, and high volume of distribution across all species. There was evidence of only limited decrease or accumulation (<2-fold) following multiple daily oral dosing in mice, rats, rabbits and dogs, which is in line with human data.

4.1.2.2. *Distribution*

The in vivo tissue distribution in rat showed that upadacitinib related radioactivity was distributed rapidly into most tissues through 4 hr post-dose, with the liver, uveal tract and adrenal gland having the highest exposure. Lowest exposure was found in the CNS, spinal cord and eye lens. Radioactivity was present in the uveal tract through 192 hours post-dose and a slower clearance in pigmented skin indicating an apparent affinity for melanin. Placental transfer and subsequent foetal exposure to [14C]-upadacitinib-related radioactivity occurred at moderate to low levels. Exposure of [14C]-upadacitinib related radioactivity was approximately 31-fold greater in milk than in plasma. Plasma protein binding of upadacitinib was low in all species (fu ranged from 0.41 in rat to 0.69 in dog) and independent of test concentration.

4.1.2.3. Metabolism

Biotransformation of upadacitinib in non-clinical species (mouse, rat, rabbit, dog) and human was, in general, low and unchanged parent was the primary drug-related component in dog (~88%) and in human (~79%) plasma, whereas unchanged parent represented about 56% of drug-related material in rats. In human plasma, the M4 metabolite was found to be a major metabolite, which was detected as a minor metabolite in rats and dogs. M4 is a Phase II conjugate, a normally non-reactive acyl glucuronide. All human metabolites, including the major metabolite M4, were observed in one or more animal species.

4.1.2.4. *Excretion*

Majority of upadacitinib is excreted as intact in the all species (61% in rats, 56% in dogs). Mass balance data were obtained from rats, dogs and humans. Overall, the results indicate that elimination pathways for upadacitinib in non-clinical species and humans are similar; the majority of absorbed drug-related radioactivity being eliminated by excretion into biliary/faecal or renal routes whereas hepatic metabolism plays a secondary role.

4.2. Toxicology

4.2.1. Repeat-dose toxicology

Upadacitinib was evaluated in repeat-dose toxicity studies in mice (4 weeks with no recovery), rats (4 weeks with 4 weeks recovery, and 26 weeks with no recovery), and dogs (4 weeks with 4 weeks recovery, and 39 weeks with no recovery). The main organs affected in the repeat-dose toxicity studies were primarily those related to JAK inhibition, that is the haematopoietic and immune system. Upadacitinib was not tolerated in mice and rats at high doses, with large exposure margins to patients. The mortalities were considered of limited clinical relevance although the observed microscopic findings were also observed in lower dose groups, but of a lesser magnitude. In all the repeat-dose toxicity studies, effects consistent with the inhibition of JAK1/3 were observed. The findings included decreases in circulating lymphocytes and lymphoid depletion in spleen, thymus, and lymph nodes. Effects consistent with JAK2 inhibition such as decreases in red blood cell parameters [red blood cells, haemoglobin, and haematocrit] and reticulocytes were observed in rats and dogs. Due to the potent pharmacological effect of upadacitinib on lymphoid tissue and subsequent secondary effects, it is not unexpected that the margin of exposure for these effects is relatively low in relation to the therapeutic doses of upadacitinib to be used in patients. However, reversible changes in haematological parameters associated with JAK inhibition generally occur earlier and at lower doses than the kidney and/or liver effects observed in the toxicological studies.

4.2.2. Genotoxicity

Upadacitinib was not mutagenic or genotoxic based on the results of *in vitro* and *in vivo* tests for gene mutations and chromosomal aberration. The exposure in the in vivo chromosomal aberration study was considered sufficient (up to 127 times the clinical based on C_{max}, and approximately 46 times on AUC for the highest dose tested).

4.2.3. Carcinogenicity

Upadacitinib, at exposures (based on AUC) approximately 4 and 10 times the clinical dose of 15 mg was not carcinogenic in a 2-year carcinogenicity study in Sprague-Dawley rats. Upadacitinib was not carcinogenic in a 26-week carcinogenicity study in CByB6F1-Tg (HRAS)2Jic transgenic mice. There was no test article related unscheduled deaths or differences in mortality in any of the studies. No neoplastic findings were identified following upadacitinib treatment.

4.2.4. Reproduction and developmental toxicity

Fertility and early embryonic development
Upadacitinib had no effect on fertility in male or female rats at doses up to 50 mg/kg/day in males and 75 mg/kg/day in females in a fertility and early embryonic development study.

Embryo-foetal development
Two embryo-foetal development studies were conducted in rats. In the first study, the animals were administered 0, 5, 25, and 75 mg/kg/day and since it was not possible to determine a NOAEL for the observed teratogenicity another study with lower doses (0, 1.5, and 4 mg/kg) was conducted. There were no observed treatment related effects on implantation sites, viable foetuses, resorption sites or litter size. The foetal body weight was slightly reduced in both male and female foetuses from dams administered 75 mg/kg/day upadacitinib. An increased number of skeletal malformations was observed

in all treatment groups, percent foetuses in the 0, 5, 25, and 75 mg/kg/day groups were 0, 1.4, 8, and 35. The skeletal malformations included misshapen humerus and bent scapula, bent, misshapen or shortened long bones of the fore- and hind limbs. In the second EFD study in rat with lower doses of upadacitinib, skeletal malformations were observed in one foetus in the 4 mg/kg group. Since these malformations were similar as the ones observed in the previous study, they were considered test-article-related. The NOAEL for developmental toxicity was the lowest dose, 1.5 mg/kg/day. The exposure in the dams at gestational day 16 was at this dose 115 ng*hr/mL, which represents 0.27 of the exposure observed in humans. The embryo-foetal development study in rabbits was conducted at 0, 2.5, 10, and 25 mg/kg. In the rabbits, an increase in post-implantation loss was observed (0%, 4.1%, 2.6%, 14.8% in the groups 0, 2.5, 10, and 25 mg/kg/day). There was no apparent increase of skeletal malformations, but an increased incidence of cardiac malformations was observed at 25 mg/kg/day. The NOAEL was considered 10 mg/kg/day and the exposure (AUC_{0-24}) at gestational day 18 was 881 ng*hr/mL, which represents approximately two-fold the exposure than observed in adult patients and 2.6-fold in paediatric patients (10 to < 20 kg).

Post and prenatal development
The potential effects of upadacitinib on development, growth, behaviour, reproductive performance and fertility of F1 generation were evaluated in rats after administration of 0, 2.5, 5, and 10 mg/kg/day to F0 females from gestation day 6 through day 20 post-partum. In the study, only F0 dams were administered upadacitinib. The exposure in the pups was not measured in the study. In the previous EFD study it was however shown that the foetuses were exposed to upadacitinib (foetal/dam ratio at 10 mg/kg/day was 0.003). Furthermore, in a study with radiolabelled upadacitinib it was shown that upadacitinib readily transferred to milk in pregnant rats (presented in the section on pharmacokinetics). Thus, it is likely that also the pups were exposed to upadacitinib. There were no treatment related effects on the F0 generation, including effects on parturition, lactation and maternal behaviour. There were no treatment related effects on the F1 generation in any of the investigated parameters, including viability, body weight, sexual maturation, behavioural testing (acoustic startle habituation, motor activity, and M-shaped water maze), or reproductive endpoints. The NOAEL for maternal systemic toxicity and F1 development was considered to be 10 mg/kg/day. This corresponds to an exposure margin of 2.6 fold on AUC and compared to AUC in adult patients with 15 mg/day and and 3.3-fold AUC in paediatric patients (10 to < 20 kg) with 3 mg twice daily.

Juvenile toxicity
In the non-GLP dose-finding study, doses ≥ 100 mg/kg/day resulted in mortality and clinical signs. In a main GLP study with juvenile Sprague-Dawley rats, dose once daily up to 50 mg/kg/day from PND 15 through PND 63, accelerated pharmacologic effects on the lymphoid system and exposures similar to those observed in adult rats were evident. A TDAR assay within this study indicated that upadacitinib suppressed a Keyhole Limpet Hemocyanin (KLH)-specific primary IgM and IgG antibody concentrations when administered to juvenile rats from PND 15 through PND 59. This effect was comparable to that of the positive control cyclophosphamide A. Dose-dependent decrease in total T cells, T helper cells, T cytotoxic cells, B cells, NK cells and NKT cells at all doses was revealed by flow cytometric analysis. The NOAEL was set to 20 mg/kg/d resulting in a combined AUC_{0-24h} exposure of 3.71 µg·h/mL.

4.2.5. Ecotoxicity/environmental risk assessment

The Applicant has provided an environmental risk assessment (ERA) to include the new indication of pcJIA, however, no new data for the ERA were included with this application. The submitted ERA was updated from the original ERA submitted for the MAA for RA approval, and the updates of the indications of PsA, AS, AD, UC, nr-axSpA, CD and GCA.

In the original ERA the results of the Phase I assessment triggered a Phase II Tier A assessment and

the standard suite of fate and effect studies were completed. Upadacitinib is very persistent in sediment according to the OECD 308 study. A Phase II Tier B extended effects on water sediment was thus triggered.

Regarding the original ERA, the applicant submitted a final report an OECD TG107 study post-approval. The overall log Kow of the test substance was determined to be 1.81 (pH4), 2.50 (pH7), and 2.48 (pH9) at 25°C. The conclusion of the assessment was that the study report provided had an acceptable experimental design and fulfilled the quality/validation criteria and that the data was also included in the updated ERA in a satisfactory manner.

Phase I

The maximum daily dose for the indication pcJIA is 15 mg/day, resulting in PEC_{SW} value of 0.075 µg/L, for each of the indications of RA, PsA, AS, nr-axSpA and GCA with the maximum daily dose of 15 mg/day, the PEC_{SW} values was 0.075 µg/L, for the indication AD with the maximum daily dose of 15 mg/day, the PEC_{SW} values was 0.15µg/L and for the indications UC and UC with the maximum daily dose of 45 mg/day, the $PEC_{SURFACEWATER}$ values was 0.225 µg/L, when using the default Fpen value of 0.01.

A $PEC_{SW\text{-}TOTAL}$ was calculated (1.05 µg/L) and was used to re-calculate the Phase II Tier A and Tier B PEC/PNEC ratios.

The Log Pow and Log D were 2.50 (pH 7) using the shake flask method (OECD 107). Since the values were below the criteria of 3 no PBT assessment was needed.

Phase II

For this application, the same PNEC values were presented as for the original ERA submitted for the MAA. In the table below the updated PEC/PNEC ratios are presented, based on the PEC value obtained for all nine indications. These ratios remain far below 0.1, and the conclusion remains: The clinical use of upadacitinib is not expected to be a risk for the environment.

The PEC values in relevant environmental compartments are compared to the PNEC values for these compartments by calculation of PEC/PNEC ratios.

Compartment	**PEC**	**PNEC**	**PEC/PNEC (action limit)**
Surface water	0.00105 mg/L	0.63 mg/L	0.017 (<1)
Groundwater	0.00026 mg/L	0.0063 mg/L	0.041 (<1)
Microorganism	0.0105 mg/L	100 mg/L	0.000105 (<1)

The PEC value in sediment (dry) was recalculated with the updated $PEC_{SURFACEWATER}$ and compared to the PNEC values for this compartment.

Compartment	**PEC**	**PNEC**	**PEC/PNEC (action limit)**
Sediment	1.19 mg/kg	15.6 mg/kg	0.076 (<1)

Table *1*: Summary table of main study results: Phase I

Substance (INN/Invented Name):	Upadacitinib		
CAS-number (if available):	2050057-56-0		
PBT/vPvB screening			
Study type	Test protocol	Result	Conclusion
Bioaccumulation potential-log Pow	OECD 107	1.81 *at pH 3* 2.50 *at pH 5* 2.48 *at pH 7*	Potential PBT: *N*
Phase I			
Parameter	**Value**	**Unit**	**Conclusion**
PEC_{sw}, default Fpen	1.05	µg/L	≥ 0.01 threshold: *Y*
Other concerns (e.g. chemical class)			N

Table 2: Summary table of main study results: Phase II

Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Result**	**Remarks**
Water solubility	OECD 105	203 ± 6.0 mg/L mg/L at 20 ± 1°C	
Dissociation in Water	OECD 112	$pK_{a,\ 1}$ = 4.7 ± 0.0 (base) $pK_{a,\ 2}$ = 12.8 ± 0.0 (acid)	
Adsorption-Desorption Soil 1 = Sandy Loam	OECD 106	 $K_{FOC,\ soil\ 1}$ = 5.58×10^3 L/kg	No trigger of terrestrial studies as <10000L/kg.
Soil 2 = Clay Loam		$K_{FOC,\ soil\ 2}$ = 1.18×10^4 L/kg	
Soil 3 = Loamy Sand		$K_{FOC,\ soil\ 3}$ = 2.31×10^4 L/kg	
Sludge 1 = ASS, Denton WWTP		$K_{FOC,\ sludge\ 1}$ = 118 L/kg_{oc}	
Sludge 2 = ASS, Easton WWTP		$K_{FOC,\ sludge\ 2}$ = 129 L/kg_{oc}	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems Sediment 1 = Brandywine Creek	OECD 308	$DT_{50,\ water\ 1}$ = 5.6d/12d $DT_{50,\ sediment\ 1}$ = 347d/741d $DT_{50,\ whole\ system\ 1}$ = 234d/499d CO_2 = 1.7 % NER_{total} = 98.7 % $NER_{type\ I}$ = 36.8%	20°C/12°C CO_2 and NER values at test end
Sediment 2 = Choptank River		$DT_{50,\ water\ 2}$ = 13d/28d $DT_{50,\ sediment\ 2}$ = 110d/235d $DT_{50,\ whole\ system\ 2}$ = 138d/295d CO_2 = % NER_{total} = 77.1% $NER_{type\ I}$ = 29.3%	20°C/12°C CO_2 and NER values at test end

Transformation products		>10% = Y TP1 (max) =7.6% DT_{50} TP1: 150d	sed. Brandywine Creek

Phase II Aquatic effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/Psuedokirchneriea subcapitata)	OECD 201	NOEC EC_{10}	31.3 36.7	mg/L	growth rate
Daphnia sp. Reproduction Test/ Daphnia magna	OECD 211	NOEC EC_{10}	1.6 3.09	mg/L	effect of on the survival, growth, and reproductive output
Fish, Pimephales promelas	OECD 210	NOEC EC_{10}	0.63 1.8	mg/L	effect on hatchability, time to hatch, fry survival, sublethal effects, and growth
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC EC_{10}	1000	mg/L	total respiration
Phase II Sediment effect studies					
Sediment Dwelling Organism Test/Chironomus riparius	OECD 218	NOEC EC_{10}	390 402	mg/kg_{dw}	o.c. content 2.5%

Risk characterisation				
Compartment	**PEC**	**PNEC**	**RQ**	**Conclusion**
Surface water	0.00105 mg/L	0.063 mg/L	0.017 (<1)	No risk
Groundwater	0.00026 mg/L	0.0063 mg/L	0.041 (<1)	No risk
Microorganism	0.0105 mg/L	100 mg/L	0.000105 (<1)	No risk
Sediment	1.19 mg/kg	15.6 mg/kg	0.076 (<1)	No risk

Considering the above data from Phase I and Phase II, upadacitinib is not expected to pose a risk to the environment.

4.3. Overall discussion and conclusions on non-clinical aspects

4.3.1. Discussion

The non-clinical aspects of upadacitinib were thoroughly evaluated during the original approval procedure for Rinvoq. No new non-clinical studies were submitted in support of the present application. This was acceptable to the CHMP.

The initial marketing authorisation concerned 15 mg daily dose in adults. This is an extension application for Rinvoq (upadacitinib) to include a new indication of pcJIA indication in juvenile patients aged 2 years and older at the maximum dose of 15 mg per day. Therefore, the safety margins have been updated for all studies relevant for the present indication of pcJIA in paediatric patients. There are no upadacitinib-related findings observed in juvenile animal studies that indicate a higher sensitivity of paediatric populations compared with adults.

4.3.2. Conclusions

No new non-clinical studies have been submitted. From a toxicological point of view, the non-clinical studies results submitted in the original marketing authorisation application covered adequately the extension of indication to paediatric patients in patients 2 years of age and older.

5. Clinical aspects

Introduction

This application includes an efficacy extrapolation approach combined with PK and safety data from Study M15-340 in paediatric patients with pcJIA and additional safety data from AD studies. The efficacy extrapolation approach is based on the 3 key criteria: 1) similarity of disease progression between children with pcJIA and adults with RA; 2) similar response to treatment intervention; and 3) a similar exposure-response or concentration-response relationship that is predictive of the clinical response.

5.1.1. GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Based on the review of clinical data, CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier.

5.1.2. Tabular overview of clinical trials

Table 3: Tabular overview of main clinical study

Type of Study	Study ID	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Enrolled	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK/ Safety	M16-049	To evaluate the PK, activity, safety and tolerability of multiple doses of upadacitinib in pediatric subjects with severe atopic dermatitis (Part 1 and Part 2). To evaluate the palatability of upadacitinib oral solution in pediatric subjects (Part 1 only).	Phase 1, multiple-dose, OL	Protocol Version 4.0: Low Dose (3 mg oral solution BID [10 to < 20 kg], 4 mg oral solution BID [20 to < 30 kg], 15 mg QD ER tablet or 6 mg BID oral solution if unable to swallow tablet [≥ 30 kg]), High Dose (6 mg BID oral solution [10 to < 20 kg], 8 mg BID oral solution [20 to < 30 kg], 30 mg QD ER Tablet or 12 mg BID oral solution [≥ 30 kg]) Prior to Protocol Version 4.0: Low Dose (1.6 mg BID oral solution [10 to < 15	35	Pediatric subjects age 2 to less than 12 years with severe AD	1-week OL treatment period in Part 1, 108-week OL treatment period in Part	Complete; Week 108 CSR Extension

				kg], 2mg BID oral solution [15 to < 25 kg], 7.5 mg ER tablet or 3 mg BID oral solution [25 to < 40 kg], 15 mg QD ER Tablet [≥ 40 kg]), High Dose (3.2 mg BID oral solution [10 to < 15 kg], 4 mg BID oral solution [15 to < 25 kg], 15 mg QD ER Tablet or 6 mg BID oral solution [25 to < 40 kg], 30 mg ED ER tablet [≥ 40 kg])				
PK/ Safety	M15-340	Part 1: To evaluate the PK, safety, and tolerability of multiple doses of upadacitinib in pediatric subjects with polyarticular course juvenile idiopathic arthritis (pcJIA). To evaluate the palatability of upadacitinib oral solution in pediatric subjects. Part 2: To evaluate the long-term safety and tolerability of upadacitinib in pediatric subjects with pcJIA who completed Part 1. Part 3: (Additional Safety Cohort): To evaluate the long-term safety and tolerability of upadacitinib in pediatric subjects with pcJIA. For Parts 1, 2, and 3: To evaluate descriptive efficacy of upadacitinib in pcJIA.	Phase 1, multiple-dose, OL	Upadacitinib, 7.5 mg tablet, oral (used in Protocol Version 1.0 to Protocol Version 7.0) Upadacitinib, 15 mg tablet, oral Upadacitinib, 30 mg tablet, oral (used in Protocol Version 1.0 to Protocol Version 8.0) Upadacitinib, 1 mg/mL (pH 2.9) solution, oral Upadacitinib, 1 mg/mL (pH 3.4) solution, oral Upadacitinib, 0.5 mg/mL (pH 3.8) solution, oral (used in Protocol Version 6.0 to Protocol Version 8.0)	122	Pediatric subjects ages 2 to less than 18 years with pcJIA	156-week open-label treatment period for Part 1/Part 2 and Part 3	Ongoing; Interim 2 Full CSR (up to Week 156)

Efficacy and Safety	M16-045	To assess the efficacy and safety of UPA for the treatment of adolescent and adult subjects with moderate to severe AD who are candidates for systemic therapy	Multicenter 2-period: 16-week randomized, DB, parallel-group, controlled treatment period followed by a long-term BE period up to Week 136	DB Period: 15 mg, 30 mg UPA or placebo QD, PO BE Period: 15 mg or 30 mg UPA QD, PO	847	Subjects ≥ 12 yrs. old and ≤ 75 yrs. 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	DB Period: 16 weeks BE Period: Up to Week 136	Ongoing; Interim Full CSR
Efficacy and Safety	M16-047	To assess the efficacy and safety of UPA combined with TCS for the treatment of adolescent and adult subjects with moderate to severe AD who are candidates for systemic therapy	Multicenter 2-period: 16-week randomized, DB, parallel-group, controlled treatment period followed by a long-term BE period up to Week 136	DB Period: 15 mg, 30 mg UPA or placebo QD, PO with TCS or TCI BE Period: 15 mg or 30 mg UPA QD, PO with TCS or TCI	901	Subjects ≥ 12 yrs. old and ≤ 75 yrs. old with a diagnosis of chronic AD who had an inadequate response to treatment with TCS or TCI	DB Period: 16 weeks BE Period: Up to Week 136	Ongoing; Interim Full CSR
Efficacy and Safety	M18-891	To assess the efficacy and safety of UPA for the treatment of adolescent and adult subjects with moderate to severe AD who are candidates for systemic therapy	Multicenter 2-period: 16-week randomized, DB, parallel-group, controlled treatment period followed by a long-term BE period up to Week 136	DB Period: 15 mg, 30 mg UPA or placebo QD, PO BE Period: 15 mg or 30 mg UPA QD, PO	836	Subjects ≥ 12 yrs. old and ≤ 75 yrs. 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	DB Period: 16 weeks BE Period: Up to Week 136	Ongoing; Interim Full CSR

AD = atopic dermatitis; BA = bioavailability; BE = blinded extension; CSR = clinical study report; DB = double-blind; OL = open-label; PBO = placebo; PK = pharmacokinetics; PO = by mouth; TCI = topical calcineurin inhibitor; TCS = topical corticosteroids; UPA = Upadacitinib

5.2. Clinical pharmacology

5.2.1. Methods

High performance liquid chromatography with tandem mass spectrometry (LC-MS/MS) is used for the quantitative determination of upadacitinib in human K_2EDTA plasma. The methods have been described in the regulatory application for the use of upadacitinib in the treatment of RA. Bioanalytical reports from the studies included in this application have been submitted and show acceptable method performance during study sample analysis including ISR and QC performance.

Population PK models were developed and used to simulate exposures in paediatric subjects (pcJIA) from 2 years old and adults (RA) to support the extrapolation approach (extrapolation of efficacy from adults with RA to paediatric subjects with age 2 years and older with pcJIA by exposure matching).

Previously developed exposure-response models for adults with RA were adapted and used to simulate response in a Virtual paediatric pcJIA population (3-17 years of age) which were compared to the model-predicted efficacy for these endpoints in adults with RA.

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

This application concerns an extension of the clinical indications for Rinvoq to include polyarticular course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older and to register a new paediatric-friendly oral solution providing upadacitinib 1 mg/mL. The proposed posology in paediatric patients would be either a 15 mg once daily (QD) extended-release tablet or a twice daily (BID) immediate-release oral solution based on their body weight and ability to swallow tablets.

Three different formulations of the oral solution (F1, S1, and F2) were used in the Phase 1 paediatric study. The oral solution is however not bioequivalent with the extended-release tablet and these formulations are not interchangeable on a mg per mg basis. Upadacitinib PK in patients with pcJIA was characterized through a population PK approach.

5.2.2.2. Evaluation and qualification of models

5.2.2.2.1. Population Pharmacokinetics

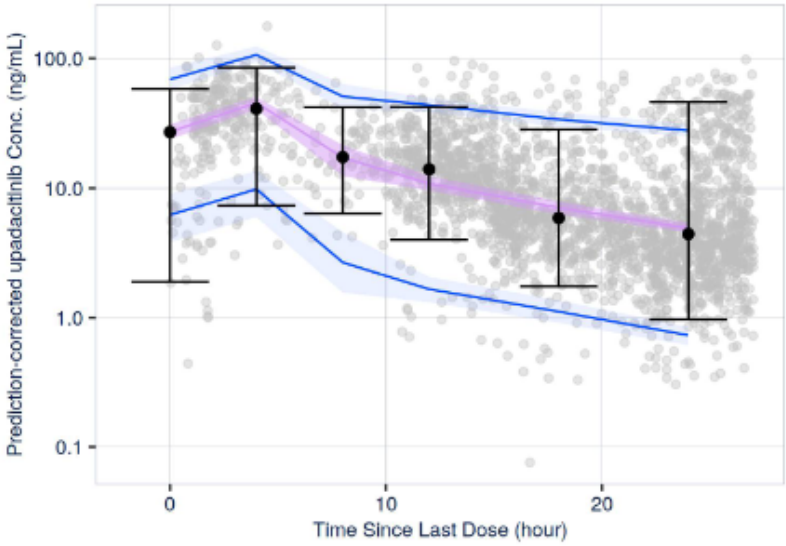
Two population PK models were developed and utilized for simulations to support the pcJIA indication. Both models employed a Bayesian pharmacokinetic modelling approach. The population pharmacokinetic analyses were performed in a stepwise manner as follows:

1. Development of population pharmacokinetic model for upadacitinib in adults and adolescents with atopic dermatitis (Model 1).
2. Development of population pharmacokinetic model for upadacitinib in paediatrics (Model 2).
3. Simulations to generate model-predicted drug exposures in paediatric subjects (using Model 2), stratified by age and body weight categories, compared to target adult exposures (derived using Model 1) at respective doses for adults with RA and PsA.

Model 1 (adult and adolescent AD model) was developed as a cross-population pharmacokinetic model using data from adult and adolescent subjects with AD and leveraging prior information from the model for upadacitinib in healthy adults and adult subjects with RA and PsA (R&D/19/1199) utilizing a Bayesian analysis approach. 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 by assuming a triple-normal prior distribution for the fixed effects and inter- and intra-individual variabilities. All covariates from its prior model (R&D/19/1199) were retained in Model 1: On CL/F: Body weight, Creatinine Clearance, Population (patients [RA, PsA or AD] versus healthy volunteers); On Vc/F: Body weight. In addition, a potential effect of disease status of AD on CL/F was evaluated.

Figure 1 shows the prediction-corrected VPC for the upadacitinib concentrations in adult and adolescent subjects with AD.

Figure *1*: Prediction-Corrected Visual Predictive Checks of Upadacitinib Concentration 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.

Note: Time bins were chosen 0, 4, 8, 12, 18, and 24 hours since last dose.

Model 2 (paediatric model) was developed as a population pharmacokinetic model using data from paediatric subjects with pcJIA (M15-340) and AD (M16-049) and leveraging prior information from Model 1 through a Bayesian analysis approach. Data from a total of 84 subjects with pcJIA and AD from Studies M16-049 and M15-340 who received upadacitinib and had at least one upadacitinib concentration greater than LLOQ were included in the population pharmacokinetic analysis (51 from Study M15-340 (Part 1) and 33 from Study M16-049 (Part 1), Table *4*). No records were below the LLOQ and no outliers were excluded.

Table 4: Demographic and Baseline Characteristics of Subjects with pcJIA 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%)

Note: Some percentages may not add up to 100 due to rounding. Age group was determined based on age at baseline.

The structural, statistical (inter- and intra-individual variability), and covariate components of the prior model were initially maintained in this paediatric 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 strong priors following the same approach as in Model 1. To inform the estimates describing the effects of body weight in paediatrics, weak adult priors for these coefficients were applied in the model (by increasing the associated variances by ten-fold). The bioavailability of upadacitinib immediate-release solution relative to immediate-release capsule formulation was fixed to 1.17 in the model. Initial assessments of the paediatric data demonstrated that upadacitinib CL/F in paediatric subjects with pcJIA and AD (for a subject with reference body weight of 74 kg) was more similar to healthy adult subjects than adult subjects with RA, PsA, or AD. Therefore, the effect of subject population on CL/F was removed from Model 2.

The following covariates were included in the model: On CL/F and Q/F: Body weight; On Vc/F and Vp/F: Body weight. The effects of body weight on upadacitinib pharmacokinetic parameters in Model 2 were primarily estimated using paediatric data. The creatinine clearance effect in paediatrics was not included in the model to avoid confounding effects on the model-estimated relationship between body weight and upadacitinib CL/F and Vc/F.

Estimates of the pharmacokinetic parameters for the final paediatric model are shown in Table *5*. Prediction-corrected VPCs for the upadacitinib concentrations in paediatric subjects with pcJIA stratified on body weight and formulation is presented in Figure *2*.

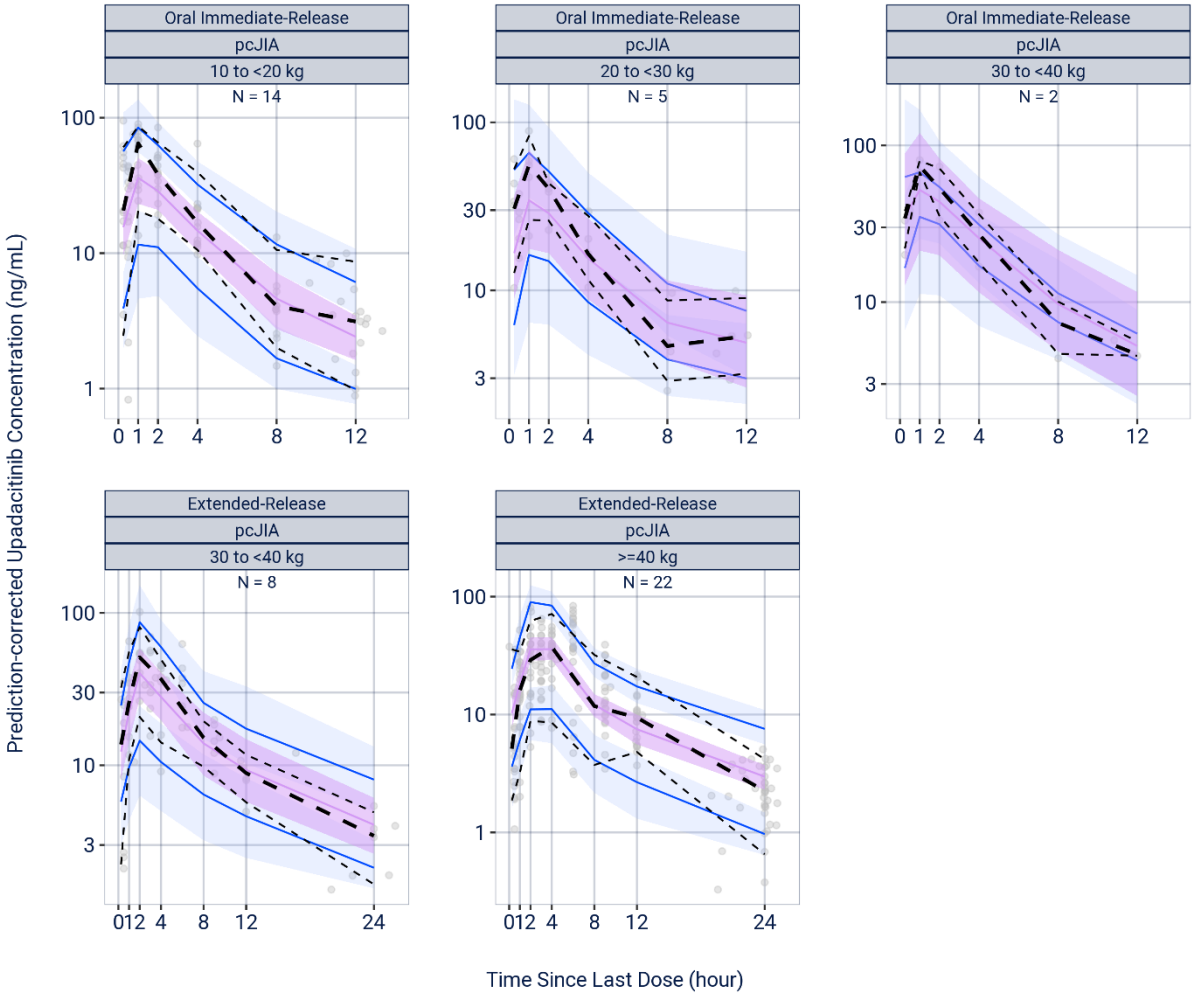
Table 5: Final Parameter Estimates and Variability of Updatacitinib Pharmacokinetics in Model 2 (Note: Body weight was included on Q/F (same exponent as on CL/F) and Vp/F (same exponent as on Vc/F) in the final model; however, the information is missing from the parameter description in this table).

Parameter	Population Estimate	%RSE	95% Confidence Interval
CL/F (L/h)	41.8	1.52	(40.6, 43.1)
Vc/F (L)	158	1.61	(153, 163)
Extended-Release Ka (1/h)	0.0571	4.62	(0.0521, 0.0625)
Extended-Release Absorption Lag Time (h)	0.152	7.08	(0.132, 0.174)
Fraction of Extended-Release Dose Absorbed through Zero-Order Process	0.720	1.69	(0.695, 0.743)
Zero-Order Absorption Duration (h)	3.33	1.54	(3.23, 3.43)
Bioavailability of the Immediate-Release Solution Formulation Relative to the Immediate-Release Capsule Formulation	1.17	Fixed	--
Bioavailability of the Extended-Release Tablet Formulation Relative to the Immediate-Release Capsule Formulation	0.756	1.33	(0.737, 0.776)
Q/F (L/h)	3.26	5.46	(2.93, 3.63)
Vp/F (L)	68.6	6.69	(60.2, 78.2)
Covariate Exponent of Body Weight on Vc/F	0.538	11.7	(0.415, 0.662)
Covariate Exponent of Body Weight on CL/F	0.388	11.1	(0.303, 0.472)
Immediate-Release Ka (1/h)	3.66	22.2	(2.38, 5.63)
Immediate-Release Absorption Lag Time (h)	0.174	5.61	(0.156, 0.194)

Parameter	Population Estimate	%RSE	%Shrinkage
IIV on CL/F (%CV)	0.141 (38.9)	17.7	6.18
IIV on Vc/F (%CV)	0.336 (63.2)	19.2	8.89
IIV on Extended-Release Ka (%CV)	0.385 (68.6)	9.12	25.6
IIV on Immediate-Release Ka (%CV)	1.28 (161)	29.2	17.4
Proportional Error Phase 1, SD (%CV)	0.198 (44.5)	7.05	--
Additive Error, SD (ng/mL)	0.0245	Fixed	--

%RSE was calculated as the standard error divided by the estimate multiplied by 100, %CV was calculated as SQRT(exp(ω^2)-1)*100. Shrinkage was calculated as (1-sd(eta)/ω)*100, with non-influential etas removed.

Figure 2. Prediction-Corrected VPCs of Upadacitinib Concentration in Model 2 pcVPCs of the pcJIA (Study M15-340 Part 1) subjects stratified by body weight and administered formulation



Model simulations

Simulations were conducted using the paediatric model (Model 2) to evaluate upadacitinib plasma exposures ($C_{max,ss}$ and $AUC_{24,ss}$) in virtual paediatric subjects receiving upadacitinib. A total of 300 virtual subjects in each of three age groups (2 to < 6 years, 6 to < 12 years, and 12 to < 18 years) were generated using U.S. Centers for disease control and prevention (CDC) growth charts for weight distributions of different ages and by using a uniform weight distribution starting from 10 kg.

The model-predicted upadacitinib plasma exposures in paediatric subjects were compared to those achieved by the respective doses of upadacitinib (15 mg QD and 30 mg QD extended-release) in adults. Simulations of drug exposures in adult subjects with RA, PsA, and AD were conducted using Model 1 and a total of 300 subjects sampled from the datasets of previously conducted population pharmacokinetic analyses in adults with RA (R&D/18/0628) and PsA (R&D/19/1199).

5.2.2.2.2. Physiology based pharmacokinetic model

Not applicable.

5.2.2.3. Absorption

Upadacitinib maximum plasma concentrations were reached within approximately 3 hours and 1 hour following the administration of the extended-release tablet formulation and the immediate-release oral solution, respectively. Upadacitinib has a high solubility and *in vitro* data indicate that permeability may be high though BCS-Class I cannot be concluded.

5.2.2.4. Bioequivalence

Bioequivalence between the commercial Rinvoq 15 mg extended-release tablet (formulation ER17) and the 15 mg extended-release tablet (formulation ER17Y) used in the two Phase 1 paediatric studies that support the efficacy extrapolation approach for pcJIA was demonstrated in Phase 1 Study M20-017 previously submitted for upadacitinib in the treatment of PsA.

The bioequivalence between the 15 mg ER7 tablet formulation (used in the phase 3 RA study) and the commercial 15 mg extended-release tablet formulation was demonstrated in the Phase 1 Study M15-878 previously submitted in the original RA application.

Phase 1 Study M16-552 evaluated the relative bioavailability between the immediate-release oral solution (F0) and extended-release tablet formulations (ER7). The study was previously submitted in the regulatory application for upadacitinib in the treatment of RA.

Formulation F0 used in the bioavailability Study M16-552 was an unsweetened extemporaneous dose preparation of the oral solution. The oral solution Formulation F1 (1 mg/mL) was developed and initially used in the paediatric studies (Studies M15-340 and M16-049). Subsequently, two additional oral solution formulations (Formulation S1: 0.5 mg/mL; Formulation F2: 1 mg/mL) were developed and used in both studies. Formulation F2 is proposed as the commercial immediate-release oral solution formulation. A biowaiver was requested between the different oral solutions, as the differences in composition are minor and updacitinib is in solution in all the formulations. It was deemed acceptable.

The mean plasma concentration-time profiles after administration of the two formulations in study M16-552 are presented in Figure *3* on linear and log-linear scale.

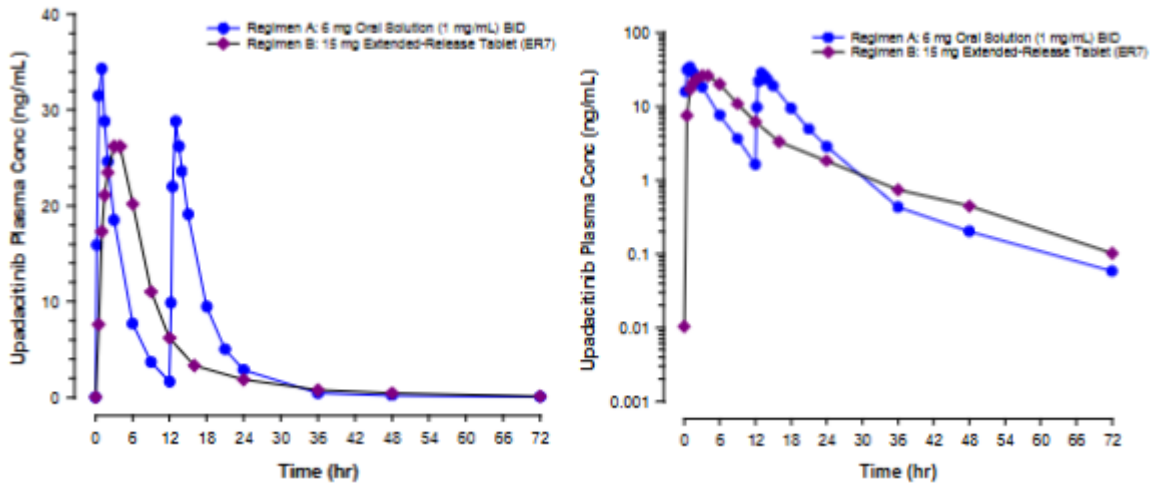


Figure 3: Mean upadacitinib plasma concentrations versus time profiles in study M16-552 comparing 6 mg BID doses of F0 oral solution with 15 mg QD extended-release tablet formulations (ER7).

Under fasting conditions, administration of two 6 mg doses of upadacitinib oral solution (1 mg/mL) 12 hours apart resulted in 30% higher Cmax and 17% higher AUC0-inf relative to administration of a single 15 mg upadacitinib extended-release tablet (ER7 formulation).

Table 6: Statistical evaluation of pharmacokinetic parameters 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

Regimen A = Two 6 mg doses of upadacitinib oral solution (1 mg/mL) administered 12 hours apart under fasting conditions (test).
Regimen B = Single 15 mg dose of upadacitinib once-daily tablet formulation (ER7) administered under fasting conditions (reference).
a. Overall C_{max} for Regimen A.

No study has been conducted to investigate the food effect on the oral solution formulation. For the commercial ER formulation, upadacitinib Cmax and AUC increased 40% and 30% respectively, relative to the fasting conditions. In studies with the upadacitinib IR capsule formulation, the effect of a high-fat, high-calorie meal resulted in no effect on AUC and a 23-30% decrease in Cmax compared to fasting conditions. In the clinical studies in patients, there were no food restrictions. In the paediatric M15-340 study, it was however recommended to, if possible, consume solid food immediately after receiving oral solution to mitigate the risk of dental erosion and gastrointestinal upset.

5.2.2.5. Distribution

Not applicable.

5.2.2.6. Metabolism

Not applicable.

5.2.2.7. Elimination

Not applicable.

5.2.2.8. Dose proportionality and time dependency

Not applicable.

5.2.2.9. Pharmacokinetics in the target population

See paediatric population below.

5.2.2.10. Special populations

Paediatric population

Study M15-340

Is a Phase 1, multiple-dose, open-label study consisting of 3 parts in paediatric subjects aged 2 to less than 18 years with pcJIA.

Study design is presented in Section 5.3.2.1.2. of this document.

Blood samples for upadacitinib assay were collected at the following time points in Part 1:

- Day 7 (QD tablet regimens): Prior to dosing (0-hour) and at 0.5, 1, 2, 3, 4, 6, 9, 12, and 24 hours after dosing.
- Day 7 (BID oral solution regimens): Prior to dosing (0-hour) and at 0.25, 0.5, 1, 2, 4, 8, and 12 hours after dosing.

In part 2, blood samples for upadacitinib assay were collected when dose adjustment was required: Prior to dosing on visit day and at 1 and 2 hours after dosing.

In Part 3, blood samples were collected at Weeks 2, 4, and 8 prior to dosing and at Weeks 24 and 36 within 4 hours after dosing (when possible).

Treatments used

The treatments used during the study are presented in Section 5.3.2.1.2. of this document.

Results

In subjects with pcJIA, upadacitinib maximum plasma concentrations were reached within approximately 3 hours and 1 hour following the administration of the extended-release tablet formulation and the immediate-release oral solution, respectively. Upadacitinib functional t1/2, calculated from the C_{max} to C_{trough} ratio at steady state, was approximately 5 hours and 2 hours, for the extended-release QD and immediate-release solution BID regimens, respectively, and was consistent between the different age groups. Upadacitinib apparent oral clearance increased with increasing body weight in subjects with pcJIA.

Table *7*: Geometric Mean (Mean, % CV) PK Parameters of Upadacitinib by Cohort and Dosing Regimen (Part 1)

PK Parameters (units)	Cohort 1 Low Dose QD (N = 9)	Cohort 2 High Dose QD (N = 9)	Cohort 3 Low Dose QD (N = 12)	Cohort 3 Low Dose BID (N = 7)	Cohort 3 Low Dose Total[g] (N = 19)	Cohort 5 Low Dose BID (N = 12)[i]
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]
$AUC_{0\text{-}24}$[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]

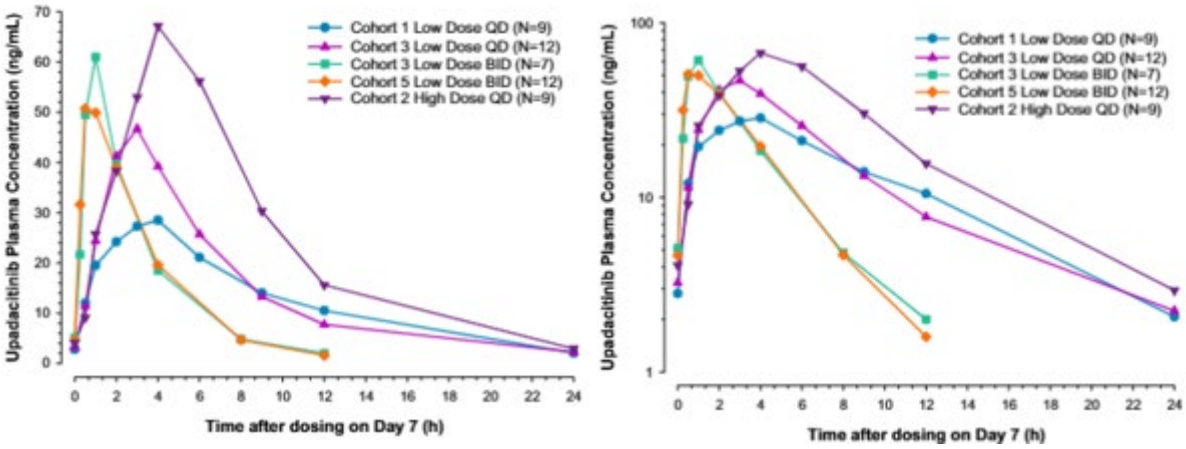


Figure 4: Mean Upadacitinib Concentration-Time Profiles by Cohort and Dosing Regimen (Part 1), Linear and Log-Linear Scales

Comparison of Model-Predicted Upadacitinib Exposures between Adults and Paediatrics to Support extrapolation of Efficacy from Adults with RA to Children with pcJIA

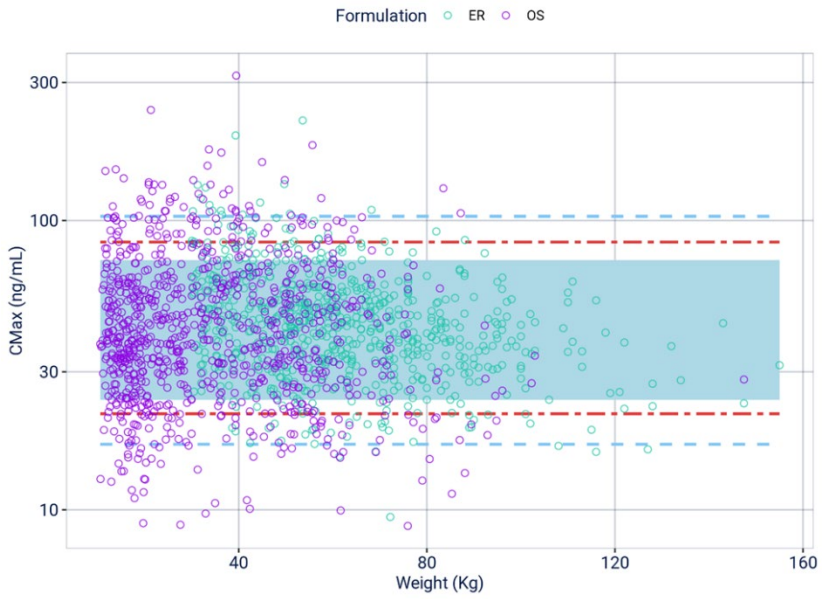
Summary statistics were calculated for the model-simulated upadacitinib exposures at steady-state ($AUC_{24,ss}$ and $C_{max,ss}$) in paediatric subjects stratified by age and body weight groups in comparison to the model-predicted target exposures in adults with RA and PsA (Table 8).

Figure 5, Figure 6 and Figure 7 show the simulated Cmax, AUC24,ss and Ctrough for the virtual population per SmPC posology, versus body weight (using a uniform weight-distribution). The shaded area in the background is the simulated exposure in adults with RA given 15 mg QD ER tablets. Figure 8 displays the median predicted upadacitinib concentration-time course in paediatric subjects by dose, age, and body weight groups compared to adult subjects with RA and PsA.

Table 8. Summary Statistics of Model-Predicted Upadacitinib Exposures in Paediatric Subjects by Body Weight Groups Compared to Adult Subjects with RA and PsA

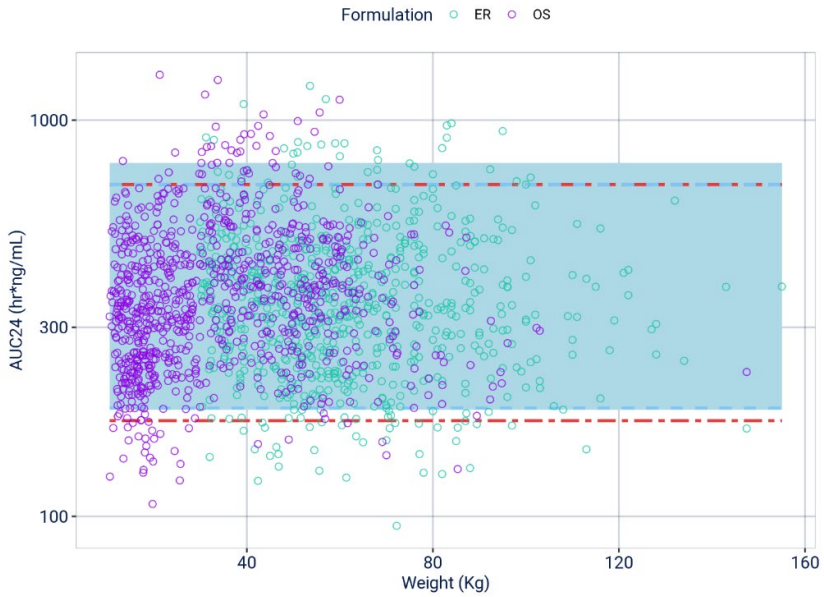
Dose Level	Body Weight Group	$AUC_{24,ss}$ (hr•ng/mL) Median (90% PI)	Ratio to Adults RA ($AUC_{24,ss}$)	Ratio to Adults PsA ($AUC_{24,ss}$)	$C_{max,ss}$ (ng/mL) Median (90% PI)	Ratio to Adults RA ($C_{max,ss}$)	Ratio to Adults PsA ($C_{max,ss}$)
Low Dose (corresponding to 15 mg QD ER in adults)	Adults RA	376 (186, 780)	-	-	42.1 (24.0, 72.9)	-	-
	Adults PsA	356 (169, 710)	-	-	38.2 (21.7, 68.4)	-	-
	10 to < 20kg	299 (168, 542)	0.796	0.839	37.6 (15.7, 92.3)	0.895	0.986
	20 to < 30kg	334 (187, 660)	0.889	0.937	39.7 (17.3, 113)	0.944	1.04
	≥ 30kg	319 (171, 625)	0.848	0.894	44.5 (19.9, 91.7)	1.06	1.17

Figure *5*: Maximum concentration (C_{max})(ng/mL) by weight simulated in a virtual population of paediatric subjects.



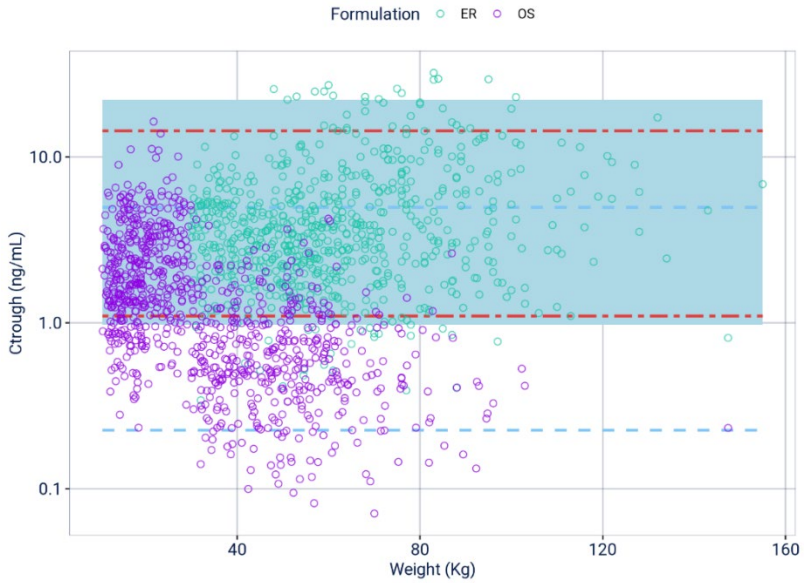
Purple circles represent the oral solution (OS), green circles designate the extended-release tablets (ER), red and blue dashed lines outline the 90% prediction interval for ER and OS respectively, and the shaded rectangle represents the 90% prediction interval of Cmax predicted in an adult RA population receiving upadacitinib ER tablets.

Figure *6*: Steady-state, 24-hour area under the curve ($AUC_{24,ss}$)(hr*ng/mL) by weight simulated in a virtual population of paediatric subjects.



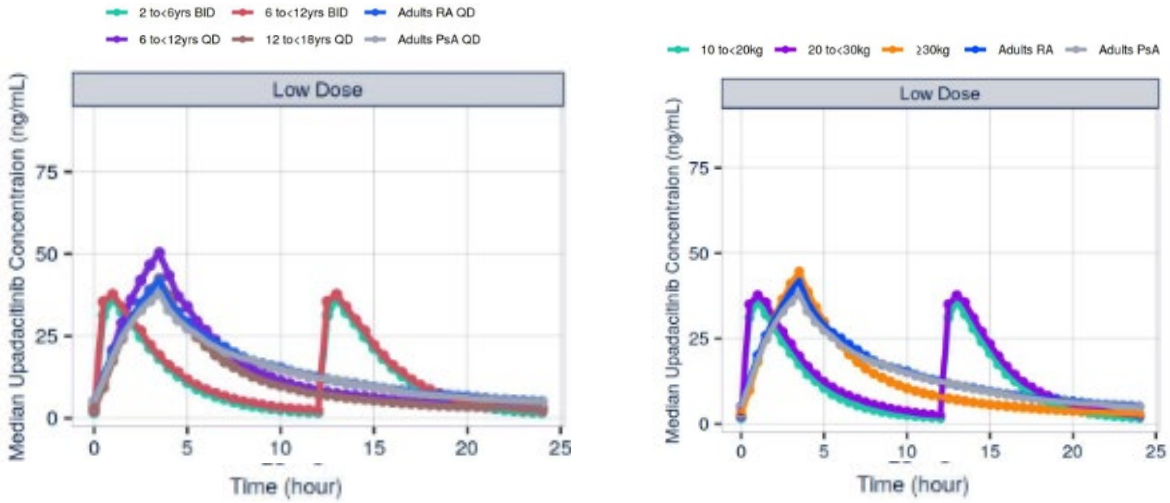
Purple circles represent the oral solution (OS), green circles designate the extended-release tablets (ER), red and blue dashed lines outline the 90% prediction interval for ER and OS respectively, and the shaded rectangle represents the 90% prediction interval of AUC24,ss predicted in an adult RA population receiving upadacitinib ER tablets.

Figure *7*: Minimum concentration (Ctrough)(ng/mL) by weight simulated in a virtual population of paediatric subjects.



Purple circles represent the oral solution (OS), green circles designate the extended-release tablets (ER), red and blue dashed lines outline the 90% prediction interval for ER and OS respectively, and the shaded rectangle represents the 90% prediction interval of Ctrough predicted in an adult RA population receiving upadacitinib ER tablets.

Figure *8*: Median Predicted Upadacitinib Concentration-Time Course in Paediatric Subjects by Dose, Age, and Body Weight Groups Compared to Adult Subjects with RA and PsA. Low dose groups correspond to 15 mg QD exposure-response in adults.



5.2.2.11. Pharmacokinetic interaction studies

The effect of drug interactions between upadacitinib and concomitant medications in pcJIA is assumed to be similar to adults. This is supported by the maturation of the two enzymes known to contribute to upadacitinib metabolism, CYP3A and CYP2D6, by 2 years of age, and maturation of two transporters that showed activity toward upadacitinib *in vitro*, P-gp, and BCRP, by 1 year of age.

5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

Upadacitinib mechanism of action is to inhibit JAK. JAKs are intracellular enzymes that transmit cytokine or growth factor signals involved in a broad range of cellular processes including inflammatory responses, haematopoiesis, and immune surveillance. They phosphorylate and activate signal transducers and activators of transcription (STATs). This phosphorylation, in turn, modulates gene expression and cellular function.

5.2.3.2. Primary and secondary pharmacology

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

No new information is provided with this application.

5.2.3.3. Pharmacodynamic interactions with other medicinal products or substances

No PD interaction studies were conducted in this study.

5.2.3.4. Genetic differences in PD response

Not applicable.

5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

A previously developed adults Markov models (R&D/18/0628) was used to simulate the longitudinal exposure-ACR20/50/70 relationship, and exposure-response of LDA/CR response variables in a Virtual paediatric population (3-17 years of age) as support.

5.2.5. Dose selection and therapeutic window

This application includes an efficacy extrapolation approach. The paediatric doses with oral solution selected for children from age 2 years with pcJIA were based on matching the exposure in children (given either oral solution or ER tablets) to adults with RA given ER tablets, 15 mg QD.

5.2.6. Overall discussion and conclusions on clinical pharmacology

5.2.6.1. Discussion

This application aimed to extend the clinical indications for Rinvoq to include pcJIA in patients 2 years of age and older and to register a new oral solution providing upadacitinib 1 mg/mL. This included an efficacy extrapolation approach, in lieu of a Phase 3 clinical study in pcJIA. A popPK model was used to describe the PK of upadacitinib administered as ER tablet (once daily) and oral solution (given twice daily) in paediatric patients. The model was subsequently used for simulation of exposure and comparison to exposure in adults with RA, to support extrapolation of efficacy from adults to paediatric patients with pcJIA.

Adequately validated bioanalytical methods were employed and bioanalytical reports provided showing acceptable method performance during study sample analysis.

The intended commercial oral solution (formulation F2) was used in the paediatric pcJIA Study M15-340 (as was two other formulations, F1 and S1). These formulations have not been compared to any tablet formulation in a direct bioavailability study. An earlier formulation of the oral solution (F0) was compared to the 15 mg ER tablet formulation used in the phase 3 studies in adult patients with RA. This study was assessed in the initial application for RA where it was concluded that the relative bioavailability of the ER tablet was approximately 70% relative to the oral solution (F0) based on dose-normalized AUCinf. The four different oral solutions were deemed similar and the applied biowaiver was found acceptable (see quality section).

Different formulations of the 15 mg ER tablet have also been administrated in the different populations included in the studies. All have shown bioequivalence to the commercial formulation but e.g. the tablet formulation used in the paediatric pcJIA study has not been directly compared to the tablet formulation used in the phase 3 adult RA studies. Given the small differences in composition between some tablet formulations and the fact that all have shown bioequivalence to the commercial tablet formulation, no concerns were raised.

On a mg per kg basis, the oral solution is not bioequivalent to the ER tablets. This is adequately reflected in the SmPC.

No study has been conducted to investigate the food effect on the PK of the oral solution. In the early development, an IR-tablet was used and the food effect on this formulation was assessed in the original MAA. The food effect on different ER-formulations has also been studied, and no clinically relevant food effect has been observed to either IR- or ER-tablets. In the paediatric pcJIA study subjects were instructed to drink water immediately after receiving oral solution and if possible, consume solid food to mitigate the risk of dental erosion and gastrointestinal upset in part 2 and 3. In part 1 subjects should take the study drug on the morning of Day 7 approximately 30 minutes after a meal. Study drug could be administered with or without food on any other day. In the SmPC, no food restrictions were proposed. This was acceptable.

Population PK Models

Two population PK models were developed to support this application. The starting point was a previously developed population PK model for upadacitinib in healthy adults and adult subjects with RA and PsA that was leveraged as the prior model for the analysis of adults and adolescents with AD (Model 1). The population estimates were similar to the original RA model previously submitted. The uncertainty was low for all parameters; however, the shrinkage was high for ER KA and Vc/F (66 and 35, respectively). The presented pcVPC of Model 1 performance appeared to adequately describe the median, however Ctrough and the variability appeared to be slightly underpredicted. This model was used to simulate the exposure in adults RA patients, which was considered acceptable.

Using Model 1 as starting point, Model 2 (paediatric population PK model) was developed using strong priors on all parameters (on CL/F from adult healthy volunteers) except for the covariate exponent for relationship between body weight on CL/F and Vc/F, where weak adult priors were implemented. The data included in this analysis was from study M15-340 (pcJIA, N=51) and study M16-049 (paediatric subjects, N=33, age 2-17 years, with AD). The relative bioavailability for oral solution was added to the model as a fixed parameter of 1.17 relative to the immediate release (IR) capsule, which was considered acceptable. The exponent for BWT on CL/F and Vc/F were estimated to 0.388 (95% CI 0.303-0.472) and 0.538 (95% CI 0.415-0.662), respectively. The parameters were estimated with a low RSE and shrinkage. The goodness-of-fit plots indicated some tendencies towards over- and underprediction of exposures. The pcVPCs stratified on body weight and formulation indicated that the Model 2 may slightly underpredict the mean Cmax in children 10 to <20 kg administered the oral solution, however, the variability was captured. Ctrough in the population <40 kg with both formulations appeared to be adequately captured. Overall, model 2 was considered acceptable for simulating the exposure in children administered oral solution, for comparison of exposures in children compared to adults. The MAH also performed a sensitivity analysis with a model without priors and inclusion of the theoretical exponents of 0.75 and 1 on clearance and distribution parameters. The model performance and outcome were similar to Model 2.

Predicted exposure (Cmax and AUC) was similar in patients receiving the oral formulation and the extended-release tablet.

Paediatrics

Due to protocol changes that affected the posology in study M15-340, the extrapolation approach was supported by simulated exposures in paediatric subjects and compared to simulated exposures in adults with RA (using Model 1 and Model 2). The 90% simulated $AUC_{24,ss}$ prediction intervals largely overlapped with the 90% prediction interval of adult RA exposure with 15 mg ER tablets. For children weighing 10 to <20 kg, 20 to <30 kg and ≥30 kg, the simulated $AUC_{24h,ss}$ ratio was 20% lower, 11% lower and 15% lower, respectively, compared to the simulated exposure in adults with

RA. For children weighing 10 to <20 kg, 20 to <30 kg and ≥30 kg, the median simulated $C_{max,ss}$ ratio was 15% lower, 5% lower and 6% higher, respectively, compared to the simulated exposure in adults with RA with 15 mg ER tablets. The upper 90% C_{max} prediction interval was higher, extended beyond, compared to the adult 90% prediction interval. The simulated C_{trough} was lower in patients administered the oral solution across all body weights compared to the predicted C_{trough} in adults, particularly for patients who weigh ≥30kg.

Supportive efficacy and safety data did not indicate that the minor differences in exposure would result in a lower efficacy or increased safety concerns. The PD data indicated that the response was similar irrespective of formulation, supporting that the difference in PK curve was not expected to result in a loss of efficacy. In addition, previously conducted exposure-response analyses from Phase 2 studies (BID dosing) and Phase 3 studies (QD dosing, ER tablet) in adult patients with RA predicted similar efficacy, which further supported that fluctuations in plasma concentration over time should likely not result in a reduced efficacy.

Overall, upadacitinib plasma exposures ($C_{max,ss}$ and $AUC_{24,ss}$) in paediatric patients with polyarticular juvenile idiopathic arthritis following the recommended weight-based paediatric dosing scheme are predicted to be similar to the target plasma exposure in adult RA patients receiving the recommended dose.

In paediatric patients with pcJIA with baseline BW ranging from 11 to 114 kg, upadacitinib clearance increased with increasing BW, which supports weight-based dosing. Age (over the range of 2 to < 18 years old) had no additional effect on upadacitinib pharmacokinetics after accounting for the effect of BW. This is reflected in SmPC section 5.2.

5.2.6.2. Conclusions

The different oral solutions formulations used in the clinical development programme were considered similar based on quality data.

The commercial ER-tablet had a 30% lower bioavailability than the oral solution and the two formulations are not interchangeable on a mg per kg basis, as indicated in the SmPC.

Predicted exposure (Cmax and AUC) was similar in patients receiving the oral formulation and the extended-release tablet.

The simulations indicated an overlapping C_{max} and $AUC_{24,ss}$ in children with pcJIA and adults with RA. The totality of the data indicated that the fluctuations in plasma concentration over time (and lower C_{trough}) were not expected to result in a reduced efficacy with the oral solution administered BID. Overall, upadacitinib plasma exposures ($C_{max,ss}$ and $AUC_{24,ss}$) in paediatric patients with pcJIA following the recommended weight-based paediatric dosing scheme were predicted to be similar to the target plasma exposure in adult RA patients receiving the recommended dose hence.

The pharmacokinetics of upadacitinib in paediatric patients (< 12 years of age) with atopic dermatitis have not been established.

5.3. Clinical efficacy

5.3.1. Dose response study(ies)

No dose-response studies were conducted.

This application includes an efficacy extrapolation approach. The paediatric doses selected for children from age 2 years with pcJIA were based on matching the exposure in children (given either oral solution or ER tablets) to adults with RA given ER tablets, 15 mg QD.

5.3.2. Main study(ies)

5.3.2.1. Study #1 identifier

M15-340

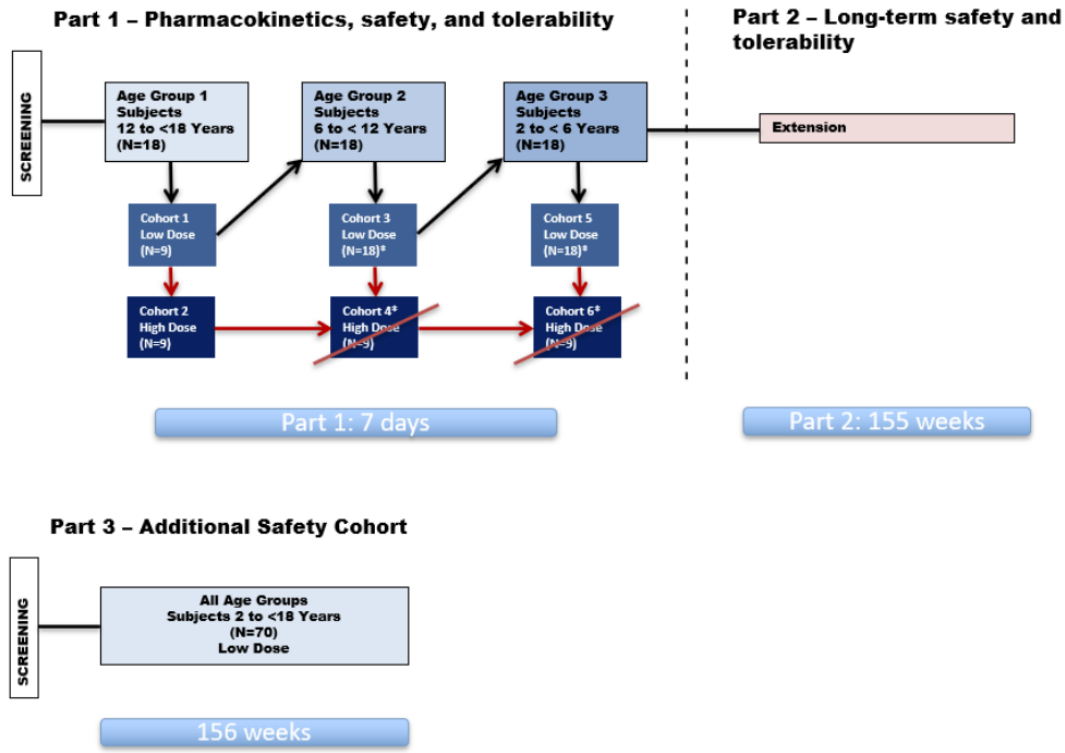
5.3.2.1.1. Study title

An open-label multiple-dose study to evaluate the pharmacokinetics, safety, and tolerability of upadacitinib in paediatric subjects with pcJIA

5.3.2.1.2. Study design

Study M15-340 is a Phase 1, multiple-dose, open-label study consisting of 3 parts in paediatric subjects aged 2 to less than 18 years with pcJIA. Approximately 124 paediatric male and female subjects with pcJIA were planned to be enrolled in the study. The schematic of the overall study is shown in Figure 9. As of the date of the study report, recruitment was complete and study conduct was ongoing.

Figure 9: *Study schema*



The study is comprised of a 35-day screening period, a 156-week open-label treatment period for Part 1/Part 2 and Part 3, and an end-of-study follow-up visit/call.

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 selected 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 (age 12 to < 18 years), Age Group 2 (age 6 to < 12 years), and Age Group 3 (age 2 to < 6 years). However, the High Dose level was only evaluated for Age Group 1 (Cohort 2), and in Protocol Version 9.0, the High Dose levels for Age Groups 2 and 3 (Cohorts 4 and 6) were removed since the MAH was no longer pursuing the development of the adult dose of 30 mg QD for RA. After the first 7 days, all subjects received the Low Dose level of upadacitinib (refer to Part 2).

Cohort 1 (Age Group 1, Low Dose) and Cohort 2 (Age Group 1, High Dose) enrolled 9 subjects each.

Cohort 3 (Age Group 2, Low Dose) and Cohort 5 (Age Group 3, Low Dose) were to enroll approximately 18 subjects each. Upadacitinib dose was administered based on the subject's body weight so that the drug exposures achieved in paediatric subjects across all weight categories were comparable to the target exposure in adults. A dosing scheme with four body weight categories was initially proposed, which was revised after a preliminary PK analysis of the data collected from 23 subjects who completed Part 1 was conducted in December 2020. PK data from 22 paediatric subjects with atopic dermatitis who received upadacitinib under the same original dosing scheme in a separate Phase 1 paediatric study of upadacitinib were also included in the analysis.

The revised dosing scheme consisted of 3 body weight categories and was employed starting in Protocol Version 8.0. All active subjects were transitioned to the new dosing scheme.

Table *9*: Revised upadacitinib dosing by body weight category and dose level

	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 if unable to swallow tablet)

Table *10*: 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 v1.0 to v7.0[a]	9	9	5	1	6	2
Protocol v8.0 or later[b]	0	0	7	6	13	12

a. Subjects were dosed according to the original dosing scheme
b. Subjects were dosed according to the updated dosing scheme
c. QD and BID regimens summarized together.

The study aimed to enroll at least 10 subjects below 30 kg. Recruitment of subjects was conducted through a staggered approach based on age. Subjects who completed Part 1 and were benefiting from the study drug with no ongoing AESI or SAEs, based on investigator's clinical judgment and with subject/family's agreement, had the option to enrol in Part 2 to receive open-label upadacitinib.

In part 2, subjects received open-label upadacitinib at the Low Dose level and per their body weight category.

In part 3, an additional safety cohort that was planned to enrol approximately 70 subjects from all age groups (ages 2 to < 18 years), was added to evaluate long-term safety and tolerability of upadacitinib without intensive PK sample collection starting with Protocol Version 10.0. Subjects in Part 3 received open-label upadacitinib at the Low Dose level and, after the Baseline and screening visits, followed an identical visit schedule as subjects in Part 2, with sparse PK sampling.

5.3.2.1.2.1. Treatment

In Part 1, doses were evaluated for each body weight category as defined in the protocol. The initial dose of upadacitinib was based on the subject's body weight at screening and the assigned study cohort. Subjects received multiple doses (QD or BID) of upadacitinib administered for 7 consecutive days prior to enrolment in Part 2.

Subjects in Parts 2 and 3 received open-label upadacitinib at the Low Dose level per body weight category until the end of the study. Change in the subject's body weight category was assessed by the investigator at each Part 2 or Part 3 study visit.

A total of three oral solution formulations were used in the study:

- The 1 mg/mL (pH 2.9) solution (F1) was initially used in the study.
- The 0.5 mg/mL (pH 3.8) solution (S1) was later developed to increase the solution pH to address the potential dental erosion concern for paediatric patients from the chronic administration of relatively low pH solution.
- With the revision in doses based on preliminary PK analysis of available paediatric data, the 1 mg/mL (pH 3.4) solution (F2) was developed to reduce the overall volume being administered to paediatric patients and increase convenience. The F2 1 mg/mL (pH 3.4) oral solution formulation is proposed as the commercial oral solution formulation for paediatric 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 in Protocol Version 9.0.

The following concomitant medications/therapies were allowed:

- Stable doses of non-steroidal anti-inflammatory drugs (NSAIDs)
- Stable doses of low-dose glucocorticoids (≤ 0.2 mg/kg/day prednisone; daily maximum, 10 mg)
- Stable doses of methotrexate ([MTX]; ≤ 20 mg/m2 body surface area/week)

In Parts 2 and 3, initiation of, change in dosing or, when required, use of NSAIDs, glucocorticoids and MTX were allowed as per local label.

5.3.2.1.2.2. Randomisation

The study was open labelled with no control group.

5.3.2.1.2.3. Patient population

The study was conducted at 26 sites located in 8 countries (United States including Puerto Rico, Canada, Germany, Hungary, Israel, Italy, Japan, and Spain).

The main inclusion/exclusion criteria were:

- Individuals, aged 2 to less than 18 years, and total body weight of 10 kg or higher at the time of screening.
- Diagnosed with pcJIA (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 enthesitis-related arthritis (ERA) or juvenile psoriatic arthritis (JPSA).
- 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.

- 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 current or past history of several infections (for example recurrent or disseminated herpes zoster, disseminated herpes simplex, active infection needing treatment, active tuberculosis (TB)).
- 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.
- A negative serum pregnancy test for all female subjects in Tanner stages $\geq$ 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 receiving MTX, have been taking MTX for at least 12 weeks immediately before and including Study Day 1 and on a stable dose of $\leq$ 20 mg/m2 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.

5.3.2.1.3. Objectives and estimands

5.3.2.1.3.1. Primary objective

Part 1: To evaluate the PK, safety, and tolerability of multiple doses of upadacitinib in pediatric subjects with pcJIA. To evaluate the palatability of upadacitinib oral solution in pediatric subjects.

Part 2: To evaluate the long-term safety and tolerability of upadacitinib in pediatric subjects with pcJIA who completed Part 1.

Part 3 (Additional Safety Cohort): To evaluate the long-term safety and tolerability of upadacitinib in paediatric subjects with pcJIA.

For Parts 1, 2, and 3: To evaluate descriptive efficacy of upadacitinib in pcJIA.

5.3.2.1.3.2. Estimand for the primary objective

The study was a single armed, open label and only descriptive data were provided.

The efficacy endpoints reported in the study were:

ACR Pediatric 30/50/70/90/100 Response: Response rate is based on ≥ 30%/50%/70%/90%/100% improvement in at least 3 of the following 6 core set criteria to define improvement of disease activity with > 30% worsening in no more than one of the six core set criteria: Patient/Caregiver's Global assessment of Overall Well-being (VAS), Physician's Global Assessment of Disease Activity (VAS), number of joints with LOM, number of active joints (swelling not due to deformity or joints with LOM and with pain/tenderness), C-HAQ (functional ability), and CRP (inflammatory biomarker).

JADAS (ESR and CRP) is a score calculated adding up the following four parameters:

- Parent's global assessment of subject's overall well-being by VAS (0 - 10 cm scale);
- Physician's global assessment of subject's disease activity by VAS (0 - 10 cm scale);
- Number of active joints (swelling not due to deformity or joints with LOM and with pain/tenderness);
- Laboratory measure of inflammation measured by:
  - For JADAS (ESR): ESR value normalized to a 0 - 10 scale according to the following formula: (ESR (mm/hour) - 20)/10. Before calculation, ESR values < 20 mm/hour are converted to 20, ESR values > 120 mm/hour are converted to 120.))
  - For JADAS (CRP): CRP value normalized to a 0 - 10 scale according to the following formula: (CRP (mg/L) - 10)/10. Before calculation, CRP values < 10 mg/L are converted to10 and CRP values > 110 mg/L are converted to 110.))

Low disease activity (LDA)*:* LDA is defined as JADAS-27 (CRP) ≤ 3.8.

Remission (ID): ID is defined as JADAS-27 (CRP) ≤ 1.

C-HAQ: Three components are evaluated: 1) Difficulty in performing daily functions, 2) use of special aids, and 3) assistance from other people.

Total number of active joints

Physician's Global Assessment of Disease Activity (VAS)

Patient/Parent Global Assessment of Overall Well Being (VAS)

Statistical methods for estimation and sensitivity analysis on primary estimand

The study was a single armed, open label study and only descriptive efficacy data provided.

5.3.2.1.4. Results

5.3.2.1.4.1. Participant flow and numbers analysed

A total of 122 paediatric subjects with pcJIA were enrolled and 122 subjects received study drug.

Subject dispostion is provided in Table 11 and summary of study drug disconitnuation in Table 12.

Table *11*: Subject Disposition in Study M15-340

	Age 2 to < 6 years N = 27 n (%)	Age 6 to < 12 years N = 53 n (%)	Age 12 to < 18 years N = 42 n (%)	Total (N = 122) n (%)
Completed Study	9 (33.3)	14 (26.4)	11 (26.2)	34 (27.9)
Completed Part 1	14 (51.9)	19 (35.8)	18 (42.9)	51 (41.8)
Completed Part 2	9 (33.3)	14 (26.4)	11 (26.2)	34 (27.9)
Completed Part 3	0	0	0	0
Ongoing Study	16 (59.3)	30 (56.6)	22 (52.4)	68 (55.7)
Ongoing Part 1	0	0	0	0
Ongoing Part 2	5 (18.5)	0	0	5 (4.1)
Ongoing Part 3	11 (40.7)	30 (56.6)	22 (52.4)	63 (51.6)
Discontinued Study	2 (7.4)	9 (17.0)	9 (21.4)	20 (16.4)
Primary Reason				
Adverse event	0	1 (1.9)	0	1 (0.8)
Withdrawal by subject	0	2 (3.8)	2 (4.8)	4 (3.3)
Lost to follow-up	0	0	1 (2.4)	1 (0.8)
Other	2 (7.4)	6 (11.3)	6 (14.3)	14 (11.5)

$ Subjects who discontinued study drug are counted under each reason given for discontinuation, therefore, the sum of the counts given for the reasons may be greater than the overall number of discontinuations.

Table *12*: Summary of Study Drug Discontinuation

	Cohort 1 (N = 9) n (%)	Cohort 2 (N = 9) n (%)	Cohort 3 (N = 19) n (%)	Cohort 5 (N = 14) n (%)	Safety Cohort (N = 71) n (%)	Total (N = 122) n (%)
Discontinued Study Drug	2 (22.2)	5 (55.6)	5 (26.3)	1 (7.1)	8 (11.3)	21 (17.2)
Primary Reason						
Adverse event	0	0	0	0	1 (1.4)	1 (0.8)
Withdrawal by subject	0	2 (22.2)	1 (5.3)	0	2 (2.8)	5 (4.1)
Lost to follow-up	1 (11.1)	0	0	0	0	1 (0.8)
Lack of efficacy	0	3 (33.3)	4 (21.1)	1 (7.1)	4 (5.6)	12 (9.8)
Other	1 (11.1)	0	0	0	1 (1.4)	2 (1.6)

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

5.3.2.1.4.2. Deviations from study plan

The original protocol (Version 1.0, 23 March 2018, 0 subjects) had 10 global amendments, 1 regional-specific amendment, and 7 administrative changes. According to the applicant, the protocol changes described in the amendments and administrative changes did not affect the interpretation of study results.

The substantive changes were the following ones:

- In version 8.0 (09 December 2020, 15 subjects), update dosing was made to remove the 30 mg QD and equivalent dosing regimen and High Dose Cohorts 4 and 6 in Part 1, and to expand

Low Dose Cohorts 3 and 5 from nine to eighteen subjects each, in place of the removed High Dose Cohorts.

- In version 10.0 (20 December 2021, 34 subjects), Part 3, an additional safety cohort, which includes approximately 70 subjects from 2 to < 18 years, was added evaluating the Low Dose of upadacitinib with no intensive pharmacokinetic sample collection.

Table *13*: Summary of the four ICH defined Protocol Deviation Categories (By Cohort) (Safety Population)

Summary of The Four ICH Defined Protocol Deviation Categories (By Cohort)
(Safety Population)

	Cohort 1 (N=9) n (%)	Cohort 2 (N=9) n (%)	Cohort 3 (N=19) n (%)	Cohort 5 (N=14) n (%)	Safety Cohort (N=71) n (%)	Total (N=122) n (%)
Category 1: Subject Entered into the Study Even Though She/He Did Not Satisfy Entry Criteria						
Inclusion Criteria						
1	5 (55.6)	0	1 (5.3)	0	0	6 (4.9)
23	0	0	0	0	1 (1.4)	1 (0.8)
Any Inclusion Criterion Not Met	5 (55.6)	0	1 (5.3)	0	1 (1.4)	7 (5.7)
Exclusion Criteria						
Any Exclusion Criterion Met	0	0	0	0	0	0
Any Inclusion/Exclusion Criterion Violated	5 (55.6)	0	1 (5.3)	0	1 (1.4)	7 (5.7)
Category 2: Subject Who Developed Withdrawal Criteria during the Study and Were Not Withdrawn	0	0	0	0	0	0
Category 3: Subject Who Received Wrong Treatment or Incorrect Dose	0	1 (11.1)	1 (5.3)	1 (7.1)	2 (2.8)	5 (4.1)
Category 4: Subject Who Received Excluded or Prohibited Concomitant Treatment	0	2 (22.2)	1 (5.3)	1 (7.1)	5 (7.0)	9 (7.4)

Program Source Code: /SDA/ABT-494/JIA/CSR/M15-340/U/14.1/PCMS_RUN/m15340pd.sas ARS_011146

5.3.2.1.4.3. Baseline data

Table *14* Demographic Summary for All Subjects

	Cohort 1 (N = 9)	Cohort 2 (N = 9)	Cohort 3 (N = 19)	Cohort 5 (N = 14)	Safety Cohort (N = 71)	Total (N = 122)
Sex, n (%)						
Male	2 (22.2)	1 (11.1)	4 (21.1)	3 (21.4)	17 (23.9)	27 (22.1)
Female	7 (77.8)	8 (88.9)	15 (78.9)	11 (78.6)	54 (76.1)	95 (77.9)
Age (years)						
Mean (SD)	14.7 (1.66)	13.7 (1.22)	9.3 (1.60)	3.1 (1.27)	9.6 (4.21)	9.5 (4.38)
Min, Max	13, 17	12, 16	6, 12	2, 5	2, 17	2, 17
Age group, n (%)						
12 to < 18 years	9 (100)	9 (100)	0	0	24 (33.8)	42 (34.4)
6 to < 12 years	0	0	19 (100)	0	34 (47.9)	53 (43.4)
2 to < 6 years	0	0	0	14 (100)	13 (18.3)	27 (22.1)
Race, n (%)						
Asian	0	0	0	0	15 (21.1)	15 (12.3)
Black or African American	0	0	1 (5.3)	0	2 (2.8)	3 (2.5)
White	8 (88.9)	9 (100)	18 (94.7)	14 (100)	53 (74.6)	102 (83.6)
Multiple	1 (11.1)	0	0	0	1 (1.4)	2 (1.6)
Ethnicity, n (%)						
Hispanic or Latino	0	2 (22.2)	4 (21.1)	3 (21.4)	14 (19.7)	23 (18.9)
Not Hispanic or Latino	9 (100)	7 (77.8)	15 (78.9)	11 (78.6)	57 (80.3)	99 (81.1)

Weight (kg)						
Mean (SD)	61.28 (14.618)	51.73 (13.044)	37.75 (14.368)	15.10 (3.240)	39.21 (22.032)	38.77 (21.291)
Min, Max	42.0, 92.9	32.5, 71.5	19.7, 72.1	11.0, 22.5	11.5, 113.6	11.0, 113.6
Weight Category, n (%)						
10 to < 20 kg	0	0	1 (5.3)	13 (92.9)	14 (19.7)	28 (23.0)
20 to < 30 kg	0	0	4 (21.1)	1 (7.1)	15 (21.1)	20 (16.4)
≥ 30 kg	9 (100)	9 (100)	14 (73.7)	0	42 (59.2)	74 (60.7)
BMI (kg/m^2)						
Mean (SD)	23.538 (4.9823)	19.821 (3.4174)	18.278 (4.0528)	15.683 (1.5674)	19.046 (5.3590)	18.929 (4.9667)
Min, Max	15.99, 33.71	14.64, 25.49	12.12, 28.34	13.94, 18.27	12.82, 40.98	12.12, 40.98

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
Safety Cohort: Age 2 to < 18 years; Low Dose from Day 1

Table *15*: Disease Characteristics Summary for All Subjects

TABLE 14.1__5.1

Disease Characteristics
(By Cohort)
(Safety Population)

	Cohort 1 (N=9)	Cohort 2 (N=9)	Cohort 3 (N=19)	Cohort 5 (N=14)	Safety Cohort (N=71)	Total (N=122)
pcJIA type - n (%)						
EXTENDED OLIGOARTICULAR JUVENILE IDIOPATHIC ARTHRITIS	0	0	3 (15.8)	3 (21.4)	12 (16.9)	18 (14.8)
RF NEGATIVE POLYARTICULAR JUVENILE IDIOPATHIC ARTHRITIS	8 (88.9)	7 (77.8)	13 (68.4)	10 (71.4)	44 (62.0)	82 (67.2)
RF POSITIVE POLYARTICULAR JUVENILE IDIOPATHIC ARTHRITIS	1 (11.1)	2 (22.2)	3 (15.8)	0	14 (19.7)	20 (16.4)
SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS WITH ACTIVE ARTHRITIS AND WITHOUT ACTIVE SYSTEMIC FEATURES	0	0	0	1 (7.1)	1 (1.4)	2 (1.6)
MISSING	0	0	0	0	0	0
History of Uveitis - n (%)						
NO	9 (100)	9 (100)	19 (100)	14 (100)	70 (98.6)	121 (99.2)
YES	0	0	0	0	1 (1.4)	1 (0.8)
MISSING	0	0	0	0	0	0
Duration of pcJIA Symptoms in years						
N	9	9	19	14	71	122
Mean (SD)	6.425 (2.4521)	5.740 (4.4025)	3.039 (3.3500)	1.817 (1.5290)	2.572 (2.6661)	3.076 (3.0671)
Median	5.843	6.253	1.229	1.006	1.207	1.532
Q1, Q3	4.767, 6.675	2.040, 7.943	0.534, 5.478	0.630, 3.080	0.567, 3.608	0.701, 4.507
Min, Max	3.45, 11.62	0.82, 13.23	0.21, 10.15	0.27, 4.34	0.13, 10.12	0.13, 13.23

	Cohort 1 (N=9)	Cohort 2 (N=9)	Cohort 3 (N=19)	Cohort 5 (N=14)	Safety Cohort (N=71)	Total (N=122)
Prior exposure to NSAID - n (%)						
NO	0	3 (33.3)	5 (26.3)	4 (28.6)	20 (28.2)	32 (26.2)
YES	9 (100)	6 (66.7)	14 (73.7)	10 (71.4)	51 (71.8)	90 (73.8)
MISSING	0	0	0	0	0	0
Prior exposure to csDMARDs - n (%)						
NO	0	3 (33.3)	10 (52.6)	8 (57.1)	35 (49.3)	56 (45.9)
YES	9 (100)	6 (66.7)	9 (47.4)	6 (42.9)	36 (50.7)	66 (54.1)
MISSING	0	0	0	0	0	0
Prior exposure to bDMARDs - n (%)						
NO	0	5 (55.6)	18 (94.7)	12 (85.7)	60 (84.5)	95 (77.9)
YES	9 (100)	4 (44.4)	1 (5.3)	2 (14.3)	11 (15.5)	27 (22.1)
MISSING	0	0	0	0	0	0
Total number of active joints						
N	9	9	19	14	71	122
Mean (SD)	11.6 (5.53)	11.9 (7.51)	11.6 (7.18)	8.0 (3.11)	11.8 (8.20)	11.3 (7.40)
Median	10.0	10.0	8.0	7.0	9.0	9.0
Q1, Q3	9.0, 11.0	6.0, 15.0	7.0, 16.0	6.0, 10.0	7.0, 16.0	7.0, 15.0
Min, Max	7, 25	5, 24	5, 30	5, 15	5, 48	5, 48

Number of joints with LOM						
N	9	9	19	14	71	122
Mean (SD)	7.1 (3.66)	9.8 (5.59)	9.3 (6.33)	5.9 (3.20)	9.7 (8.23)	9.0 (7.14)
Median	7.0	8.0	7.0	6.0	7.0	7.0
Q1, Q3	6.0, 7.0	6.0, 11.0	5.0, 11.0	5.0, 7.0	5.0, 10.0	5.0, 10.0
Min, Max	3, 16	3, 22	3, 28	0, 12	1, 46	0, 46
Childhood Health Assessment Questionnaire (C-HAQ)						
N	9	9	19	14	67	118
Mean (SD)	1.403 (0.7009)	0.681 (0.6468)	1.072 (0.7607)	0.898 (0.6453)	0.879 (0.7408)	0.937 (0.7307
Median	1.875	0.375	1.250	1.063	0.875	1.000
Q1, Q3	0.750, 2.000	0.125, 1.250	0.375, 1.750	0.125, 1.375	0.250, 1.375	0.250, 1.500
Min, Max	0.38, 2.13	0.00, 1.63	0.00, 2.13	0.00, 2.00	0.00, 2.88	0.00, 2.88
Physician's Global Assessment of Disease Activity (visual analog scale [VAS])						
N	7	8	19	14	66	114
Mean (SD)	82.9 (16.21)	44.5 (22.03)	59.3 (20.91)	51.5 (12.39)	54.3 (22.17)	55.9 (21.78)
Median	88.0	37.0	60.0	51.0	50.5	51.5
Q1, Q3	84.0, 92.0	32.5, 52.5	42.0, 70.0	44.0, 53.0	39.0, 72.0	40.0, 72.0
Min, Max	47, 94	20, 92	29, 100	28, 73	9, 100	9, 100
Patient/Parent Global Assessment of Overall Well Being (VAS)						
N	9	9	19	14	67	118
Mean (SD)	54.8 (21.12)	36.8 (14.75)	42.3 (22.68)	50.3 (23.94)	41.6 (26.05)	43.4 (24.34)
Median	48.0	37.0	50.0	53.0	41.0	44.5
Q1, Q3	41.0, 64.0	33.0, 41.0	26.0, 57.0	41.0, 68.0	18.0, 61.0	27.0, 60.0
Min, Max	28, 88	6, 56	0, 74	1, 88	0, 100	0, 100
Erythrocyte sedimentation rate (ESR)						
N	7	9	19	12	69	116
Mean (SD)	11.9 (8.25)	14.9 (12.53)	18.8 (16.42)	25.8 (21.19)	19.6 (17.64)	19.3 (17.12)
Median	11.0	10.0	14.0	13.5	13.0	13.0
Q1, Q3	6.0, 18.0	8.0, 18.0	7.0, 22.0	9.0, 44.0	7.0, 27.0	7.0, 26.0
Min, Max	2, 26	5, 45	2, 55	6, 63	1, 94	1, 94
C-reactive protein (CRP)						
N	9	9	19	14	71	122
Mean (SD)	1.18 (1.052)	4.37 (7.689)	4.34 (5.525)	17.66 (25.993)	9.26 (15.834)	8.50 (15.626)
Median	0.58	0.64	1.11	4.25	3.31	2.05
Q1, Q3	0.28, 1.95	0.22, 0.96	0.20, 7.90	0.25, 33.80	0.44, 9.56	0.29, 8.69
Min, Max	0.2, 3.0	0.2, 18.9	0.2, 16.9	0.2, 83.8	0.2, 92.3	0.2, 92.3
JADAS27 [CRP]						
N	7	8	19	14	66	114
Mean (SD)	24.33 (7.440)	16.77 (7.616)	19.40 (7.061)	16.96 (3.614)	18.59 (7.109)	18.75 (6.909)
Median	23.70	14.25	20.30	16.85	17.99	18.66
Q1, Q3	22.30, 30.80	12.00, 20.90	12.00, 26.79	14.10, 20.28	13.30, 23.10	13.30, 23.10
Min, Max	11.5, 35.2	8.3, 31.6	8.0, 30.4	10.5, 23.3	6.5, 40.2	6.5, 40.2
JADAS27 [ESR]						
N	7	8	19	12	65	111
Mean (SD)	24.41 (7.588)	16.91 (8.092)	19.91 (7.341)	16.61 (3.889)	18.80 (6.976)	18.97 (6.995)
Median	23.70	13.90	21.50	16.30	18.80	19.10
Q1, Q3	22.30, 30.80	12.00, 21.00	12.00, 26.30	13.70, 19.95	13.90, 23.70	13.30, 23.70
Min, Max	11.5, 35.8	8.3, 33.2	8.0, 30.6	10.9, 23.3	6.5, 39.3	6.5, 39.3

Note: Percentages calculated on non-missing values.
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.
Safety Cohort: age 2 to < 18 years; low dose from day 1.

Prior and concomitant medication:

The majority of subjects (95.9%) reported prior medications; the most frequently reported prior medications were methotrexate (48.4%), folic acid (40.2%), naproxen (39.3%), and ibuprofen (35.2%).

NSAIDs, csDMARDs, oral corticosteroids, and non-oral corticosteroids were reported as concomitant medications during the study; no subjects received concomitant bDMARDs, IL-6 inhibitors, TNF inhibitors, or JAK inhibitors during the study.

The majority of subjects (90.2%) reported at least 1 concomitant NSAID medication during the study; the most frequently reported concomitant NSAID medications were ibuprofen (63.1%) and naproxen (36.9%). A total of 51 subjects (41.8%) reported at least 1 concomitant csDMARD medication during the study; methotrexate (41.0%) was the most frequently reported concomitant csDMARD medication.

A total of 39 subjects (32.0%) reported concomitant use of oral corticosteroids; the most frequently reported concomitant oral corticosteroid medications were prednisolone (16.4%) and prednisone (9.8%).

A total of 23 subjects (18.9%) reported concomitant use of non-oral corticosteroids; triamcinolone acetonide (10.7%) was the most frequently reported concomitant non-oral corticosteroid medication.

5.3.2.1.4.4. Outcomes and estimation

The number of subjects with available efficacy data at each visit varied slightly by efficacy endpoint. Actual subject numbers are included in the below tables and figures. Through the data cutoff date, 114 subjects had ACR Paediatric 30/50/70/90/100 response data available at Week 12, 109 subjects had response data at Week 48, and 33 subjects had response data through Week 156.

Table *16*:Summary of ACR Paediatric 30/50/70/90/100 Response Rate at Week 12 (As Observed) (ITT Population, Parts 1, 2, and 3)

	n (%) [95% CI]			
ACR Pediatric Response	**Age 2 to < 6 years (N = 24)**	**Age 6 to < 12 years (N = 51)**	**Age 12 to < 18 years (N = 39)**	**Overall (N = 114)**
ACR Pediatric 30	21 (87.5) [67.6, 97.3]	47 (92.2) [81.1, 97.8]	35 (89.7) [75.8, 97.1]	103 (90.4) [83.4, 95.1]
ACR Pediatric 50	19 (79.2) [57.8, 92.9]	47 (92.2) [81.1, 97.8]	33 (84.6) [69.5, 94.1]	99 (86.8) [79.2, 92.4]
ACR Pediatric 70	18 (75.0) [53.3, 90.2]	40 (78.4) [64.7, 88.7]	23 (59.0) [42.1, 74.4]	81 (71.1) [61.8, 79.2]
ACR Pediatric 90	9 (37.5) [18.8, 59.4]	26 (51.0) [36.6, 65.2]	12 (30.8) [17.0, 47.6]	47 (41.2) [32.1, 50.8]
ACR Pediatric 100	6 (25.0) [9.8, 46.7]	18 (35.3) [22.4, 49.9]	8 (20.5) [9.3, 36.5]	32 (28.1) [20.1, 37.3]

Note: Exact confidence intervals based on Clopper-Pearson method.

Table *17*: Summary of ACR Paediatric 30/50/70/90/100 Response Rate at Week 48 (As Observed) (ITT Population, Parts 1, 2, and 3)

	n (%) [95% CI]			
ACR Pediatric Response	**Age 2 to < 6 years (N = 25)**	**Age 6 to < 12 years (N = 47)**	**Age 12 to < 18 years (N = 37)**	**Overall (N = 109)**
ACR Pediatric 30	25 (100) [86.3, 100.0]	45 (95.7) [85.5, 99.5]	35 (94.6) [81.8, 99.3]	105 (96.3) [90.9, 99.0]
ACR Pediatric 50	25 (100) [86.3, 100.0]	43 (91.5) [79.6, 97.6]	34 (91.9) [78.1, 98.3]	102 (93.6) [87.2, 97.4]
ACR Pediatric 70	25 (100) [86.3, 100.0]	42 (89.4) [76.9, 96.5]	30 (81.1) [64.8, 92.0]	97 (89.0) [81.6, 94.2]
ACR Pediatric 90	23 (92.0) [74.0, 99.0]	36 (76.6) [62.0, 87.7]	20 (54.1) [36.9, 70.5]	79 (72.5) [63.1, 80.6]
ACR Pediatric 100	18 (72.0) [50.6, 87.9]	30 (63.8) [48.5, 77.3]	15 (40.5) [24.8, 57.9]	63 (57.8) [48.0, 67.2]

Note: Exact confidence intervals based on Clopper-Pearson method.

Figure *10*: Summary of Select Efficacy Endpoints at Week 12 (As Observed) (ITT Population, Parts 1, 2, and 3)

Efficacy Endpoint Age Group	N	Baseline Mean	Visit Mean	Within Group Change from Baseline	
				Mean (95% CI)	Median (Min, Max)
C-HAQ					
2 to < 6 years	24	0.89	0.54	-0.35 (-0.65, -0.05)	-0.25 (-1.4, 1.1)
6 to < 12 years	51	0.94	0.34	-0.59 (-0.77, -0.42)	-0.25 (-2.4, 0.3)
12 to < 18 years	40	0.99	0.64	-0.36 (-0.52, -0.19)	-0.25 (-2.1, 0.5)
Overall	115	0.95	0.49	-0.46 (-0.57, -0.35)	-0.25 (-2.4, 1.1)
Total number of active joints					
2 to < 6 years	27	9.0	1.7	-7.3 (-8.5, -6.0)	-6.0 (-16, -3)
6 to < 12 years	51	11.1	1.6	-9.5 (-11.1, -8.0)	-8.0 (-26, -2)
12 to < 18 years	42	12.3	1.8	-10.5 (-13.0, -8.0)	-9.0 (-45, 0)
Overall	120	11.1	1.7	-9.4 (-10.5, -8.2)	-8.0 (-45, 0)
Physician's Global Assessment of Disease Activity (VAS)					
2 to < 6 years	23	56.7	9.3	-47.4 (-55.1, -39.6)	-46.0 (-100, -16)
6 to < 12 years	49	53.6	6.5	-47.1 (-53.0, -41.1)	-48.0 (-100, -3)
12 to < 18 years	35	56.9	14.5	-42.5 (-50.8, -34.1)	-38.0 (-94, 9)
Overall	107	55.3	9.7	-45.6 (-49.7, -41.5)	-45.0 (-100, 9)
Patient/Parent Global Assessment of Overall Well Being (VAS)					
2 to < 6 years	25	41.7	12.6	-29.1 (-42.2, -16.0)	-26.0 (-81, 37)
6 to < 12 years	51	38.7	13.5	-25.2 (-33.4, -17.0)	-25.0 (-80, 51)
12 to < 18 years	40	50.2	29.7	-20.5 (-26.9, -14.1)	-21.0 (-75, 13)
Overall	116	43.3	18.9	-24.4 (-29.4, -19.5)	-23.0 (-81, 51)
JADAS27-CRP					
2 to < 6 years	23	17.30	3.60	-13.69 (-15.99, -11.40)	-13.70 (-22.4, -5.1)
6 to < 12 years	49	17.71	3.38	-14.34 (-16.33, -12.34)	-14.30 (-28.9, -0.4)
12 to < 18 years	35	20.11	6.19	-13.92 (-16.02, -11.83)	-14.40 (-31.1, -0.3)
Overall	107	18.41	4.34	-14.06 (-15.27, -12.86)	-14.30 (-31.1, -0.3)

Note: N is the number of subjects for whom both the visit value and the Baseline value were present. Confidence intervals based on normal approximation.

Table *18*: Summary of Select Efficacy Endpoints at Week 48 (As Observed) (ITT Population, Parts 1, 2, and 3)

Efficacy Endpoint Age Group	N	Baseline Mean	Visit Mean	Within Group Change from Baseline	
				Mean (95% CI)	Median (Min, Max)
C-HAQ					
2 to < 6 years	24	0.90	0.23	-0.67 (-0.99, -0.35)	-0.56 (-2.6, 0.8)
6 to < 12 years	47	0.87	0.19	-0.67 (-0.87, -0.48)	-0.50 (-2.5, 0.4)
12 to < 18 years	37	1.01	0.42	-0.58 (-0.79, -0.38)	-0.38 (-2.5, 0.1)
Overall	108	0.92	0.28	-0.64 (-0.77, -0.51)	-0.50 (-2.6, 0.8)
Total number of active joints					
2 to < 6 years	26	9.0	0.2	-8.8 (-10.3, -7.3)	-7.0 (-19, -5)
6 to < 12 years	50	11.1	1.0	-10.0 (-11.7, -8.4)	-8.0 (-28, -3)
12 to < 18 years	40	12.4	1.3	-11.1 (-13.9, -8.3)	-9.5 (-46, 10)
Overall	116	11.1	0.9	-10.1 (-11.4, -8.9)	-8.0 (-46, 10)
Physician's Global Assessment of Disease Activity (VAS)					
2 to < 6 years	24	55.8	2.1	-53.7 (-61.4, -45.9)	-51.5 (-100, -27)
6 to < 12 years	46	55.0	3.4	-51.6 (-57.9, -45.3)	-50.0 (-100, -11)
12 to < 18 years	33	58.8	8.5	-50.3 (-60.6, -40.1)	-45.0 (-94, 33)
Overall	103	56.4	4.7	-51.7 (-56.2, -47.1)	-50.0 (-100, 33)
Patient/Parent Global Assessment of Overall Well Being (VAS)					
2 to < 6 years	25	43.6	4.4	-39.2 (-50.7, -27.6)	-40.0 (-87, 7)
6 to < 12 years	47	38.0	12.3	-25.7 (-33.6, -17.8)	-28.0 (-84, 47)
12 to < 18 years	37	51.3	20.1	-31.2 (-38.7, -23.7)	-32.0 (-73, 20)
Overall	109	43.8	13.1	-30.7 (-35.6, -25.7)	-31.0 (-87, 47)
JADAS27-CRP					
2 to < 6 years	24	17.14	0.78	-16.36 (-18.34, -14.38)	-17.15 (-23.4, -7.9)
6 to < 12 years	45	17.74	2.54	-15.20 (-17.31, -13.09)	-13.00 (-29.6, -2.9)
12 to < 18 years	31	21.54	4.00	-17.53 (-20.32, -14.75)	-17.60 (-35.4, 4.4)
Overall	100	18.78	2.57	-16.20 (-17.54, -14.86)	-16.90 (-35.4, 4.4)

Note: N is the number of subjects for whom both the visit value and the Baseline value were present. Confidence intervals based on normal approximation.

Table *19*: Summary of JADAS27-CRP ≤ 3.8 and JADAS27-CRP ≤ 1 at Week 12 (As Observed) (ITT Population, Parts 1, 2, and 3)

	n (%) [95% CI]			
	Age 2 to < 6 years (N = 24)	Age 6 to < 12 years (N = 50)	Age 12 to < 18 years (N = 40)	Overall (N = 114)
JADAS27-CRP ≤ 3.8	15 (62.5) [40.6, 81.2]	36 (72.0) [57.5, 83.8]	11 (27.5) [14.6, 43.9]	62 (54.4) [44.8, 63.7]
JADAS27-CRP ≤ 1	7 (29.2) [12.6, 51.1]	18 (36.0) [22.9, 50.8]	3 (7.5) [1.6, 20.4]	28 (24.6) [17.0, 33.5]

Note: Exact confidence intervals based on Clopper-Pearson method.

Table *20*: Summary of JADAS27-CRP ≤ 3.8 and JADAS27-CRP ≤ 1 at Week 48 (As Observed) (ITT Population, Parts 1, 2, and 3*)*

	n (%) [95% CI]			
	Age 2 to < 6 years (N = 25)	**Age 6 to < 12 years (N = 45)**	**Age 12 to < 18 years (N = 37)**	**Overall (N = 107)**
JADAS27-CRP ≤ 3.8	25 (100) [86.3, 100.0]	37 (82.2) [67.9, 92.0]	23 (62.2) [44.8, 77.5]	85 (79.4) [70.5, 86.6]
JADAS27-CRP ≤ 1	18 (72.0) [50.6, 87.9]	23 (51.1) [35.8, 66.3]	12 (32.4) [18.0, 49.8]	53 (49.5) [39.7, 59.4]

Note: Exact confidence intervals based on Clopper-Pearson method.

Table *21*: Summary of JIA ACR 70/100, JADAS27-CRP LDA and JADAS27-CRP Remission (NRI) (ITT Population, Study Parts 1, 2 and 3*)*

Visit		**Responder**	
Endpoint	**N**	**n (%)**	**[95% CI]$**
Week 12			
JIA ACR70	122	81 (66.4)	[57.3, 74.7]
JIA ACR100	122	32 (26.2)	[18.7, 35.0]
JADAS-27 [CRP] <= 3.8	122	62 (50.8)	[41.6, 60.0]
JADAS-27 [CRP] <= 1	122	28 (23.0)	[15.8, 31.4]
Week 48			
JIA ACR70	122	97 (79.5)	[71.3, 86.3]
JIA ACR100	122	63 (51.6)	[42.4, 60.8]
JADAS-27 [CRP] <= 3.8	122	85 (69.7)	[60.7, 77.7]
JADAS-27 [CRP] <= 1	122	53 (43.4)	[34.5, 52.7]

Note: Non-Responder Imputation (NRI): the NRI analysis will categorize any subject who does not have evaluation during a specific post-baseline visit window as a non-responder for that visit.

$ = Exact Clopper-Pearson CI for proportions.

5.3.2.1.4.5. Pre-defined and post-hoc subgroup analyses.

Data were presented by age group or cohorts. Post hoc analysis by baseline weight category, upadacitinib formulation and concomitant Methotrexate treatment was provided upon request.

Table *22*: Summary of ACR Paediatric 70 Response Rate at Week 12 and Week 48 by Subgroup (weight, upadacitinib formulation, concomitant MTX) (NRI)(Overall) (ITT Population, Study Parts 1, 2 and 3)

Visit Subgroup Subgroup category	N	Responder n (%)	[95% CI]	Missing n (%)
Week 12				
Overall	122	81 (66.4)	[57.3, 74.7]	8 (6.6)
Baseline weight				
>= 10 kg to < 20 kg	28	19 (67.9)	[47.6, 84.1]	3 (10.7)
>= 20 kg to < 30 kg	20	15 (75.0)	[50.9, 91.3]	1 (5.0)
>= 30 kg	74	47 (63.5)	[51.5, 74.4]	4 (5.4)
Upadacitinib formulation				
Oral solution only	38	27 (71.1)	[54.1, 84.6]	3 (7.9)
Tablets only	69	43 (62.3)	[49.8, 73.7]	4 (5.8)
Concomitant MTX				
No	71	49 (69.0)	[56.9, 79.5]	5 (7.0)
Yes	51	32 (62.7)	[48.1, 75.9]	3 (5.9)
Week 48				
Overall	122	97 (79.5)	[71.3, 86.3]	13 (10.7)
Baseline weight				
>= 10 kg to < 20 kg	28	24 (85.7)	[67.3, 96.0]	4 (14.3)
>= 20 kg to < 30 kg	20	17 (85.0)	[62.1, 96.8]	1 (5.0)
>= 30 kg	74	56 (75.7)	[64.3, 84.9]	8 (10.8)
Upadacitinib formulation				
Oral solution only	38	32 (84.2)	[68.7, 94.0]	5 (13.2)
Tablets only	69	51 (73.9)	[61.9, 83.7]	8 (11.6)
Concomitant MTX				
No	71	56 (78.9)	[67.6, 87.7]	8 (11.3)
Yes	51	41 (80.4)	[66.9, 90.2]	5 (9.8)

Note: Non-Responder Imputation (NRI): the NRI analysis will categorize any subject who does not have evaluation during a specific post-baseline visit window as a non-responder for that visit.
Upadacitinib formulation subgroups include only subjects who received exclusively oral solution or exclusively tablets during the study. Subjects who switched upadacitinib formulation during the study are excluded.
Exact confidence intervals based on Clopper-Pearson method.

Table *23*: Proportion of Subjects with JADAS-27 [CRP] <= 3.8 at Week 12 and Week 48 by Subgroup (weight, upadacitinib formulation) (NRI) (Overall) (ITT Population, Study Parts 1, 2 and 3)

Week 12				
Overall	122	62 (50.8)	[41.6, 60.0]	8 (6.6)
Baseline weight				
>= 10 kg to < 20 kg	28	17 (60.7)	[40.6, 78.5]	2 (7.1)
>= 20 kg to < 30 kg	20	11 (55.0)	[31.5, 76.9]	4 (20.0)
>= 30 kg	74	34 (45.9)	[34.3, 57.9]	2 (2.7)
Upadacitinib formulation				
Oral solution only	38	24 (63.2)	[46.0, 78.2]	4 (10.5)
Tablets only	69	29 (42.0)	[30.2, 54.5]	2 (2.9)
Week 48				
Overall	122	85 (69.7)	[60.7, 77.7]	15 (12.3)
Baseline weight				
>= 10 kg to < 20 kg	28	23 (82.1)	[63.1, 93.9]	5 (17.9)
>= 20 kg to < 30 kg	20	15 (75.0)	[50.9, 91.3]	2 (10.0)
>= 30 kg	74	47 (63.5)	[51.5, 74.4]	8 (10.8)
Upadacitinib formulation				
Oral solution only	38	30 (78.9)	[62.7, 90.4]	7 (18.4)
Tablets only	69	42 (60.9)	[48.4, 72.4]	8 (11.6)

Note: Non-Responder Imputation (NRI): the NRI analysis will categorize any subject who does not have evaluation during a specific post-baseline visit window as a non-responder for that visit.
Upadacitinib formulation subgroups include only subjects who received exclusively oral solution or exclusively tablets during the study. Subjects who switched upadacitinib formulation during the study are excluded.
Exact confidence intervals based on Clopper-Pearson method.

Table 24: Proportion of Subjects with JADAS-27 [CRP] <= 1 at Week 12 and Week 48 by Subgroup (weight, upadacitinib formulation) (NRI) (Overall) (ITT Population, Study Parts 1, 2 and 3)

Visit / Subgroup / Subgroup category	N	Responder n (%)	Responder [95% CI]	Missing n (%)
Week 12				
Overall	122	28 (23.0)	[15.8, 31.4]	8 (6.6)
Baseline weight				
>= 10 kg to < 20 kg	28	8 (28.6)	[13.2, 48.7]	2 (7.1)
>= 20 kg to < 30 kg	20	6 (30.0)	[11.9, 54.3]	4 (20.0)
>= 30 kg	74	14 (18.9)	[10.7, 29.7]	2 (2.7)
Upadacitinib formulation				
Oral solution only	38	10 (26.3)	[13.4, 43.1]	4 (10.5)
Tablets only	69	13 (18.8)	[10.4, 30.1]	2 (2.9)
Week 48				
Overall	122	53 (43.4)	[34.5, 52.7]	15 (12.3)
Baseline weight				
>= 10 kg to < 20 kg	28	16 (57.1)	[37.2, 75.5]	5 (17.9)
>= 20 kg to < 30 kg	20	11 (55.0)	[31.5, 76.9]	2 (10.0)
>= 30 kg	74	26 (35.1)	[24.4, 47.1]	8 (10.8)
Upadacitinib formulation				
Oral solution only	38	22 (57.9)	[40.8, 73.7]	7 (18.4)
Tablets only	69	23 (33.3)	[22.4, 45.7]	8 (11.6)

Note: Non-Responder Imputation (NRI): the NRI analysis will categorize any subject who does not have evaluation during a specific post-baseline visit window as a non-responder for that visit.
Upadacitinib formulation subgroups include only subjects who received exclusively oral solution or exclusively tablets during the study. Subjects who switched upadacitinib formulation during the study are excluded.
Exact confidence intervals based on Clopper-Pearson method.

5.3.3. Clinical studies in special populations

MAH's rationale for an efficacy extrapolation from adult to paediatric patients of the use of upadacitinib in pcJIA.

Children with pcJIA share similar pathophysiology and clinical manifestation to adults with RA.

pcJIA is defined as arthritis of unknown aetiology that begins before the 16th birthday, persists for at least 6 weeks, and affects 5 or more joints in the first 6 months of disease. Similarly, to meet the classification criteria for RA, an adult must have inflammatory arthritis in multiple joints for at least 6 weeks. Both pcJIA and RA can affect small and large joints, and the cervical spine, but typically spare the axial skeleton. Both conditions are characterized by a chronic, relapsing-remitting course, although extended drug-free remissions are more likely with pcJIA (up to 24%) than RA (13%). RA and pcJIA share similar risk factors. Both pcJIA and RA predominantly affect females, with the similar 2:1 – 3:1 female-to-male ratio in children and adults. Heritability for both RA and JIA (all subtypes) is estimated at approximately 60%. Genetically, RA and JIA patients share several risk alleles within the HLA and non-HLA regions. The closest genetic association is observed between RF positive pcJIA and adult seropositive RA, with the same amino acid (histidine) at position 13 in the HLA-DRB1 allele. Furthermore, oligoarticular JIA and RF negative pcJIA share an HLA association with adult seronegative RA.

While the aetiologies of RA and pcJIA are not completely understood, they share similar pathobiology. Both conditions are characterised by inflammatory arthritis, with marked proliferation of the synovium and neovascularization, and abundance of CD4+ T cells and B-cell infiltrates in the synovium. There are similarly increased levels of inflammatory cytokines, IL-6 and TNF-α, and complement cleavage

products in synovial fluid from patients with pcJIA and RA. Furthermore, in both conditions, a subset of patients have positive RF and anti-citrullinated peptide antibodies. Although fewer pcJIA patients than adult RA patients have RF or anti-citrullinated peptide antibodies, 10 to 25% versus 80 to 85%, respectively, the presence of these antibodies in both conditions is associated with poor prognosis and erosive disease. Notable distinctions between pcJIA and adult RA include the high incidence of uveitis in pcJIA, which is not commonly seen in RA, and the different genetic risk composition in very young patients with pcJIA < 6 years of age. However, according to the MAH, these manifestations may be a sign of age-specific physiology and exposures rather than indicative of a different disease.

Children with pcJIA, when compared with adults with RA, have a similar response to intervention.

Based on existing evidence, the 2019 ACR/Arthritis Foundation guideline recommends csDMARDs (MTX, sulfasalazine) and bDMARDs (TNF-α inhibitors, CTLA4-IG, IL-6 receptor inhibitor) for the treatment of children of all ages with pcJIA. All of these DMARDs are also recommended for the management of adult RA. A notable difference in the treatment patterns of pcJIA and RA is a longer time to initiation of MTX in pcJIA patients compared with RA, which is, according to the applicant, likely due to safety concerns associated with MTX use in children and adolescents. Efficacy of TNF-α inhibitors for pcJIA was demonstrated for multiple agents in the class, including adalimumab, infliximab, golimumab, and etanercept, with ACR Paediatric 30 response rates ranging between 64 to 89% at 12 to 16 weeks. These are similar to ACR20 response rates to TNF-α inhibitors of 50 to 66% in adults with RA naïve to bDMARDs. Such comparisons should be interpreted with caution, given differences in study methodologies and outcomes. IL-6 receptor blockade, a mechanism relevant to the mechanism of action of upadacitinib, is also effective in children with pcJIA and in adults with RA. Tocilizumab, an IL-6 receptor inhibitor, is approved for both indications in the US. In clinical trials of adults with RA naïve to biologics, the ACR20 response to tocilizumab was around 60% at Week 24. In children, by Week 16, 89% of subjects with pcJIA achieved ACR Paediatric 30 response to tocilizumab in an open-label phase of a randomized withdrawal trial; those who continued tocilizumab had significantly fewer flares during the randomized withdrawal phase compared with placebo. JAK inhibitors, including tofacitinib, baricitinib, and upadacitinib, have demonstrated a favourable benefit-risk profile in adult RA and have been approved for this indication. Tofacitinib was also approved by FDA in 2020 and by the EMA in 2021 for the treatment of children and adolescents 2 years of age and older with pcJIA, based on one Phase 3 randomized, double-blind withdrawal study in subjects aged 2 to < 18 years with pcJIA, JPsA, or ERA. In the primary analysis, efficacy was demonstrated for tofacitinib treatment in 184 subjects with pcJIA; 77% of subjects achieved ACR Paediatric 30 response at Week 18 during the open-label run-in phase and were eligible for randomized withdrawal; during the randomized withdrawal phase up to Week 44, 29% of subjects experienced a JIA flare on tofacitinib versus 53% on placebo. Safety events were similar to those observed in adults with RA. Baricitinib was evaluated in a similarly designed Phase 3 randomized, double-blind withdrawal study in subjects aged 2 to < 18 years with extended oligo-JIA or polyarticular JIA, ERA, or JPsA. The study demonstrated ACR Paediatric 30 response rates of 76.3% at Week 12 of the open-label lead-in period across JIA subtypes. During the 34-week randomized withdrawal period, significantly reduced time to and frequency of flares in the baricitinib group versus placebo was observed (flare rate of 17.1% versus 50.6%). Safety findings were consistent with the known safety profile of baricitinib in adult RA. Taken together, the applicant states that there is evidence of clinical, pathophysiologic, and genetic similarities between pcJIA and adult RA, supported by similar responses to therapies.

Upadacitinib plasma concentrations are predictive of clinical response and a similar exposure-response or concentration-response relationship is expected **between adult RA and pcJIA**

Upadacitinib PK has been evaluated in Phase 1 studies as well as in Phase 2 and 3 studies in adult subjects with RA. Exposure-response analyses using data across RA Phase 2 and 3 studies demonstrated that the efficacy of upadacitinib was exposure-dependent.

According to the applicant, similarity of upadacitinib exposure-response relationship between adult RA and pcJIA is expected based on available results from the JAK inhibitor tofacitinib, which has been approved for the treatment of active pcJIA in patients 2 years of age and older. A weight-based dosing approach was implemented for the tofacitinib paediatric programme. Tofacitinib PK in paediatric subjects with pcJIA was first evaluated in a Phase 1 study, which informed appropriate tofacitinib doses in pcJIA that provided comparable plasma exposures to 5 mg BID in adults with RA. Available results from tofacitinib Phase 1 and Phase 3 studies in pcJIA indicate that the selected tofacitinib doses, which provided similar plasma exposures between pcJIA and RA, were efficacious in both diseases. Given the similar mechanism of action between JAK inhibitors tofacitinib and upadacitinib, the applicant assumed that plasma exposures of upadacitinib identified as optimally efficacious in RA are also expected to be optimally efficacious in pcJIA.

In addition to PK and safety, Study M15-340 evaluates efficacy of upadacitinib in paediatric (2 to < 18 years) subjects with pcJIA using descriptive assessments of subject symptoms and QoL. Results of this study are presented in Section 5.3.2.1.

5.3.4. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

5.3.5. Overall discussion and conclusions on clinical efficacy

5.3.5.1. Discussion

To support the extension of indication in children with pcJIA, the MAH proposed an efficacy extrapolation approach based on the following criteria: 1) similar pathophysiology and clinical manifestation between children with pcJIA and adults with RA; 2) similar response to treatment intervention between children with pcJIA and adults with RA; and 3) similar exposure-response or concentration-response relationship that is predictive of the clinical response. Hence, upadacitinib plasma exposures which are identified to be optimally efficacious in adult patients with RA were expected to also be optimally efficacious in paediatric patients with pcJIA. Extrapolation of efficacy from adults with RA to children with JIA was also supported by the Guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis (EMA/CHMP/239770/2014 Rev. 2). Additionally, the extrapolation approach that may obviate the need for a formal efficacy study was accepted by the PDCO (EMEA-001741-PIP01-14-M05). As concluded in the section on clinical pharmacology, upadacitinib plasma exposures ($C_{max,ss}$ and $AUC_{24,ss}$) in paediatric patients with pcJIA following the recommended weight-based paediatric dosing scheme were predicted to be similar to the target plasma exposure in adult RA patients receiving the recommended dose .Hence, the extrapolation concept was endorsed by the CHMP.

Efficacy of upadacitinib was extrapolated from the 5 Phase 3 randomised, double-blind, multicentre studies in patients with moderately to severely active rheumatoid arthritis (Select-Early, Select-Monotherapy, Select-Next, Select-Compare, Select-Beyond) which supported the marketing authorisation of upadacitinib in adults with RA (EMEA/H/C/004760/0000). In addition, results from

the clinical study M15-340, a phase 1, open label study in patients with pcJIA were submitted in this procedure. However, only descriptive efficacy data were available from this study.

The study M15-340 included patients with an active polyarticular course JiA, defined as 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, with 5 or more active joints at the time of screening). The following subtypes were represented in the study: RF-positive polyarticular JiA (16.4%), RF-negative polyarticular JiA (67.2%), extended oligoarticular JiA (14.8%) and systemic JiA without active systemic features (1.6%). Patients with enthesitis-related arthritis (ERA) or juvenile psoriatic arthritis (JPSA) were excluded from the study. The subtypes are in line with the current ILAR criteria. Patients with ongoing or active uveitis within 3 months were excluded from the study. There was only one patient with a history of uveitis included in the study.

Around 22% of the study population were previously exposed to a biologic DMARD and around 40% were currently on concomitant conventional DMARD, mainly Methotrexate. This has been reflected in the SmPC.

The initially proposed indication was not acceptable and differed from approved indications for other products in the field, by using a broader nomenclature and by proposing first line treatment. However, since efficacy data were extrapolated from an adult population with similar disease, the wording of the indication for the paediatric population needed to be harmonized with the adult indication. The CHMP agreed that patients with RF-positive polyarticular JiA, RF-negative polyarticular JiA and also extended oligoarticular JiA were similar enough regarding pathophysiology, clinical manifestations and response to therapeutic interventions for data extrapolated from adults with RA to these populations. However, systemic JiA are not regarded as a similar disease as RA and Rinvoq is not approved for adult-onset Stills disease (the adult variant of systemic JiA). Thus, upon CHMP's request, the MAH revised the wording of the therapeutic indication to the following:

"Rinvoq is indicated for the treatment of active polyarticular juvenile idiopathic arthritis (polyarticular rheumatoid factor positive [RF+] or negative [RF-], extended oligoarticular), in patients 2 years of age and older who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). Rinvoq may be used as monotherapy or in combination with methotrexate"

Study M15-340 is still ongoing and expected to continue for a total of 156 weeks. As of the data cutoff date of 21 March 2025, a total of 34 subjects had completed the study, 68 subjects were ongoing and 20 subjects discontinued the study. Twenty one (17.2%) subject discontinued the study drug and the most frequent (primary) reason for study drug discontinuation was lack of efficacy (n=12, 9.8%) and withrawal by subject (n=5, 4.1%). Upon CHMP's request, the MAH presented further information regarding the patients who discontinued due to lack of efficacy and there were no signs that this was due to a lack of appropriate exposure of medication.

The selected efficacy endpoints of paediatric ACR 30/50/70/90/100 response were considered relevant for the paediatric JiA population. These endpoints are also reflected in the Guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis (EMA/CHMP/239770/2014 Rev. 2). The CHMP noted that it is similar to the adult ACR 20/40/70 response, however, not fully interchangeable.

In addition, JADAS-27 (CRP) was calculated, allowing for a determination of patients achievement of low disease activity (JADAS-27≤ 3.8) or remission (JADAS-27≤ 1.). The CHMP noted that JADAS-27 is similar to the adult DAS-28, however, not fully interchangeable.

Nevetherless, the CHMP considered that both paediatric ACR response and JADAS-27 are based on several subjective measurements and are principally not suitable for use in an open label setting. No isuse was raised since these efficacy data are supportive only.

Efficacy results:

Efficacy results were only presented in observed cases.

At week 12, the proportions of patients achieving paediatric ACR 30/50/70/90/100 were 90.4%/86.8%/71.1%/41.2%/28.1% of the 114 evaluated patients. These results were in line with the results seen in the adult population where an ACR 20/50/70 response was seen in 64-76%/34-52%/12-32%, with highest efficacy in the Mtx-naïve population and lesser in the bio-experienced population.

The proportions of patients with low disease activity and remission were 54% and 24% in the paediatric population and 43-53% and 28-36% in adults.

At week 48 the proportions of patients achieving paediatric ACR 30/50/70/90/100 were 96.3%/93.6%/89.0%/72.5%/57.8% of the 109 evaluated patients. For the adult population ACR 20/50/70 was 65%/49%/36% in Mtx nonresponders.

At Week 48, the proportion of patients with low disease activity (JADAS27-CRP $\leq$ 3.8) or remission (JADAS27-CRP $\leq$ 1) was 79.4% and 49.5% in the children and 50-59% (for LDA DAS28-CRP $\leq$3.2) and 38-49% (for CR DAS28-CRP <2.6) in adults. Remission rate was lower in the population >12 years of age, which may reflect the higher number of bDMARD-experienced patients in that group.

Changes in background medication was allowed during the study. Upon CHMP's request, the MAH reported that only one patient had a body surface area-adjusted dose increase in methotrexate during the study. Although no further information regarding changes in other background medication (corticosteroids, NSAID) was provided, the statement in the SmPC Section 5.1 that changes in these medications were allowed was considered sufficient as it is agreed with the applicant that this is not anticipated to have any major impact on the result.

Although the study M15-340 was conducted in an open-label manner, the observed paediatric ACR response rates were sufficiently high to be considered clinically relevant and in line with the results seen in the adult RA studies. In addition, although acknowledging the limitation of comparison between studies, the proportion of patients achieving inactive disease was not smaller than the proportion seen in JiA patients in studies with other JAK-inhibitors.

However, the actual numbers and proportion of patients with a response are probably overestimated due to the open label design with no control group. In addition, since the majority of the patients who withdrew the study did so due to lack of efficacy, a presentation of the ITT population with non-responder imputation (NRI) was considered more appropriate. The results with a NRI analysis provided upon CHMP's request showed, as expected< a slightly lower response rate, although did not deviate more than 10% in any of the endpoints presented. The CHMP agreed to include results from the selected endpoints in the SmPC Section 5.1 with the appropriate NRI analysis.

Overall, the observed results were considered compatible with an effect at the proposed posology and supportive to the results seen with the PK-matching. Additional data provided by the MAH indicated a similar response between weight groups and also between formulations. In addition, there were no major differences in response rate between patients with or without concomitant Mtx treatment.

5.3.5.2. Conclusions on the clinical efficacy

The extension of indication in children with pcJIA, was supported by an efficacy extrapolation approach based on 1) similar pathophysiology and clinical manifestation between children with pcJIA and adults with RA; 2) similar response to treatment intervention between children with pcJIA and adults with RA; and 3) similar exposure-response or concentration-response relationship that is predictive of the clinical response. The extrapolation concept was endorsed by the CHMP.

In addition, the efficacy results achieved from the uncontrolled, open label study M15-340 in paediatric patients with pcJIA provided support to the PK data for an effect in line with the adult RA population.

Overall, the efficacy of upadacitinib was considered established for the treatment of active polyarticular juvenile idiopathic arthritis (polyarticular rheumatoid factor positive [RF+] or negative [RF-], extended oligoarticular), in patients 2 years of age and older who have responded inadequately to, or who are intolerant to one or more DMARDs. Rinvoq may be used as monotherapy or in combination with methotrexate.

5.4. Clinical safety

Please refer to the table of studies in section 5.1.2.

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse Drug Reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.4.0. Safety data collection

Safety data for upadacitinib administered using a QD extended-release tablet (15 mg) formulation, or a twice daily immediate-release oral solution (1 mg/mL) formulation, in subjects with pcJIA was collected in clinical trial. According to the MAH, safety data was collected per protocol at all required on-site study visits which consisted of 18 or 20 visits across 156 weeks, depending on the cohort, plus a follow-up call or visit, 30 days post last dose. Modifications to study visits were permitted, when necessary, due to a state of emergency or pandemic-related restrictions. At these study visits, the primary investigator (PI) asked the subjects and discussed if any AEs had occurred. The PI recorded the AEs on the eCRFs. Depending on the AE and/or SAEs reported, the PI would then follow up the AEs until resolution and document the follow up in the eCRFs. In addition, serum labs were drawn during on site assessments and tested at the central lab. A follow-up phone call may have been initiated by

the PI to follow up on previously reported AEs or in order to perform repeat laboratory testing. In addition, the 30 days post last dose follow up visit was conducted via phone call, to elucidate if any further AEs had occurred. Safety information was not collected via subject diaries.

The clinical programme for upadacitinib in pcJIA includes one ongoing Phase 1 Study (M15-340) in subjects 2 to < 18 years of age with pcJIA. Study design is presented in Section 5.3.2.1.2. of this document.

Safety evaluations include incidence of Treatment Emergent Adverse Events (TEAEs), physical examination results, change in vital sign measurements, and clinical laboratory testing (haematology and chemistry) as measures of safety and tolerability for the entire study duration.

All subjects who received at least 1 dose of study drug were included in the safety analyses (Safety Population). There are 3 sets of safety analysis: safety analysis for Part 1, safety analysis for Parts 2 and 3 together, and safety analysis for all parts together. Primarily, data from safety analysis of all parts together are summarised and presented by age group.

In addition to the phase I study in pcJIA, supportive upadacitinib paediatric and adolescent safety data from completed AD Phase 1 Study M16-049 and ongoing AD Phase 3 Studies M16-045, M16-047, and M18-891 (data cutoff 15 August 2024) were included and described.

5.4.1. Patient exposure

Table *25*: Patient exposure

Studies in JIA (data cutoff 21 March 2025)

		Age 2 to <6	Age 6 to <12	Age 12 to <18	Total
Open label phase I study in paediatric patients (M15-340)	Total subjects:	27	53	42	122
	Median exposure (days):	989.0	765.0	619.5	729.5
	Patient years:	62.5	110.7	81.4	254.6

Supportive studies in paediatric patients with AD (data cutoff 15 August 2024)

		Age 2 to <6	Age 6 to <12	Age 12 to <18	Total
Phase I paediatric AD study (M16-049)*	Total subjects:	16	17	0	33
	Median exposure (days):	742.0	753.0	-	748.0
Long-term adolescent data from AD studies (M16-045, M16-047, M18-891)	Total subjects:	0	0	264 (15 mg) 265 (30 mg)	541
	Median exposure (days):	-	-	1437.0 (15 mg) 1463.0 (30 mg)	

*Numbers refer to subjects enrolled in Part 2 – a multiple-dose open-label, long-term extension (up to 2 years). A total of 35 children with AD were included in Part 1 of the study (see Table 32).

In Phase 1 Study M15-340, 122 subjects received at least 1 dose of upadacitinib through the data cutoff date of 21 March 2025, including 27 subjects age 2 to < 6 years, 53 subjects age 6 to < 12 years, and 42 subjects age 12 to < 18 years, representing a total exposure to any dose of upadacitinib of 254.6 PY. Of the 122 subjects, 113 (92.6%) had exposure to upadacitinib treatment for at least 52 weeks.

Supportive upadacitinib safety data in paediatric patients from completed AD Phase 1 Study (M16-049) (35 subjects ages 2 to < 12 years) and ongoing AD Phase 3 Studies (M16-045, M16-047, and M18-891) (541 subjects ages 12 to < 18 years; data cutoff 15 August 2024) are also described.

Table *26*: Upadacitinib duration of exposure in pcJIA

	15 mg QD		30 mg QD		Other Doses Tablets[a]		Other Doses Oral Solution[b]	
Duration of exposure	**n**	**PYs**	**n**	**PYs**	**n**	**PYs**	**n**	**PYs**
≥ 1 day	84	175.8	7	0.2	4	2.4	53	105.5
≥ 4 weeks (28 days)	83	175.8	0	--	4	2.4	53	105.5
≥ 12 weeks (84 days)	80	175.3	0	--	4	2.4	51	105.4
≥ 24 weeks (168 days)	80	175.3	0	--	3	2.1	50	105.0
≥ 36 weeks (252 days)	75	172.6	0	--	2	1.4	49	104.5
≥ 48 weeks (336 days)	75	172.6	0	--	0	--	49	104.5
≥ 52 weeks (364 days)	73	170.7	0	--	0	--	43	98.9
≥ 72 weeks (504 days)	59	154.2	0	--	0	--	37	91.4
≥ 96 weeks (672 days)	36	117.9	0	--	0	--	28	77.5
≥ 120 weeks (840 days)	27	99.2	0	--	0	--	19	59.7
≥ 144 weeks (1008 days)	18	76.8	0	--	0	--	14	46.8
≥ 168 weeks (1176 days)	15	67.8	0	--	0	--	8	29.2

a. Other doses (tablets) include upadacitinib 3, 18, and 24 mg BID and 7.5 and 24 mg QD.

b. Other doses (oral solution) include upadacitinib 1, 1.5, 1.6, 2, 3, 3.2, 3.5, 4, 5, 6, 8, and 12 mg BID.

Table 27: Upadacitinib Exposure in pcJIA by Age Group and Sex (data cutoff 21 March 2025)

	Male		Female	
Age Group (years)	**n**	**PYs**	**n**	**PYs**
0 to 11	19	47.0	60	138.1
12 to 17	8	24.3	35	74.5
≥ 18	0	--	0	--

Table *28* :Upadacitinib Exposure in pcJIA by Dose (data cutoff 21 March 2025)

Dose of Exposure	**n**	**PYs**
Upadacitinib 15 mg QD	84	175.8
Upadacitinib 30 mg QD	7	0.2
Upadacitinib other doses (tablets)[a]	4	2.4
Upadacitinib other doses (oral solution)[a]	53	105.5

[a]Other doses (tablets) include upadacitinib 3, 18, and 24 mg BID and 7.5 and 24 mg QD. Other doses (oral solution) include upadacitinib 1, 1.5, 1.6, 2, 3, 3.2, 3.5, 4, 5, 6, 8, and 12 mg BID.

Exposure in children with Atopic Dermatitis (supportive data)

Safety data from a 2-part, Phase 1 study designed to characterise the PK, activity, safety, tolerability, and palatability of upadacitinib in paediatric subjects (2 to < 12 years of age) with severe Atopic Dermatiis (AD), are supportive information for upadacitinib in children.

Part 1 of Study M16-049 was a 7-day, multiple-dose, open-label, multiple-cohort study which consisted of two dose levels. The same formulations as in Study M15-340 were used. Likewise, as with Study M15-340, the same Low Dose and High Dose levels were selected to achieve comparable upadacitinib plasma exposures in paediatric subjects to those in adults after administration of 15 mg and 30 mg extended-release QD tablets, respectively. Subjects who completed Part 1 had the option to enrol at the investigator's discretion in Part 2, a multiple-dose, open-label, long-term extension and receive open-label Low Dose upadacitinib (up to 2 years).

Table *29*: Extent of exposure in children with AD in study M16-049

	Part 1				
	Cohort 1 (N = 9)	**Cohort 2 (N = 8)**	**Cohort 3 (N = 9)**	**Cohort 4 (N = 9)**	**Total (N = 35)**
Duration (days)					
Mean (SD)	7.1 (0.33)	7.0 (0.00)	6.8 (2.28)	6.7 (1.41)	6.9 (1.32)
Median	7.0	7.0	7.0	7.0	7.0
Min, Max	7, 8	7, 7	1, 9	3, 8	1, 9
	Part 2				
	Aged 6 to < 12 years (N = 17)		**Aged 2 to < 6 years (N = 16)**		**Total (N = 33)**
Duration (days)					
Mean (SD)	547.9 (282.79)		576.5 (246.27)		561.8 (261.97)
Median	753.0		742.0		748.0
Min, Max	49, 772		105, 763		49, 772

Cohort 1 = Low Dose, 6 to < 12 years.

Cohort 2 = High Dose, 6 to < 12 years.

Cohort 3 = Low Dose, 2 to < 6 years.

Cohort 4 = High Dose, 2 to < 6 years.

Note: Part 1 Duration of treatment = The date of last dose of study drug in Part 1 - the date of first dose of study drug in Part 1 + 1. Part 2 Duration of treatment = The date of last dose of study drug in Part 2 - the date of first dose of study drug in Part 2 + 1.

The final results from this study are based on data from 35 subjects, including 34 subjects who received at least 1 dose of upadacitinib at the Low Dose level.

Exposure in adolescents with AD (supportive data)

Accumulated, integrated, long-term adolescent safety data from the global Phase 3 pivotal studies in AD (Studies M16-045, M16-047, and M18-891) are supportive information for upadacitinib in pcJIA patients. These studies enrolled adolescent subjects 12 to < 18 years of age and evaluated both the 15 and 30 mg QD tablet formulations of upadacitinib.

A total of 541 adolescent subjects is summarised in the global Phase 3 AD studies, including 264 and 265 subjects who received at least 1 dose of upadacitinib 15 mg and 30 mg, respectively. Overall, subjects had a median duration of 1437.0 days and 1463.0 days exposure to upadacitinib 15 mg and 30 mg, respectively, through the data cutoff. Total exposure to upadacitinib 15 mg and 30 mg was 864.5 PY and 915.0 PY, respectively.

5.4.2. Adverse events

Table *30*: Overview of TEAEs per 100 PY by Age Group (Study M15-340, Parts 1, 2, and 3; Safety Population)

	Age 2 to < 6 years (N = 27) (PY = 62.5) E (E/100 PY)	**Age 6 to < 12 years (N = 53) (PY = 110.7) E (E/100 PY)**	**Age 12 to < 18 years (N = 42) (PY = 81.4) E (E/100 PY)**	**Total (N = 122) (PY = 254.6) E (E/100 PY)**
AE	365 (584.1)	603 (544.9)	304 (373.2)	1272 (499.6)
SAE	5 (8.0)	10 (9.0)	11 (13.5)	26 (10.2)
AE with reasonable possibility of being related to study drug	21 (33.6)	203 (183.4)	85 (104.4)	309 (121.4)
AE leading to discontinuation of study drug	0	4 (3.6)	3 (3.7)	7 (2.7)
Severe (Grade 3+) AE	4 (6.4)	10 (9.0)	11 (13.5)	25 (9.8)
AE leading to death	0	0	0	0
All deaths	0	0	0	0

Table *31*: TEAEs Reported in ≥ 10% of Subjects in any Age Group by Decreasing Frequency (Study M15-340 Parts 1, 2, and 3; Safety Population)

MedDRA 27.1 Preferred Term	Age 2 to < 6 Years (N = 27) n (%)	Age 6 to < 12 Years (N = 53) n (%)	Age 12 to < 18 Years (N = 42) n (%)	Total (N = 122) n (%)
Any AE	27 (100)	51 (96.2)	42 (100)	120 (98.4)
Upper respiratory tract infection	18 (66.7)	21 (39.6)	17 (40.5)	56 (45.9)
Nasopharyngitis	10 (37.0)	25 (47.2)	17 (40.5)	52 (42.6)
COVID-19	7 (25.9)	20 (37.7)	14 (33.3)	41 (33.6)
Pyrexia	12 (44.4)	19 (35.8)	4 (9.5)	35 (28.7)
Gastroenteritis	13 (48.1)	11 (20.8)	8 (19.0)	32 (26.2)
Abdominal pain	4 (14.8)	8 (15.1)	7 (16.7)	19 (15.6)
Headache	0	12 (22.6)	5 (11.9)	17 (13.9)
Nausea	2 (7.4)	7 (13.2)	7 (16.7)	16 (13.1)
Influenza like illness	7 (25.9)	5 (9.4)	3 (7.1)	15 (12.3)
Influenza	5 (18.5)	5 (9.4)	5 (11.9)	15 (12.3)
Vomiting	8 (29.6)	4 (7.5)	2 (4.8)	14 (11.5)
Juvenile idiopathic arthritis	4 (14.8)	7 (13.2)	3 (7.1)	14 (11.5)
Cough	3 (11.1)	8 (15.1)	3 (7.1)	14 (11.5)
Otitis media	7 (25.9)	5 (9.4)	1 (2.4)	13 (10.7)
Pharyngitis	5 (18.5)	4 (7.5)	4 (9.5)	13 (10.7)
Arthralgia	1 (3.7)	7 (13.2)	5 (11.9)	13 (10.7)
Bronchitis	6 (22.2)	1 (1.9)	4 (9.5)	11 (9.0)
Viral infection	2 (7.4)	8 (15.1)	0	10 (8.2)
Abdominal pain upper	0	6 (11.3)	2 (4.8)	8 (6.6)
Pharyngitis streptococcal	5 (18.5)	2 (3.8)	1 (2.4)	8 (6.6)
Contusion	0	6 (11.3)	2 (4.8)	8 (6.6)
Gastrointestinal infection	1 (3.7)	6 (11.3)	0	7 (5.7)
Conjunctivitis	5 (18.5)	1 (1.9)	0	6 (4.9)
Rhinitis	3 (11.1)	2 (3.8)	1 (2.4)	6 (4.9)
Diarrhoea	4 (14.8)	1 (1.9)	0	5 (4.1)
Enterobiasis	3 (11.1)	0	0	3 (2.5)

Adverse drug reactions

The most frequently reported TEAEs considered by the investigator to have a reasonable possibility of being related to study drug (≥ 5% of subjects overall) were nasopharyngitis, upper respiratory tract infection, abdominal pain, nausea, and headache. The MAH's assessment of data from the pcJIA clinical programme did not identify any new ADRs beyond those currently listed in the upadacitinib product information.

Table 32: TEAEs with a Reasonable Possibility of Being Related to Upadacitinib Reported in ≥ 5% of Subjects in any Age Group, by Decreasing Frequency by PT in the Total Group, in Parts 1, 2, and 3 (Safety Population)

MedDRA 27.1 Preferred Term	Age 2 to < 6 years (N = 27) n (%)	Age 6 to < 12 years (N = 53) n (%)	Age 12 to < 18 years (N = 42) n (%)	Total (N = 122) n (%)
Any AE	5 (18.5)	24 (45.3)	22 (52.4)	51 (41.8)
Nasopharyngitis	1 (3.7)	10 (18.9)	8 (19.0)	19 (15.6)
Upper respiratory tract infection	2 (7.4)	2 (3.8)	5 (11.9)	9 (7.4)
Abdominal pain	1 (3.7)	5 (9.4)	2 (4.8)	8 (6.6)
Nausea	0	3 (5.7)	4 (9.5)	7 (5.7)
Headache	0	4 (7.5)	3 (7.1)	7 (5.7)
Gastrointestinal infection	0	6 (11.3)	0	6 (4.9)
Abdominal pain upper	0	4 (7.5)	2 (4.8)	6 (4.9)
Pyrexia	1 (3.7)	5 (9.4)	0	6 (4.9)
Monocyte count decreased	0	5 (9.4)	1 (2.4)	6 (4.9)
COVID-19	0	3 (5.7)	2 (4.8)	5 (4.1)
Gastroenteritis	2 (7.4)	1 (1.9)	2 (4.8)	5 (4.1)
Blood triglycerides increased	1 (3.7)	4 (7.5)	0	5 (4.1)
Eosinophil count increased	0	4 (7.5)	1 (2.4)	5 (4.1)
Diarrhoea	2 (7.4)	1 (1.9)	0	3 (2.5)
Monocyte count increased	0	3 (5.7)	0	3 (2.5)
Reticulocyte count decreased	0	3 (5.7)	0	3 (2.5)

Among TEAEs reported in <5% of subjects, acne (2.5% overall, 4.8% in adolescents) and skin papilloma (1.6% overall) are notable, as these were reported in higher frequency in paediatric patients with AD and are listed as ADRs in the SmPC.

5.4.3. AEs of special interest, serious adverse events and deaths, other significant events

Table 33: Subjects with Treatment-Emergent SAEs by Age Group by Decreasing Frequency (Study M15-340 Parts 1, 2, and 3; Safety Population)

MedDRA 27.1 Preferred Term	Age 2 to < 6 years (N = 27) n (%)	Age 6 to < 12 years (N = 53) n (%)	Age 12 to < 18 years (N = 42) n (%)	Total (N = 122) n (%)
Any SAE	4 (14.8)	6 (11.3)	7 (16.7)	17 (13.9)
Juvenile idiopathic arthritis	1 (3.7)	1 (1.9)	2 (4.8)	4 (3.3)
Splenic cyst	0	1 (1.9)	0	1 (0.8)
Vertigo	0	1 (1.9)	0	1 (0.8)
Abdominal pain	0	0	1 (2.4)	1 (0.8)
Constipation	0	1 (1.9)	0	1 (0.8)
Melaena	0	0	1 (2.4)	1 (0.8)
Nausea	0	0	1 (2.4)	1 (0.8)
Pain	0	0	1 (2.4)	1 (0.8)
Papillitis	0	1 (1.9)	0	1 (0.8)
Escherichia urinary tract infection	0	1 (1.9)	0	1 (0.8)
Influenza	0	1 (1.9)	0	1 (0.8)
Sepsis	1 (3.7)	0	0	1 (0.8)
Upper respiratory tract infection	0	0	1 (2.4)	1 (0.8)
Abnormal loss of weight	0	1 (1.9)	0	1 (0.8)
Arthritis	1 (3.7)	0	0	1 (0.8)
Muscular weakness	0	1 (1.9)	0	1 (0.8)
Musculoskeletal chest pain	0	0	1 (2.4)	1 (0.8)
Headache	0	1 (1.9)	0	1 (0.8)
Conversion disorder	0	0	1 (2.4)	1 (0.8)
Suicidal ideation	0	0	1 (2.4)	1 (0.8)
Ovarian cyst	0	0	1 (2.4)	1 (0.8)
Adenoidal hypertrophy	1 (3.7)	0	0	1 (0.8)
Tonsillar hypertrophy	1 (3.7)	0	0	1 (0.8)

AESIs (identified based on the safety profile for upadacitinib and other JAK inhibitors) include serious infection, opportunistic infection excluding TB and herpes zoster, herpes zoster, active TB, malignancy (all types), adjudicated GI perforation, anaemia, neutropenia, lymphopenia, renal dysfunction, hepatic disorder, CPK elevation, adjudicated CV events, and adjudicated thrombotic events.

Retinal detachment, serious hypersensitivity reaction, and bone fracture were not included as AESIs in the Study M15-340 protocol or SAP but were considered AESIs in the latest Investigator Brochure.

No deaths were reported through the data cutoff date.

No treatment-emergent SAEs were reported in Part 1 (7 days at two dose levels). Across Parts 2 and 3 (low dose, long-term), a total of 26 SAEs were reported. By PT, no treatment-emergent SAE was reported in more than 1 subject, with the exception of JIA (worsening) (4 subjects [3.3%]).

No treatment-emergent AESIs of malignancy (including NMSC, malignancy excluding NMSC, lymphoma), adjudicated GI perforation, renal dysfunction, active TB, adjudicated CV events, adjudicated thrombotic events, retinal detachment, and serious hypersensitivity reactions were reported in study M15-340. All other AESIs are summarised in *Table 34*.

Table 34: Overview of Treatment-Emergent AESIs per 100 PY by Age Group (Study M15-340 Parts 1, 2, and 3; Safety Population)

Any Treatment-Emergent	Age 2 to < 6 years (N = 27) (PY = 62.5) E (E/100 PY)	Age 6 to < 12 years (N = 53) (PY = 110.7) E (E/100 PY)	Age 12 to < 18 years (N = 42) (PY = 81.4) E (E/100 PY)	Total (N = 122) (PY = 254.6) E (E/100 PY)
Serious infections	1 (1.6)	2 (1.8)	1 (1.2)	4 (1.6)
Opportunistic infection excluding TB and herpes zoster	0	1 (0.9)	1 (1.2)	2 (0.8)
Herpes zoster	0	1 (0.9)	0	1 (0.4)
Hepatic disorder	2 (3.2)	11 (9.9)	6 (7.4)	19 (7.5)
Anemia	2 (3.2)	3 (2.7)	1 (1.2)	6 (2.4)
Neutropenia	0	7 (6.3)	0	7 (2.7)
Lymphopenia	0	2 (1.8)	2 (2.5)	4 (1.6)
CPK elevation	0	6 (5.4)	3 (3.7)	9 (3.5)
Bone fracture	1 (1.6)	7 (6.3)	3 (3.7)	11 (4.3)

AESI: Infections

Background

The MAH put forward that adults with RA are at increased risk of hospitalised infection relative to individuals without RA (Smitten 2008[1]), and that disease activity is associated with an increased risk of infections (Au 2011[2]). Less is understood about paediatric patients with JIA relative to the general population. A US study using Medicaid data found an increased risk of infection in JIA patients not currently taking MTX or a tumour necrosis factor inhibitor relative to children (aged < 19) in a comparator cohort without JIA (Beukelman 2012[3]). In the study, the estimated rate of hospitalised bacterial infection in JIA patients not currently on oral glucocorticoid treatment was 2.3 (95% CI 2.1-2.6) per 100 person-years. As with adults, the infection risk in paediatric patients is complicated by exposure to glucocorticoids, MTX, and other treatments potentially impacting risk as well as the impact of the disease process itself.

Applicant's analysis

The MAH commented that, in the study of children with pcJIA exposed to upadacitinib (M15-340), the EAERs of TEAEs of serious infections were similar across age groups. Serious infection TEAEs included 1 event each of *Escherichia* (*E. coli*) urinary tract infection (drug interrupted; Age Group 6 to < 12 years), sepsis (drug interrupted; Age Group 2 to < 6 years), upper respiratory tract infection (drug not interrupted; Age Group 12 to < 18 years), and influenza (drug not interrupted; Age Group 6 to < 12 years).

Sepsis

The event of sepsis was reported as culture-negative sepsis in a subject who was admitted to the hospital for 5 days with fever, dehydration, tachycardia, hypotension, malaise, and vomiting, and was found to have negative urine and blood cultures, negative nasopharyngeal panel, and a negative strep

[1] Smitten AL, Choi HK, Hochberg MC, et al. The risk of hospitalized infection in patients with rheumatoid arthritis. J Rheumatol. 2008;35(3):387-93.
[2] Au K, Reed G, Curtis JR, et al. High disease activity is associated with an increased risk of infection in patients with rheumatoid arthritis. Ann Rheum Dis. 2011;70(5):785-91.
[3] Beukelman T, Xie F, Chen L, et al. Rates of hospitalized bacterial infection associated with juvenile idiopathic arthritis and its treatment. Arthritis Rheum. 2012;64(8):2773-80.

test. According to the investigator, a viral process was most likely consistent with the constellation of symptoms. Prior to the event, the subject was diagnosed with asthma requiring salbutamol, fluticasone, and intermittent prednisolone, and subsequently experienced multiple infectious events primarily of the upper respiratory tract. The event of sepsis resolved with appropriate treatment, and the study drug was not discontinued due to the event.

Opportunistic Infections Excluding TB and Herpes Zoster

One TEAE each of opportunistic infection excluding TB and herpes zoster were reported in the Age Group 6 to < 12 years (BK virus infection) and Age Group 12 to < 18 years (oesophageal candidiasis). Both events were nonserious and did not lead to discontinuation of study drug. The subject with BK virus infection was reported to be asymptomatic.

Herpes Zoster

A single TEAE of herpes zoster was reported (Age Group 6 to < 12 years). The event was nonserious, involved a single dermatome, led to interruption of study drug, and was considered by the investigator as having no reasonable possibility of being related to study drug.

AESI: Hepatic Disorders and Chemistry Laboratory-Related TEAEs

Hepatic disorders

In the study of children with pcJIA exposed to upadacitinib (M15-340), the EAER of TEAEs of hepatic disorder was lower in the Age Group 2 to < 6 years than in the Age Group 6 to < 12 years and Age Group 12 to < 18 years. Almost all events were transaminase elevations, while 1 event each of blood bilirubin increased and hepatosplenomegaly was reported, neither of which led to interruption of study drug. All TEAEs of hepatic disorder were classified as nonserious and none led to discontinuation of study drug. The event of blood bilirubin increased occurred in a female subject in the Age Group 12 to < 18 years with no relevant history for the event. It was reported as mild. The event resolved and blood bilirubin values returned to normal ranges without study drug interruption. The event of hepatosplenomegaly occurred in a female subject in the Age Group 6 to < 12 years with a history of obesity and hypertriglyceridemia. Except for elevated triglycerides, there were no abnormal laboratory findings or AEs associated with the event and an ultrasound evaluation remained without findings except for mild splenomegaly. The subject was subsequently diagnosed with metabolic syndrome. The hepatosplenomegaly resolved without study drug interruption.

There were no potentially clinically significant Grade 3 or 4 laboratory increases in AST or bilirubin. Three subjects had Grade 3 laboratory increases in ALT (1 subject in the Age Group 6 to < 12 years [also reported with a TEAE of ALT increased] and 2 subjects in the Age Group 12 to < 18 years [1 with a TEAE of ALT increased and the other with a TEAE of hypertransaminasemia]). The potentially clinically significant laboratory increases in ALT resolved without discontinuation of study drug for 2 of the subjects. One of these 2 subjects had an isolated increase in ALT which occurred at a single visit. In the third subject with Grade 3 laboratory increase in ALT (with reported TEAE of hypertransaminasemia), the laboratory abnormality occurred on the subject's Follow-up Visit (i.e., final visit of the study) after the subject had been off the study drug. There were no events of drug-induced liver injury, and no subject met the biochemical criteria for Hy's Law.

CPK Elevations

TEAEs of CPK elevation were only reported in the Age Group 6 to < 12 years and Age Group 12 to < 18 years, all of which were considered mild, nonserious, and did not lead to study drug discontinuation. No TEAEs of rhabdomyolysis were reported.

Few subjects had Grade 3 laboratory increases in CPK, all of which occurred in the older age groups (1 subject in the Age Group 6 to < 12 years and 3 subjects in the Age Group 12 to < 18 years). Grade 4 laboratory increases in CPK only occurred in the Age Group 12 to < 18 years (3 subjects). All Grade 3 or 4 laboratory increases in CPK returned to normal upon retesting.

AESI: Haematology Laboratory-Related TEAEs

Anaemia

In the study of children with pcJIA exposed to upadacitinib (M15-340), the EAERs of TEAEs of anaemia were higher in the Age Group 2 to < 6 years and Age Group 6 to < 12 years than the Age Group 12 to < 18 years. All events were assessed as mild or moderate, nonserious, and did not lead to discontinuation of study drug. No Grade 3 or 4 laboratory decrease in haemoglobin count was reported.

Neutropenia

TEAEs of neutropenia were only reported in the Age Group 6 to < 12 years (7 events in 2 subjects), all of which were assessed as mild or moderate and nonserious, and none of which led to interruption or discontinuation of study drug. Two subjects in the Age Group 2 to < 6 years experienced a single Grade 3 laboratory decrease in neutrophil count that resolved at the next visit; c vvvstudy drug was not discontinued. No Grade 4 laboratory decrease in neutrophil count was reported. One subject had an infection (nonserious streptococcal pharyngitis) within 2 weeks of the Grade 3 laboratory decrease in neutrophil count; the infection resolved 3 days prior to the onset of a Grade 3 laboratory decrease in neutrophil count.

Lymphopenia

TEAEs of lymphopenia were only reported in the Age Group 6 to < 12 years and Age Group 12 to < 18 years at similar rates. All events were classified as mild or moderate, nonserious, and did not lead to study drug discontinuation. No Grade 3 or 4 laboratory decrease in lymphocyte count was reported.

AESI: Bone fractures

Background

The MAH commented that in childhood and adolescence, fracture is common, with incidence reports ranging from 128 to 361 per 10,000 person-years across several studies in Europe (Hedström 2010[4]). The occurrence of fracture varies by many factors including individual and environmental in addition to factors associated with bone health. To help contextualize the fracture risk in JIA, information on factors influencing risk in the general population was provided first. Fracture is more common in boys than girls across age groups, with lifetime childhood risk of 42 to 64% in boys and 27 to 40% in girls (Valerio 2010[5]). Risk in childhood appears to increase with age with incidence peaking around 11 to 12 years of age for girls and 13 to 14 years for boys (Choudhary 2023[6]). The most common anatomical site of fracture in paediatric and adolescent patients is the forearm (Hedström 2010[4], Valerio 2010,

[4] Hedström EM, Svensson O, Bergström U, et al. Epidemiology of fractures in children and adolescents. Acta Orthop. 2010;81(1):148-53.
[5] Valerio G, Gallè F, Mancusi C, et al. Pattern of fractures across pediatric age groups: analysis of individual and lifestyle factors. BMC Public Health. 2010;10:656.
[6] Choudhary RS, Mathias LJ, Somayaji H. Fracture pattern in paediatric age group. Int J Case Rep Orthop. 2023;5(1):70-4.

Choudhary 2023[6]). Children with rheumatologic disorders including JIA have multiple risk factors for impaired bone health and impact fracture risk above the underlying risk in childhood and adolescence in general (Burnham 2004[7]). Across subtypes of JIA, reduced bone mineral density has been observed relative to controls, and in polyarticular JIA (and systemic and oligoarticular subtypes), this difference was significant (Stagi 2010[8]). In a study using the United Kingdom General Practice Research Database (GPRD), an increased fracture risk was seen in patients with JIA relative to healthy controls across age groups, with incidence rate ratios of 1.49 (95% CI 0.91-2.31) for children < 10 years of age, 3.13 (2.21-4.33) for ages 10 to 15 years, and 1.75 (1.18 2.51) for ages 15 to 20 years (Burnham 2006[9]). The largest relative increase in fracture risk (JIA vs. healthy control) appears in the 10-to-15-year age group, which aligns with the age of peak fracture risk among boys and girls without JIA, and with the Age Group 6 to < 12 years and Age Group 12 to < 18 years in Study M15-340.

Applicant's Analysis

In the study of children with pcJIA exposed to upadacitinib (M15-340), bone fracture TEAEs were primarily reported in the Age Group 6 to < 12 years and Age Group 12 to < 18 years. In total, there were 11 events in 9 subjects, of which more than half were in males, which is considered notable as the majority of the study population is female. The majority of events consisted of upper limb fractures. All events were assessed as nonserious and considered by the investigator as having no reasonable possibility of being related to study drug. All were reported to be traumatic in origin except for 2 fractures (foot fracture [little toe fracture] and fibula fracture) in which the cause of the fracture was reported to be unknown.

ADRs of special interest, serious ADRs and deaths causally related to the medicinal product.

The majority of SAEs did not have a reasonable possibility of being related to upadacitinib, as assessed by the investigator. By PT, treatment-emergent SAEs considered by the investigator to have a reasonable possibility of being related to upadacitinib included *Escherichia* urinary tract infection, constipation, upper respiratory tract infection, nausea, conversion disorder, and headache (reported as SAE in one patient each).

Infections are an identified risk of upadacitinib treatment and an AESI (described in section 6.4.4.1).
Headache and nausea are listed as common ADRs in the SmPC section 4.8.
Constipation was reversible, did not lead to interruption of upadacitinib treatment, and considered by the MAH as having no reasonable possibility of being related to the study drug.

The SAE of **conversion disorder** was reported in a female subject (age 12 to < 18 years) with no prior history of psychiatric or behaviour disorders and no history of substance use/abuse but a relevant history of having been bullied at school prior to the event. The subject was hearing voices and exhibited self-hurting behaviour due to bullying at school and was seen by a psychiatrist. The subject also experienced the concurrent event of auditory hallucinations. Further neurological workup resulted in no findings. Study drug was discontinued during the event for lack of efficacy, and the events of conversion disorder and auditory hallucinations remained ongoing at the time of study discontinuation. The events were assessed by the investigator as having a reasonable possibility of being related to upadacitinib.

[7] Burnham JM, Leonard MB. Bone disease in pediatric rheumatologic disorders. Curr Rheumatol Rep. 2004;6(1):70-8.
[8] Stagi S, Masi L, Capannini S, et al. Cross-sectional and longitudinal evaluation of bone mass in children and young adults with juvenile idiopathic arthritis: the role of bone mass determinants in a large cohort of patients. J Rheumatol. 2010;37(9):1935-43.
[9] Burnham JM, Shults J, Weinstein R, et al. Childhood onset arthritis is associated with an increased risk of fracture: a population based study using the General Practice Research Database. Ann Rheum Dis. 2006;65(8):1074-9.

An overview of TEAEs in the SOC of Psychiatric Disorders is provided in Table *35*. Of the 5 subjects who experienced TEAEs depression (PTs of depression or major depression), 1 subject had a medical history of depression, and 1 subject had a family history of psychiatric disorder (this subject also experienced a TEAE of suicidal ideation). Of the 2 subjects who experienced anxiety, none had a prior medical history of psychiatric disorder.

Table *35*: TEAEs in the SOC of Psychiatric Disorders by Decreasing Frequency in the Total Group in Parts 1, 2, and 3 (Safety Population)

MedDRA 27.1 System Organ Class Preferred Term	Age 2 to < 6 years (N = 27) n (%)	Age 6 to < 12 years (N = 53) n (%)	Age 12 to < 18 years (N = 42) n (%)	Total (N = 122) n (%)
Psychiatric disorders	2 (7.4)	9 (17.0)	7 (16.7)	18 (14.8)
Depression	0	2 (3.8)	2 (4.8)	4 (3.3)
Initial insomnia	0	2 (3.8)	2 (4.8)	4 (3.3)
Attention deficit hyperactivity disorder	0	2 (3.8)	1 (2.4)	3 (2.5)
Anxiety	0	0	2 (4.8)	2 (1.6)
Mood altered	2 (7.4)	0	0	2 (1.6)
Aversion	0	1 (1.9)	0	1 (0.8)
Conversion disorder	0	0	1 (2.4)	1 (0.8)
Enuresis	0	1 (1.9)	0	1 (0.8)
Hallucination, auditory	0	0	1 (2.4)	1 (0.8)
Irritability	1 (3.7)	0	0	1 (0.8)
Major depression	0	0	1 (2.4)	1 (0.8)
Somnambulism	0	1 (1.9)	0	1 (0.8)
Suicidal ideation	0	0	1 (2.4)	1 (0.8)

5.4.4. Discontinuation due to adverse events

On overview of TEAEs leading to discontinuation of study drug by age group is provided in Table 36. One of the events of juvenile idiopathic arthritis (worsening) leading to discontinuation of study drug was serious.

Table 36: Summary of number and percentage of subjects with TEAES leading to discontinuation of study drug by age group, by decreasing frequency by pt in the total group, in Parts 1, 2, and 3 (Safety Population)

MedDRA 27.1 Preferred Term	Age 2 to < 6 years (N = 27) n (%)	Age 6 to < 12 years (N = 53) n (%)	Age 12 to < 18 years (N = 42) n (%)	Total (N = 122) n (%)
Any AE leading to Discontinuation of Study Drug	0	3 (5.7)	3 (7.1)	6 (4.9)
Juvenile idiopathic arthritis	0	2 (3.8)	2 (4.8)	4 (3.3)
Abdominal pain	0	1 (1.9)	0	1 (0.8)
Nausea	0	1 (1.9)	0	1 (0.8)
Nasopharyngitis	0	0	1 (2.4)	1 (0.8)

5.4.5. Safety in special populations

Safety in children: Phase 1 Paediatric AD Study M16-049 (Supportive Data)

An overview of TEAE in children with AD exposed to upadacitinib is provided in Table 37.

Table 37: Overview and percentage of subjects with TEAE in children with AD exposed to upadacitinib

	Part 1				
Subjects with any Treatment-Emergent, n (%)	**Cohort 1 (N = 9)**	**Cohort 2 (N = 8)**	**Cohort 3 (N = 9)**	**Cohort 4 (N = 9)**	**Total (N = 35)**
AE	1 (11.1)	1 (12.5)	5 (55.6)	0	7 (20.0)
AE with reasonable possibility of being drug related	0	0	1 (11.1)	0	1 (2.9)
Severe AE	0	0	0	0	0
Serious AE	0	0	0	0	0
SAE with reasonable possibility of being drug related	0	0	0	0	0
AE leading to discontinuation of study drug	0	0	0	0	0
AE leading to death	0	0	0	0	0
All deaths	0	0	0	0	0

	Part 2		
Subjects with any Treatment-Emergent, n (%)	**Aged 6 to < 12 years (N = 17)**	**Aged 2 to < 6 years (N = 16)**	**Total (N = 33)**
AE	15 (88.2)	14 (87.5)	29 (87.9)
AE with reasonable possibility of being drug related	2 (11.8)	7 (43.8)	9 (27.3)
Severe AE	3 (17.6)	1 (6.3)	4 (12.1)
Serious AE	3 (17.6)	0	3 (9.1)
SAE with reasonable possibility of being drug related	1 (5.9)	0	1 (3.0)
AE leading to discontinuation of study drug	3 (17.6)	1 (6.3)	4 (12.1)
AE leading to death	0	0	0
All deaths	0	0	0

Cohort 1 = Low Dose, 6 to < 12 years.

In Part 1, no TEAE by PT was reported in more than 1 subject. In Part 2, the most frequently reported TEAEs (≥ 3 subjects in any given age group) were cough, COVID-19, headache, asthma, and vomiting.

Table 38: Overview of Subjects with Treatment-Emergent AESIs by Age Group (Study M16-049 Part 2, Safety Population)

Subjects with any Treatment-Emergent	**Age 2 to < 6 years (N = 16) n (%)**	**Age 6 to < 12 years (N = 17) n (%)**	**Total (N = 33) n (%)**
Serious infection	0	2 (11.8)	2 (6.1)
Opportunistic infection	1 (6.3)	0	1 (3.0)
Herpes zoster	1 (6.3)	1 (5.9)	2 (6.1)
Neutropenia	2 (12.5)	0	2 (6.1)
CPK elevation	1 (6.3)	0	1 (3.0)

Safety in adolescents: Long-Term Adolescent Data from AD Studies M16-045, M16-047 and M18-891 (Supportive Data)

An overview of TEAEs is provided in Table 39.

Table 39: Overview of TEAEs in Exposure-Adjusted Rate per 100 PY (Long-Term Upadacitinib Phase 3 AD Adolescent Analysis Set)

	UPA 15 mg QD (N = 264) (PY = 864.5)	**UPA 30 mg QD (N = 265) (PY = 915.0)**
EAER (events [E/100 PY])		
TEAE	1626 (188.1)	1775 (194.0)
TEAE with reasonable possibility of being drugrelated[a]	493 (57.0)	521 (56.9)
Severe TEAE	108 (12.5)	91 (9.9)
Treatment-emergent SAE	49 (5.7)	40 (4.4)
TEAE leading to discontinuation of study drug	25 (2.9)	27 (3.0)
TEAE leading to death	0	0
EAIR (n/PY)		
All deaths	0/864.5	0/915.0

There were no TEAEs in the following AESI categories: active TB, adjudicated GI perforation, renal dysfunction, retinal detachment, NMSC, lymphoma, adjudicated MACE, and adjudicated VTE .

An overview of treatment-emergent AESIs is provided in Table **40**.

Serious infections occurring more than once were eczema infected and impetigo. Other serious infections occurring only once were COVID-19, eczema herpeticum, herpes zoster cutaneous disseminated, and pneumonia. The EAER of treatment-emergent opportunistic infections excluding TB and herpes zoster was higher on upadacitinib 15 mg than 30 mg. Most of the opportunistic infections excluding TB and herpes zoster were eczema herpeticum. The EAER of herpes zoster was higher in the upadacitinib 30 mg group than the upadacitinib 15 mg group. Two disseminated herpes zoster (1 in each treatment group) and 2 ophthalmic herpes zoster (both in the upadacitinib 30 mg group) cases occurred, with no cases involving the central nervous system.

One malignancy (SAE) was reported in a subject who developed headaches less than 1 month after the start of study drug and was diagnosed with medulloblastoma approximately 7.5 months after the start of upadacitinib. Study drug was discontinued, and the investigator assessed the event as having no reasonable possibility of being related to the study drug.

Hepatic disorders TEAEs were primarily transaminase elevations. Consistent with the overall safety profile for upadacitinib and JAK class effect, a dose-response was observed for neutropenia and CPK elevation. No clear association between low neutrophil counts and the occurrence of serious or opportunistic infections has been observed.

Table 40: Overview of Treatment-Emergent AESIs per 100 PY (Long-Term Upadacitinib Phase 3 AD Adolescent Analysis Set)

	UPA 15 mg QD (N = 264) (PY = 864.5)	UPA 30 mg QD (N = 265) (PY = 915.0)
EAER (events [E/100 PY])		
Serious infection	17 (2.0)	11 (1.2)
Opportunistic infection excluding TB and herpes zoster	13 (1.5)	5 (0.5)
Herpes zoster	17 (2.0)	25 (2.7)
Hepatic disorder	40 (4.6)	25 (2.7)
Anaemia	17 (2.0)	8 (0.9)
Neutropenia	16 (1.9)	25 (2.7)
Lymphopenia	3 (0.3)	0
CPK elevation	52 (6.0)	75 (8.2)
Bone fracture	10 (1.2)	18 (2.0)
Serious hypersensitivity reaction	0	5 (0.5)
EAIR (n/PY [n/100 PY])		
Malignancy	1/864.3 (0.1)	0/915.0
Malignancy excluding NMSC	1/864.3 (0.1)	0/915.0

Note: Data cutoff = 15 August 2024.

Pregnancy

Lactating or pregnant females were excluded from the studies in the upadacitinib clinical development program, and all female subjects of childbearing potential were required to use protocol-specified pregnancy avoidance measures. No pregnancies were reported in Study M15-340 in paediatric subjects with pcJIA through the data cutoff date.

5.4.6. Immunological events

Not applicable.

5.4.7. Safety related to drug-drug interactions and other interactions

The potential for drug-drug interactions between upadacitinib and commonly used concomitant medications was reviewed in the regulatory application for the use of upadacitinib in the treatment of RA in adults. The effect of drug interactions between upadacitinib and concomitant medications in pcJIA is, by the MAH, assumed to be similar to adults.

5.4.8. Vital signs and laboratory findings

In addition to the laboratory markers of special interest discussed above, the following parameters were reported:

Lipid effects

The MAH stated that similar to observations in subjects from other upadacitinib clinical programmes, upadacitinib treatment was associated with an increase in lipid parameters (cholesterol, HDL-C, and LDL-C) in subjects with pcJIA (Study M15-340). While total lipids did increase, the atherogenic index, as assessed by ratios of total cholesterol/HDL-C and LDL C/HDL-C, decreased (improved) post-baseline. The MAH put forward that the mean changes were generally small and attributed to natural variations that occur among the population analysed. One subject had multiple Grade 3 laboratory increases in triglycerides with fluctuating levels (Study M15-340). No Grade 4 laboratory increase in triglycerides or Grade 3 or 4 laboratory increase in cholesterol was reported.

Vital signs Physical Findings, and Other Observations Related to Safety

Mean changes from Baseline in vital signs over time were not considered clinically meaningful by the applicant (Study M15-340). No safety concerns from vital signs were identified.

Paediatric growth and development assessment

Background

The MAH commented that JIA has been associated with negative impacts on growth and development due to chronic inflammation and long-term glucocorticoid treatment (Bechtold 2014[10], d'Angelo 2021[11]). These impacts include growth impairment, short stature, and delayed puberty (d'Angelo 2021[11]). In a cohort of patients in the United Kingdom with JIA followed over time, severe growth restriction (defined as change in height z-score $\leqslant$ -1) was seen across all subtypes and in 17% of patients with JIA overall, resulting in short stature (defined as height z-score < -2) in 7% of patients by 3 years (McErlane 2018[12]). In an earlier French cohort, impacts on growth and final height were also observed (Simon 2001[13]). However, in a Canadian cohort of JIA patients (Guzman 2017[14]), impacts on growth appeared limited to patients with systemic arthritis, uncontrolled disease, or prolonged use of corticosteroids. Cumulative incidence of growth delay at 3 years of follow-up from diagnosis (defined as change in height z-score $\leqslant$ -1) was 8.5% (95% CI 6.8-10.6) overall, 7.4% (4.5-12.0) for RF-negative polyarthritis, and 9.9% (3.1-28.7) for RF-positive polyarthritis (Guzman 2017[14]). Short stature at 3 years of follow-up was also < 5% for all JIA subtypes except sJIA (9.3%) and PsA (9.5%). Similarly, height, weight, and BMI z-scores remained stable over follow-up across all subtypes except sJIA, indicating the growth impacts were minimal outside of that group.

Treatment with TNF inhibitors resulted in restored growth velocity in a cohort of JIA patients receiving anti-TNF treatment, and change in inflammatory activity was a significant predictor of growth velocity (Tynjälä 2006[15]).

Subjects with reduced height and height velocity

In the study of children with pcJIA exposed to upadacitinib (M15-340), height was collected at various timepoints at Baseline and throughout the study, as defined in the protocol. Six subjects (4.9%) met the criteria for decrease of at least 1 unit in height z-score from Baseline to last available measurement: 2 subjects (Age Group 2 to < 6 years), 3 subjects (Age Group 6 to < 12 years), and 1

[10] Bechtold S, Simon D. Growth abnormalities in children and adolescents with juvenile idiopathic arthritis. Rheumatol Int. 2014;34(11):1483-8.
[11] d'Angelo DM, Di Donato G, Breda L, et al. Growth and puberty in children with juvenile idiopathic arthritis. Pediatr Rheumatol Online J. 2021;19(1):28.
[12] McErlane F, Carrasco R, Kearsley-Fleet L, et al. Growth patterns in early juvenile idiopathic arthritis: Results from the Childhood Arthritis Prospective Study (CAPS). Semin Arthritis Rheum. 2018;48(1):53-60.
[13] Simon D, Lucidarme N, Prieur AM, et al. Linear growth in children suffering from juvenile idiopathic arthritis requiring steroid therapy: natural history and effects of growth hormone treatment on linear growth. J Pediatr Endocrinol Metab. 2001;14(Suppl 6):1483-6.
[14] Guzman J, Kerr T, Ward LM, et al. Growth and weight gain in children with juvenile idiopathic arthritis: results from the ReACCh-Out cohort. Pediatr Rheumatol Online J. 2017;15(1):68.
[15] Tynjälä P, Lahdenne P, Vähäsalo P, et al. Impact of anti-TNF treatment on growth in severe juvenile idiopathic arthritis. Ann Rheum Dis. 2006;65(8):1044-9.

subject (Age Group 12 to < 18 years). Upon medical review, 1 female subject (Age Group 6 to < 12 years) entered the study as Tanner Stage 4, was noted to be Tanner Stage 5 at age 11.3 years and seemed to have almost reached full adult height and plateaued in growth velocity. In the remaining 5 subjects, it was reported that though there were variations in growth patterns exhibited, normal growth velocity was maintained over time throughout the study through the data cutoff date.

No TEAEs related to abnormal growth or growth deficiency (PTs of growth disorder, growth failure, growth retardation, body height below normal, body height abnormal, body height decreased) were reported.

BMI

Standardisation for BMI was done using the WHO clinical growth charts for BMI z-scores.

Consistent with general BMI changes in the paediatric population, larger mean changes in BMI from Baseline were observed in the 2 older age groups (6 to < 12 years and 12 to < 18 years) than the youngest age group (2 to < 6 years).

The MAH stated that mean changes from Baseline in BMI z-scores over time were small across all age groups. At Week 24, Week 48, Week 72, and Week 96, representing approximately every 6 months, the mean changes in BMI z-scores overall ranged from 0.26 to 0.35 with mean and median z-scores close to 0, suggesting no impact on subject BMI curves.

Weight

The MAH commented that consistent with general weight increases in the paediatric population (WHO 2006[16]), the largest mean changes in weight from Baseline were observed in the Age Group 6 to < 12 years.

Weight was collected throughout the study, as defined in the protocol. The following analyses were conducted:

- Weight and change from Baseline in weight over time by sex
- Meeting criteria for potentially clinically important (PCI) values for weight:
    - >5% decrease from maximum weight
    - Children < 10 years of age with weight gain of less than 2 kg in visits approximately 1 year apart

The MAH put forward that the majority of subjects exhibited normal weight trajectory as shown on the CDC growth curves. Overall, most subjects that met the criteria for PCI values for weight were female.

Twenty-eight subjects (23.0%) met the criteria for > 5% decrease from maximum weight: 5 subjects (Age Group 2 to < 6 years), 10 subjects (Age Group 6 to < 12 years), and 13 subjects (Age Group 12 to < 18 years).

Sixteen subjects (13.1%) met the criteria for children < 10 years of age with weight gain of less than 2 kg in visits approximately 1 year apart: 13 subjects (Age Group 2 to < 6 years) and 3 subjects (Age Group 6 to < 12 years).

All subjects in the Age Group 2 to < 6 years with PCI values for weight (11 female and 3 male subjects) had normal weight gain over time with a trajectory generally along the same z score throughout the study. None of these subjects met criteria for PCI values for height.

[16] WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards Geneva: World Health Organization; 2006. Available from: https://www.who.int/tools/child-growth-standards.

All subjects in the 6 to < 12 years age group with PCI values for weight (10 female and 3 male subjects) gained weight from start of study through the data cutoff with normal growth in height (i.e., did not meet criteria for PCI values for height). CDC growth curves were reported to exhibit normal weight trajectory over time. Weight fluctuations occurred; however, these were not considered clinically meaningful.

In the Age Group 12 to < 18 years, among subjects with PCI values for weight (11 female and 2 male subjects):

- 6 female subjects lost weight over time from Baseline to the data cutoff date; and 5 female subjects either gained weight or plateaued through the study, all reported to exhibit minor fluctuations in weight. All female subjects were reported to exhibit normal growth in height (i.e., did not meet criteria for PCI values for height), and the majority were either nearing final adult height or had already reached adult height at Baseline. One female subject also met criteria for PCI values for BMI.
- 1 male subject experienced a decrease in height velocity; and 1 male subject had normal growth in height (i.e., did not meet criteria for PCI values for height). Neither male subject met criteria for PCI values for BMI.

Tanner staging

Through the data cutoff date, it was reported that almost all subjects achieved the appropriate Tanner stage at all applicable visits during the study. There were 5 subjects (4 female and 1 male subject) with inappropriate Tanner stage at some point during the study.

5.4.9. Post marketing experience

Upadacitinib was first approved for the treatment of RA on 16 August 2019 (international birth date) in the US. Subsequently, upadacitinib has received marketing authorisation in multiple countries for the treatment of adults with RA, ankylosing spondyloarthritis, non-radiographic axial spondyloarthritis, UC, CD, and giant cell arteritis; adults and adolescents with AD; adults and paediatric patients 2 years of age and older with PsA; and patients 2 years of age and older with pcJIA. Through 31 March 2025, the estimated cumulative post-marketing exposure is 1,032,568 patient treatment years.

All indications

The overall safety of upadacitinib therapy was evaluated by the MAH through review of post-marketing reports (spontaneous, solicited, literature) received from 16 August 2019 through 21 March 2025 occurring in paediatric patients (age < 18 years), using MedDRA version 28.0. The most frequently reported MedDRA SOC was Skin and subcutaneous tissue disorders, in which dermatitis atopic, acne, and pruritus had the highest number of events within this SOC. Among all the reports, the most common AEs reported included off-label use (9.5%), dermatitis atopic (6.3%), and acne (4.7%). Indications with the most reported AEs were AD (59.2%), unknown (12.5%), UC (9.2%), CD (7.4%), eczema (2.3%), and JIA (1.5%). The remaining indications reported less than 1% of AEs.

The most commonly reported SAEs were hospitalization and ulcerative colitis, which accounted for 11.3% of all SAEs and less than 1.0% of all reports. The remaining SAEs were reported in less than 0.5% of all retrieved reports.

Regarding bone fracture, a search of the MAH's global safety database, cumulatively through 31 December 2025 using the Bone Fractures CMQ, MedDRA Version 28.1, retrieved 21 paediatric/adolescent postmarketing reports, including 18 solicited reports and 3 spontaneous reports,

none of which were fatal. The cases primarily occurred in patients with atopic dermatitis. There were no events of fracture in patients receiving upadacitinib for JIA.

JIA

Among the 108 reports of patients receiving upadacitinib for JIA, the most frequently reported MedDRA SOC was Injury, poisoning, and procedural complications, in which off-label use, product used in unapproved indication, and product use issue were the highest number of events within this SOC. The PT of product use issue was used to describe reports in which upadacitinib was used in paediatric patients for an unapproved indication. The most common AEs reported were off-label use (14.1%), drug ineffective (7.3%), product use in unapproved indication (4.4%), arthralgia (3.9%), pyrexia (3.4%), and headache (3.4%). SAEs consisted of less than 5% of all AEs in this population and includes PTs such as abdominal pain upper, ear operation, and headache.

Among the 108 reports of JIA indication, age was available for 90 patients. There were 5 patients 2 to < 6 years old. These reports contained 19 events. The most common events were nasopharyngitis (10.5%) and pyrexia (10.5%). There were 15 reports in patients 6 to < 12 years old. These reports contained 22 events. The most common events included drug ineffective (22.7%), off-label use (18.2%), and therapeutic product effect incomplete (9.1%). There were no SAEs occurring in patients 2 to < 12 years old. There were 70 reports in patients 12 to < 18 years old. The most common AEs included off-label use (10.5%), drug ineffective (6.3%), product use in unapproved indication (5.6%), arthralgia (4.2%), JIA (4.2%), headache (3.5%), pyrexia (3.5%), and nausea (3.5%). There were 8 SAEs within this age group, including peripheral artery thrombosis and ovarian cyst.

5.4.10. Overall discussion and conclusions on clinical safety

5.4.10.0. Discussion

5.4.10.0.1. Overall assessment of available safety data

The safety assessment of upadacitinib in children with pcJIA relies primarily on extrapolation based on similar exposures in the paediatric population and the adult RA population in which a larger number of patients have been exposed and placebo-controlled studies were performed. Upadacitinib was previously approved for children from 12 years of age with AD, but this is the first application regarding use in children aged 2 to < 12 years.

To facilitate use in the paediatric subjects, an oral solution of upadacitinib (1 mg/mL) was introduced with this application. This formulation contains the excipient sodium benzoate as a preservative. Acknowledging that older publications suggested cross-reactivity from sodium benzoate in patients with ASA/NSAID-induced bronchoconstriction, a review of the literature available at the time of procedure did not support the introduction of a warning. Sodium benzoate is appropriately declared in the package leaflet.

Safety data collection

Safety data for upadacitinib administered using a QD extended-release tablet (15 mg) formulation, or a twice daily immediate-release oral solution (1 mg/mL) formulation, in subjects with pcJIA was collected in one open-label Phase 1 Study (M15-340) in subjects 2 to < 18 years. The study comprised three parts (7 days at two dose levels [part 1], a 156-week open-label treatment period at

the low dose [part 2], and an additional 156-week safety cohort with the low dose [part 3, that was added as a PIP modification agreed by the PDCO]).

Extent of exposure

A total of 122 paediatric patients with pcJIA were exposed to at least one dose of upadacitinib in an open phase 1 study. Of these, 113 patients had exposure for at least 52 weeks. Relatively few subjects in each age group have been exposed to upadacitinib (27 subjects age 2 to < 6 years, 53 subjects age 6 to < 12 years, 42 subjects age 12 to < 18 years). Supportive paediatric safety data from studies of upadacitinib in patients with AD were also provided (541 adolescents aged 12 to < 18 and 35 subjects aged 2 to < 12 years).

Although the size of the safety database in children with pcJIA was limited, it was considered overall sufficient to support the proposed indication and dose in this application that included extrapolation from adults through PK-matching. Further, the overall safety profile as observed in the paediatric study was generally consistent with the safety observed with upadacitinib in adult RA and adolescent AD. However, long-term safety in children is still limited and requires follow-up in line with the Guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis, EMA/CHMP/239770/2014 Rev.2.

Common adverse events

Overall, in patients with pcJIA, TEAEs per patient year were more frequent in the youngest children (2 to < 12 years) than in adolescents (12 to < 18 years). 98.4 % of patients had at least one TEAE and among these, infections were reported most frequently. Most TEAEs were mild or moderate in severity and not considered related to study drug by the investigator. AEs with reasonable possibility of being related to the study drug occurred in 41.8% of patients exposed to upadacitinib and were not more frequent in the youngest children. Among these, nasopharyngitis (15.6 %), upper respiratory tract infection (7.4 %), abdominal pain (6.6 %), nausea (5.7 %), and headache (5.7 %) were the most common.

Of note, **acne** was only reported in 3 subjects (2.5% overall, 4.8% in adolescents), which is similar to what was reported in adults with RA exposed to upadacitinib. In contrast, a higher frequency of acne was reported in AD studies in children where it was identified as a very common ADR (10.0 % in 15 mg group and 15.8 % in 30 mg group). As this was attributed to acne being more common in children and to the investigators being dermatologists (Rinvoq variation EPAR; EMEA/H/C/004760/X/0006/G), the lower frequency in children in a non-dermatologic indication as pcJIA is noted. Acne is currently listed as very common (>10 %) in the SmPC. No change regarding this adverse reaction was deemed necessary based on the new data presented.

In the SmPC, **skin papilloma** is described as an ADR observed in the paediatric population in AD studies (3.4% and 6.8% of adolescent patients with atopic dermatitis in the upadacitinib 15 mg and 30 mg groups, respectively). This information was added to the SmPC after review of data from long-term studies of upadacitinib in adolescents with AD (II/0052). Two cases of skin papilloma (1.6%) were reported in the 122 children with pcJIA exposed to upadacitinib. Hence, no update of product information was deemed necessary.

Overall, assessment of data from the pcJIA clinical programme did not identify any new ADRs beyond those currently listed in the upadacitinib product information. The safety profile seemed generally consistent with the safety observed with upadacitinib in adult RA. However, the CHMP acknowledged the limitations of the safety data for upadacitinib in pcJIA based on one open uncontrolled study and precluding direct comparisons with the data from the RA populations.

Importantly, as study M15-340 did not include a control arm, the assessment of safety in children with pcJIA also, to a great extent, relies on extrapolation based on similar exposures in the paediatric population and the adult RA population in which a larger number of patients have been exposed and placebo-controlled studies were performed. In the paediatric study, oral solution (BID) or tablet (QD) were administered, whereas only tablets were administered in the adult studies. However, the similar safety profile in adolescents with AD exposed to 15 or 30 mg upadacitinib was considered reassuring even with minor potential differences in Cmax. Notably, there was a higher frequency of drug-related AEs in children > 6 years (mainly receiving the tablet formulation) than in children 2-6 years (mainly receiving the oral solution). This difference was likely attributed to the different populations and did not indicate a different safety profile between the two formulations. Predicted exposure (Cmax and AUC) was similar in patients receiving the oral formulation and the extended-release tablet (see also PK section).

Adverse events of special interest (AESIs)

No treatment-emergent AESIs of malignancy (including NMSC, malignancy excluding NMSC, lymphoma), adjudicated GI perforation, renal dysfunction, active TB, adjudicated CV events, adjudicated thrombotic events, retinal detachment, and serious hypersensitivity reactions were reported in study M15-340.

Serious and opportunistic infections including TB are an identified risk of upadacitinib treatment and a warning regarding this risk is described in the current product information. The frequency of serious infections reported in children with pcJIA receiving upadacitinib (1.6 events per 100 PY) is in line with the known safety profile in adults with RA where the overall long-term rate of serious infections for the upadacitinib 15 mg group was 3.8 events per 100 PY as per the approved SmPC.

Treatment with upadacitinib is associated with an increased incidence of **CPK** and **liver enzyme elevations** and 'Blood CPK increased', 'ALT increased' and 'AST increased' are common (1 to < 10 %) adverse drug reactions in the product information. Overall, no new concerns arose from the data in pcJIA patients regarding hepatic disorders.

Anaemia, **neutropenia** and **lymphopenia** are identified risks of upadacitinib treatment and are listed as common ADRs (1 to < 10 %) in the current product information. In children with pcJIA receiving upadacitinib in study M15-340, the reported frequencies were 2.4, 2.7 and 1.6 events per 100 PY for anaemia, neutropenia and lymphopenia, respectively. This is in line with the known safety profile of upadacitinib.

Eleven events of **bone fracture** occurred in the 122 children exposed to upadacitinib in study M15-340, corresponding to 1.6 E/100 PYs in age group 2 to < 6 years, 6.3 E/100 PYs in age group 6 to < 12 years, and 3.7 E/100 PYs in age group 12 to < 18 years. This is higher than in the background paediatric population (incidence reports ranging from 1.3 to 3.6 E/100 PY across several studies in Europe [Hedström et al 2010[17]]) and what has been reported in upadacitinib studies in other indications. Of the 11 events, 9 could be attributed to high energy trauma. For two events of fracture (little toe fracture and fibula fracture), the cause was reported to be unknown.

Fracture is listed as an important potential risk in the RMP (EMEA/H/C/004760/X/0012/G) as post-marketing data of another JAK inhibitor (tofacitinib) showed an increased risk for fractures in subjects with RA treated with tofacitinib compared with TNF inhibitor (ORAL Surveillance study, Hansen 2022). In a recently published disproportionality analysis of data from the WHO global

[17] Hedström EM, Svensson O, Bergström U, et al. Epidemiology of fractures in children and adolescents. Acta Orthop. 2010;81(1):148-53.

individual case safety report (ICSR) database, VigiBase, reporting of fractures was significantly increased compared with other medications for JAK inhibitors overall (ROR 3.35; 95% CI 3.20, 3.48) and for upadacitinib (ROR 4.23; 95% CI 3.80, 4.48), tofacitinib (ROR 3.34; 95% CI 3.20, 3.48), filgotinib (ROR 2.24; 95% CI 1.11, 3.94) and baricitinib (ROR 1.80; 95% CI 1.52, 2.11) (De La Torre et al. 2024[18]). The authors suggested that bone fractures may be a class effect of JAK inhibitors and speculated that reduction of cytokines (with key roles in maintaining bone formation) by JAK inhibition could disturb the bone remodelling balance and be a mechanism behind the observed increased risk.

For upadacitinib, a trend towards an increased risk of bone fracture has been noted also in placebo-controlled studies in other indications but causality has not been established, e.g. in giant cell arthritis, an increased risk for bone fractures was noted in patients treated with 15 mg upadacitinib compared to placebo (6.2% vs. 5.4%). However, the treated group also had slightly more risk factors for osteoporosis at baseline (EMEA/H/C/004760/II/0056). Regarding long-term risk in adolescents with AD, the upadacitinib 30 mg group reported a higher rate of TEAEs of bone fracture (1.9 E/100 PY) compared with upadacitinib 15 mg (1.1 E/100 PY).

The relatively high frequency of bone fractures observed in study M15-340 may be at least partly attributed to the increased risk of bone fractures in the JIA population. Without a control group, no further conclusions can be made. Nevertheless, fractures is an important potential risk listed in the RMP and will be further characterised from the ongoing Category 3 PASS as agreed in the RMP (see Section 6.3.).

Serious adverse events (SAEs) and deaths related to the medical product

No deaths were reported in the study of upadacitinib in paediatric patients with pcJIA through the data cutoff date of 15 August 2024. SAEs considered by the investigator to have a reasonable possibility of being related to upadacitinib were reported as SAE in one patient each and included the followings:

- *Escherichia* urinary tract infection and upper respiratory tract infection. Serious and opportunistic infections including TB
- are an important identified risk of upadacitinib treatment and an AESI as previously discussed.
- Constipation. This SAE did not lead to interruption of upadacitinib treatment, and the MAH considered there was no reasonable possibility of this event being related to the study drug. The CHMP agreed with the MAH's rationale. Hence, no concern was raised.
- Headache and nausea: both are already listed as common ADRs in the product information.
- Conversion disorder: the MAH did not regard this SAE as being unexpected, based on the known risk of psychiatric disorders in the JIA paediatric population. As this was a single case, the MAH's position was agreed. Overall, 14.8% of subjects experienced a TEAE in the psychiatric disorders SOC. This is in line with literature data, reporting a high prevalence of psychiatric disorders in children with JIA (Delcoigne et al 2023[19]).

Discontinuation due to adverse events

Among the 7 patients with pcJIA who discontinued the study drug prematurely, worsening of JIA was the most frequently reported reason (4 events). This is an expected TEAE that can be attributed

[18] Martinez de la Torre A, Clausen AB, Burden AM, Weiler S. Fracture-Related Safety Reporting of JAK Inhibitors: An Analysis from the WHO Global VigiBase. Drug Saf. 2025 Feb;48(2):191-201. doi: 10.1007/s40264-024-01490-w. Epub 2024 Nov 27. PMID: 39604587; PMCID: PMC11785614.
[19] Delcoigne B, Horne A, Reutfors J, et al. Risk of Psychiatric Disorders in Juvenile Idiopathic Arthritis: Population- and Sibling-Controlled Cohort and Cross-Sectional Analyses. ACR Open Rheumatol. 2023;5(5):277-84.

to lack of effect in a relapsing-remitting disease. None of the other TEAEs leading to discontinuation of study drug (abdominal pain, nausea and nasopharyngitis) were classified as serious.

Safety in special populations

In addition to the study in pcJIA, safety of upadacitinib in the **paediatric population** was supported by studies in children with atopic dermatitis. Studies M16-045, M16-047 and M18-891 in adolescents with AD were assessed by the CHMP in the MAA for Rinvoq in AD (EMEA/H/C/004760/X/0006/G). In addition, 35 children aged 2 to < 12 years with AD were exposed in study (M16-049). No new safety concern was identified further to skin papilloma. Please refer to the discussion under common adverse events.

Laboratory and other findings

In study M15-340, upadacitinib treatment was associated with **increased HDL-C and LDL-C** in paediatric subjects with pcJIA. The mean change from baseline was generally small. Hypercholesterolaemia and hyperlipidaemia are listed as common ADRs in the product information and the risk was previously described in SmPC section 4.4. Monitoring guidance for lipids is given in SmPC section 4.2. No product information update was deemed necessary.

Growth impairment, short stature, and delayed puberty are overrepresented in the JIA population, associated with negative effect of chronic inflammation and long-term use of glucocorticoids. Successful treatment can therefore be expected to have a positive impact on growth.

In a cohort of patients with JIA followed over time in the United Kingdom, severe growth restriction (defined as change in height z-score ≤ -1) was seen across all subtypes and in 17% of patients with JIA overall, resulting in short stature (defined as height z-score < -2) in 7% of patients by 3 years (McErlane 2018[20]).

In study M15-340 of upadacitinib in children with pcJIA, findings of **reduced height velocity** (4.9%), **reduced weight gain** (23%) and **delayed puberty** (5 subjects) occurred at a frequency expected for the population. As the safety of upadacitinib in pcJIA referred here relies on one open uncontrolled study, no firm conclusion on potential effects on growth and development could be drawn. Long term safety in children was added as missing information in the RMP in order to further characterize potential long-term effects on growth and development. This safety concern will be further characterised in the Category 3 PASS Study M15-340 (final report expected in Q4 2027).

Post-marketing data

Upadacitinib was approved in the US for the treatment of pcJIA in patients 2 years of age and older on April 26, 2024, and post-market experience in this indication is still limited. Overall, there is little long-term experience of upadacitinib use in the youngest children (below 12 years of age). Potential long-term effects, including effects on growth and development in children need to be followed up post marketing. Long term safety in children was added as missing information in the RMP and will be further characterised in the Category 3 PASS Study M15-340 (final report expected in Q4 2027).

Regarding bone fractures, discussed above, there were no post-marketing events reported in patients receiving upadacitinib for JIA.

[20] McErlane F, Carrasco R, Kearsley-Fleet L, et al. Growth patterns in early juvenile idiopathic arthritis: Results from the Childhood Arthritis Prospective Study (CAPS). Semin Arthritis Rheum. 2018;48(1):53-60.

5.4.10.0.2. Adverse drug reactions in the SmPC

The MAH considered that, overall, the safety profile observed in paediatric patients with pcJIA treated with upadacitinib was consistent with the known safety profile for upadacitinib. No new safety findings were identified and no new ADRs were proposed to be included in the SmPC.

The MAH proposed the following addition to section 4.8 of the SmPC under subheading 'paediatric population':

"A total of 122 paediatric patients (2 to < 18 years of age) with polyarticular juvenile idiopathic arthritis were treated in an open-label, single-arm study, representing 254.6 patient-years of exposure, of whom 113 were exposed to upadacitinib for at least one year. Overall, the safety profile observed in paediatric patients with polyarticular course juvenile idiopathic arthritis treated with upadacitinib was consistent with the known safety profile for upadacitinib.".

The CHMP agreed with the MAH that the safety profile observed in paediatric patients with pcJIA treated with upadacitinib was consistent with the known safety profile for upadacitinib and thus the proposed addition to section 4.8 was accepted.

5.4.10.1. Conclusions on clinical safety

The safety database for upadacitinib in children was relatively small, at least in terms of long-term treatment. However, the available data indicated a similar safety profile and an overall similar upadacitinib tolerability in children aged 2 to < 18 years with JIA as in adolescents with AD and adults with RA, where the exposure was similar as concluded in the clinical pharmacology section.

Long term safety in children was added as missing information in the RMP in order to further characterize potential long-term effects on growth and development. This safety concern will be further characterised in the Category 3 PASS Study M15-340 (final report expected in Q4 2027).

6. Risk management plan

6.1. Safety specification

6.1.1. Proposed safety specification

Table 41: Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	• Serious and opportunistic infections including TB • Herpes zoster • NMSC • GI perforation
Important potential risks	• Malignancies excluding NMSC • MACE • VTEs (deep venous thrombosis and pulmonary embolus) • DILI • Fetal malformation following exposure in utero • Fractures
Missing information	• Use in very elderly (≥ 75 years of age) • Use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C • Use in patients with moderate hepatic impairment • Use in patients with severe renal impairment • Long-term safety in adults • Long-term safety in adolescents with AD • Long-term safety in children

Long-term safety in children was added as a new category for missing information with the addition of the indication polyarticular JIA in patients 2 years of age and older to the RMP. Long-term upadacitinib clinical safety data are currently limited in children (from 2 years), including potential effects of upadacitinib on height in growing children.

The missing information category for long-term safety was updated to long-term safety in adults to clearly differentiate it from other missing information categories for long-term safety (i.e., long-term safety in adolescents with AD and long-term safety in children).

6.1.2. Discussion on proposed safety specification

The MAH added long-term safety in children to the missing information category, due to limited long-term treatment experience in children below 12 years of age, in order to further characterize potential long-term effects on growth and development. Missing information long-term safety was renamed to long-term safety in adults. The proposed changes to the safety specification were acceptable.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan.

No changes of the routine pharmacovigilance activities were proposed.

In addition, the MAH has proposed the following changes of the additional pharmacovigilance activities:

Table 42: Planned additional pharmacovigilance activities

Summary **Table of Additional Pharmacovigilance Activities**

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable	--	--	--	--
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable	--	--	--	--
Category 3 – Required additional pharmacovigilance activities				
Study P19-150 Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe/Ongoing	The primary objectives are to assess comparability across users of upadacitinib and other select systemic treatments for RA through in-depth assessments of drug utilization and patient characteristics at baseline; to describe the incidence of the following safety outcomes in patients with RA treated with upadacitinib: malignancy excluding non-melanoma skin cancer, including malignancy by type, NMSC, MACE, VTE, serious and opportunistic infections (including herpes zoster and TB), GI perforations, liver injury (including DILI), bone fractures, and all-cause mortality; if a suitable comparator is identified, to describe and compare (when feasible) the incidence of the above safety outcomes in patients with RA treated with upadacitinib relative to those treated other select systemic RA treatments (excluding other JAK inhibitors).	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures	• Draft protocol • Progress report • Interim report • Final study report	• Submitted 16 March 2020 • Submitted in 2022 and 2023. No longer needed per EMA advice. • Estimated Q3 2025 • Estimated Q1 2030

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	Secondary objectives are to describe the incidence of the safety outcomes mentioned under the primary objective among the following patient subcohorts of upadacitinib users: the very elderly (≥ 75 years of age), patients with moderate hepatic impairment (when possible using proxy measures available within a given data source), patients with severe renal impairment (when possible using proxy measures available within a given data source), and patients with evidence of chronic infection with HBV or HCV; if a suitable comparator is identified, to describe the incidence of the safety outcomes mentioned under primary objectives in the following patient subcohorts of other select systemic RA treatments: the very elderly (≥ 75 years of age), patients with moderate hepatic impairment (when possible using proxy measures available within a given data source), and patients with severe renal impairment (when possible using proxy measures available within a given data source) and patients with evidence of chronic infection with HBV or HCV.	Missing Information: use in very elderly (≥ 75 years of age); use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C; use in patients with moderate hepatic impairment; use in patients with severe renal impairment; long-term safety in adults		

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study P19-141 Long-Term Safety Study of Upadacitinib Use in RA Patients in the US/Ongoing	The primary objective is to compare the incidence of malignancy (excluding NMSC), NMSC, MACE, VTE, serious infection events, and all-cause mortality in adults with RA who receive upadacitinib in the course of routine clinical care relative to those who receive biologic therapy for the treatment of RA. Secondary objectives are to describe the incidence rates of herpes zoster, opportunistic infections, active TB, GI perforations, evidence of DILI, and fractures; to describe the incidence of the above outcomes in very elderly patients (aged ≥ 75 years); and to describe the incidence rates of events in primary and secondary objectives in the following subgroups of interest: patients with moderate hepatic impairment at the time of Rinvoq or biologic therapy start; patients with evidence of chronic infection with HBV or HCV at the time of Rinvoq or biologic therapy start; and patients with severe renal impairment at the time of Rinvoq or biologic therapy start. An exploratory objective is to describe the distribution of risk factors for VTE in those treated with Rinvoq and those treated with biologic therapy, and in those who do and do not experience VTE during follow-up, in a subset of participating patients providing laboratory samples.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures Missing information: use in very elderly (≥ 75 years of age); long-term safety in adults; use in patients with moderate hepatic impairment; use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C; use in patients with severe renal impairment.	• Draft protocol • Progress report • Update on prevalence of baseline biomarkers and clinical risk factors within PSUR • Interim report • Final study report	• Submitted 16 March 2020 • Submitted in 2022 and 2023. No longer needed per EMA advice. • Annually for the first 2 years and thereafter in accordance with the PSUR reporting schedule • Estimated Q2 2029 • Estimated Q1 2030

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study P20-199 Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation in RA/ Ongoing	This study aims to evaluate the use of upadacitinib in routine clinical care through the following specific objectives: to describe the baseline characteristics of new users of, and in a similar manner, to describe new users of a selected bDMARD for comparison; to evaluate prescribers' adherence to the upadacitinib aRMMs, specifically: compliance to recommendations for patient screening and laboratory monitoring prior to and during treatment; compliance to recommendations for limitations of use, including: Use in patients with risk factors for GI perforation; use in patients with risk factors for VTE; use in the patients aged 65 years and older; use in patients with risk factors for CVD; use in patients with risk factors for malignancy; use in patients with risk factors for serious infections; and contraindicated use (active TB and pregnancy); and to describe changes in the utilisation of upadacitinib following the updated recommendations and limitations for use implemented after the Article 20 referral procedure.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; and fetal malformation following exposure in utero	• Draft protocol • Progress reports • Final study report	• Submitted 16 March 2020) • Submitted Q2 2022, Q1 2023; next estimated Q1 2024, Q2 2025 • Estimated Q3 2026
Study P20-390 Long-Term Safety Study of Upadacitinib Use in AD Patients/ Ongoing	To evaluate and characterise the important identified and potential risks of upadacitinib and missing information on the safety of upadacitinib. Primary objectives: To assess comparability across upadacitinib and other select systemic treatments for AD through in-depth assessments of treatment pattern and patient disposition at baseline;	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTE; DILI; fractures	• Draft protocol • Progress report • Interim report • Final Study Report	• Submitted 18 March 2021 • Annually starting 2023, except 2028 • Estimated Q4 2028 • Estimated Q4 2033

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	To describe the incidence of the following safety outcomes in adolescent and adult individuals with AD treated with upadacitinib: malignancy (excluding NMSC) including malignancy by type, NMSC, MACE, VTE, serious infections (incl. OI), HZ, EH/ KVE, active TB, GI perforation, DILI, fractures, and all-cause mortality; If a suitable comparator is identified: to describe and compare (when feasible) the incidence of the above safety outcomes in adolescent and adult individuals with AD treated with upadacitinib, relative to those treated with other selected systemic AD treatments. Secondary objectives: To describe the incidence of the outcomes above in upadacitinib users by: dose of upadacitinib (15 mg and 30 mg); age group (adolescents 12 – 17 years, 18 – 64 years, 65 – 74 years and ≥ 75 years) at the time of upadacitinib initiation; history of moderate hepatic impairment at the time of upadacitinib initiation; history of chronic infection with HBV or HCV at the time of upadacitinib initiation; history of severe renal impairment at the time of upadacitinib initiation. • If a suitable comparator is identified, to describe the incidence of the outcomes above in adolescent and adult individuals with AD treated with other selected systemic AD treatments by: age group (adolescents 12 – 17 years, 18 – 64 years, 65 – 74 years and ≥ 75 years) at the time of treatment initiation; history of moderate hepatic impairment at the time of treatment initiation; history of chronic infection with HBV or HCV at the time of treatment initiation; history of severe renal impairment at the time of treatment initiation.	Missing information: use in very elderly (≥ 75 years of age); long-term safety in adults; use in patients with moderate hepatic impairment at the time of initiation of upadacitinib or other systemic drug therapies; use in patients with evidence of chronic infection with HBV or HCV at the time of initiation of upadacitinib or other systemic drug therapies; use in patients with severe renal impairment at the time of initiation of upadacitinib or other systemic drug therapies; long-term safety in adolescents with AD		
Study P21-825 Drug Utilization Study Evaluating Additional Risk Minimization Measures for Upadacitinib in the Treatment of Atopic Dermatitis in Europe/ Planned	To evaluate the use of upadacitinib in individuals with AD through the following objectives: To describe the baseline characteristics of individuals with AD who are new users of upadacitinib; To the extent measurable, evaluate healthcare utilization in routine clinical care as an indicator of physician adherence to the aRMMs among individuals with AD who are new users of upadacitinib, by: a) Quantifying the compliance to recommendations for posology (average daily dose) and by describing the duration of use; b) Quantifying the compliance to recommendations for the use among individuals who have risk factors for GI perforation, serious infections, malignancy, MACE, and VTE; c) Quantifying the compliance to the recommendations for the use among patients aged 65 years and older; d) Quantifying the compliance to the recommendations for contraindicated use including pregnancy, and active TB; e) Quantifying the compliance to recommendations for patient screening and laboratory monitoring prior to and during upadacitinib treatment (Denmark, Germany, and Spain only).	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC, GI perforation Important potential risks: MACE; VTEs; malignancies excluding NMSC; and fetal malformation following exposure in utero	• Draft protocol • Progress Report 1 • Progress Report 2 • Final Study Report	• Submitted 27 May 2021 • Q4 2024 • Q3 2025 • Q3 2026

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	To describe the changes in the utilization of upadacitinib following the implementation of revised aRMMs from the Article 20 referral procedure, specifically: a) Describe the use of upadacitinib among patients with risk factors for VTE, MACE, malignancy, and serious infections; b) Describe the use of upadacitinib among patients aged 65 years and older; c) Describe the use of upadacitinib 30 mg.			

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study P21-824 A Study of Growth in Adolescents with AD Who Receive Upadacitinib/Ongoing	To evaluate the growth, development, and maturation in North American (US and Canada)-residing adolescents with moderate to severe AD who receive upadacitinib vs. biologic and other non-biologic, non-JAK inhibitor systemic comparators in routine clinical care. Where feasible, a cohort of European-residing adolescents with moderate to severe AD will also be evaluated. The primary objective is to compare differences in changes from baseline in height SDS and weight SDS, age at peak height velocity, age at Tanner stage progression, and incidence of bone fractures in adolescents with moderate to severe AD being treated with upadacitinib and those treated with comparator medications for AD. The secondary objectives of the study are to describe changes from baseline in standing height, height percentiles, height velocity, height velocity SDS, weight, weight percentiles, BMI, BMI percentiles, and BMI SDS, as well as the frequency of delayed puberty in adolescents with moderate to severe AD being treated with upadacitinib and those treated with comparator medications for AD.	Important potential risk: fractures Missing information: long-term safety in adolescents with AD	• Draft Protocol • Annual reports • Interim report 1 • Interim report 2 • Final study report	• Submitted 27 May 2021 • Annually starting Q4 2024 • Estimated Q4 2027 • Estimated Q4 2030 • Estimated Q4 2033

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study P24-343 Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe /Planned	Primary Objectives: To describe and compare the incidence of GI perforation in adults with UC or CD treated with upadacitinib, relative to those treated with select biologic IBD treatments at a similar line of therapy; To describe and compare, where possible, the incidence of fractures and DILI in adults with UC or CD treated with upadacitinib, relative to those treated with select biologic IBD treatments at a similar line of therapy. Comparability across upadacitinib and biological IBD treatments will be evaluated through in-depth assessments of number of users, treatment patterns and patient disposition at baseline to determine whether suitable comparators are identified and number of users allow for incidence comparison of fractures and DILI. Secondary objectives: To describe and compare, where possible, the incidence of the following secondary safety outcomes in adults with UC or CD treated with upadacitinib, relative to those treated with biological drug therapies at a similar line of therapy for UC and CD in the course of routine clinical care: malignancy excluding NMSC (stratified by type), NMSC, MACE, VTE, serious infections (defined as all infections that require hospitalization, including opportunistic infections), herpes zoster, active TB, and all-cause mortality. Comparability across upadacitinib and biological IBD treatments will be evaluated through in-depth assessments of number of users, treatment	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures Missing Information: use in very elderly (≥ 75 years of age); long-term safety in adults; use in patients with: moderate hepatic impairment at the time of initiation of upadacitinib or other systemic drug therapies; evidence of chronic infection with HBV or HCV at the time of initiation of upadacitinib or other systemic drug therapies; severe renal impairment at the time of initiation of upadacitinib or other systemic drug therapies.	• Draft protocol • Progress report • Interim study report • Final study report	• Submitted 09 August 2023 • Annually starting Q4 2025, except 2029 • Estimated Q4 2029 • Estimated Q2 2035

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	patterns and patient disposition at baseline to determine whether suitable comparators are identified and number of users allow for the incidence comparison of the secondary outcomes. In addition, incidence of the primary and secondary safety outcomes will be described in patients with UC or CD who receive upadacitinib by dosing pattern (45 mg induction followed by 15 mg and/or 30 mg maintenance dosing). When possible, the occurrence of the safety outcomes will be described in the following subgroups of interest, with limited or missing information from the clinical development program: very elderly (aged ≥ 75 years) at the time of treatment initiation; patients with moderate hepatic impairment at the time of treatment initiation; patients with severe renal impairment at the time of treatment initiation; patients with evidence of chronic infection with HBV or HCV at the time of treatment initiation.			

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study P24-344 Effectiveness Evaluation of aRMMs for Upadacitinib in UC/Planned	To evaluate the use of upadacitinib in routine clinical care for UC through the following specific objectives: To describe the baseline characteristics of UC patients who are new users of upadacitinib; To the extent measurable, evaluate healthcare utilization in routine clinical care as indicator of physician adherence to the aRMMs among patients with UC who are new users of upadacitinib, by: a) Quantifying the compliance to recommendations for posology (average daily dose) and duration of use; b) Quantifying the compliance to recommendations for the use among patients who have risk factors for GI perforation, malignancy, MACE, VTE, and serious infections; c) Quantifying the compliance to the recommendations for the use among patients aged 65 years and older; d) Quantifying the compliance to the recommendations for contraindicated use including pregnancy and active TB; e) Quantifying the compliance to recommendations for patient screening and laboratory monitoring prior to and during upadacitinib treatment (Denmark and Spain only).	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: MACE; VTEs; malignancies excluding NMSC; and fetal malformation following exposure in utero	• Draft protocol • Progress report • Final study report	• Submitted 21 October 2022 • Annually starting 2024 • Estimated Q3 2027

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	To describe the changes in the utilization of upadacitinib following the implementation of revised aRMMs from the Article 20 referral procedure (Sweden only), specifically: a) Describe the use of upadacitinib among patients with risk factors for VTE, MACE, malignancy, and serious infections; b) Describe the use of upadacitinib among patients aged 65 years and older; Describe the use of higher maintenance dose of upadacitinib 30 mg.			
Long-Term Extension Portion of Study M14-465/ Ongoing	To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD in subjects with RA who have completed Period 1.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; fetal malformation following exposure in utero Missing Information: long-term safety in adults	• Final study report • Targeted submission of final study report to EMA	• 30 August 2028 • 30 November 2028

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M15-554/ Ongoing	To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with PsA who have completed Period 1.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; fetal malformation following exposure in utero Missing Information: long-term safety in adults	• Final study report • Targeted submission of final study report to EMA	• 31 December 2024 • 30 April 2025
~~Long-Term Extension Portion of Study M15-572/ Ongoing~~	~~To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with PsA who have completed Period 1.~~	~~Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation~~ ~~Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; fetal malformation following exposure in utero~~ ~~Missing Information: long-term safety~~	~~• Final study report~~ ~~• Targeted submission of final study report to EMA~~	~~• 30 September 2025~~ ~~• 31 December 2025~~

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M19-944 (Study 1)/ Ongoing	To evaluate the safety and tolerability of upadacitinib 15 mg QD in extended treatment in adult subjects with active bDMARD-IR AS (Study 1), who have completed the Double-Blind Period.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI, fractures; fetal malformation following exposure in utero Missing Information: long-term safety in adults	• Final study report • Targeted submission of final study report to EMA	• Q2 2026 • Q3 2026
Long-Term Extension Portion of Study M19-944 (Study 2)/ Ongoing	To evaluate the safety and tolerability of upadacitinib 15 mg QD in extended treatment in adult subjects with active nr-axSpA (Study 2), who have completed the Double-Blind Period.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI, fractures, fetal malformation following exposure in utero Missing Information: long-term safety in adults	• Final study report • Targeted submission of final study report to EMA	• Q2 2026 • Q3 2026

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M16-045/ Ongoing	To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in adolescent and adult subjects with AD who have completed the Double-Blind Period.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; fetal malformation following exposure in utero Missing Information: long-term safety in adults; long-term safety in adolescents with AD	• Targeted submission of final study report to EMA	• Q2 2026

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M16-047/ Ongoing	To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in combination with TCS in adolescent and adult subjects with AD who have completed the Double-Blind Period.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; fetal malformation following exposure in utero Missing Information: long-term safety in adults; long-term safety in adolescents with AD	• Interim report • Targeted submission of final study report to EMA	• Q3 2026 • Q2 2031

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M18-891/ Ongoing	To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in adolescent and adult subjects with AD who have completed the Double-Blind Period.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; fetal malformation following exposure in utero Missing Information: long-term safety in adults; long-term safety in adolescents with AD	• Targeted submission of final study report to EMA	• Q2 2026
Long-Term Extension Study M14-533/ Ongoing	To evaluate the long-term safety and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with UC who were nonresponders in Study M14-234 Substudy 1, subjects who lost response during Study M14-234 Substudy 3, and subjects who completed Study M14-234 Substudy 3	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; fetal malformation following exposure in utero Missing Information: long-term safety in adults	• Final study report	• Q3 2027

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M14-430/ Ongoing	To evaluate safety and efficacy of long-term administration of upadacitinib in subjects with moderately to severely active CD who participated in the Phase 3 upadacitinib induction and maintenance studies.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; fetal malformation following exposure in utero Missing Information: long-term safety in adults	• Final study report • Targeted submission of final study report to EMA	• Q1 2028 • Q2 2028
Long-Term Extension Portion of Study M16-852/ Ongoing	To evaluate the safety and efficacy of continuing versus withdrawing upadacitinib in maintaining remission in subjects with GCA who achieved remission in Period 1.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; fetal malformation following exposure in utero Missing Information: use in very elderly (≥ 75 years of age); long-term safety in adults	• Final CSR • Target submission of final CSR to EMA	• Q1 2026 • Q2 2026

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Part 2 and Part 3 of Phase 1 Study M15-340/ Ongoing	To evaluate the long-term safety and tolerability of upadacitinib in pediatric subjects with pcJIA.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; fetal malformation following exposure in utero. Missing Information: long-term safety in children	• Final report submission	• Q4 2027

6.2.2. Discussion on the Pharmacovigilance Plan

6.2.2.1. Routine pharmacovigilance activities

The MAH did not propose changes to routine pharmacovigilance activities. This was agree.

6.2.2.2. Additional pharmacovigilance activities

In this revision of RMP, the MAH added 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) as an additional pharmacovigilance activity. This is a phase 1, multiple-dose, open-label study consisting of 3 parts:

- Part 1: To evaluate the pharmacokinetics, safety, and tolerability of multiple doses of upadacitinib in paediatric subjects with pcJIA. To evaluate the palatability of upadacitinib oral solution in paediatric subjects.

- Part 2: To evaluate the long-term safety and tolerability of upadacitinib in paediatric subjects with pcJIA who completed Part 1.
- Part 3 (Additional Safety Cohort): To evaluate the long-term safety and tolerability of upadacitinib in paediatric subjects with pcJIA.

Parts 2 and 3 of this study are included as additional pharmacovigilance activity in RMP. Part 2 is an open-label, long-term extension to evaluate long-term safety and tolerability of upadacitinib. Subjects in Part 2 will receive open-label upadacitinib at the equivalent of the Low Dose level per body weight category. Part 3 is an additional safety cohort from all age groups (2 to < 18 years) which was added to evaluate long-term safety and tolerability of upadacitinib without intensive pharmacokinetic sample collection. Safety concerns addressed in this study include important identified risks (serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation), important potential risks (malignancies excluding NMSC; MACE; VTEs; DILI; fractures; fetal malformation following exposure in utero) and missing Information (long term safety). The addition of this study in the RMP is agreed. The list of safety concerns which will be addressed in this study is supported. All important identified risks and all important potential risk of upadacitinib are included as safety concerns which will be addressed in this study.

The study will also address missing information long term safety in children with specific focus on effects on growth and bone development. Subjects will be followed for additional 2 years (or until age 18) and data on height, weight and Tanner stage assessments will be collected.

Additionally, the MAH removed completed Study M15-572 from the pharmacovigilance plan. Study results were submitted and evaluated as part of type II variation EMA/VR/0000317563 which was completed in March 2026.

Changes to the pharmacovigilance plan were considered acceptable.

6.3. Plans for post-authorisation efficacy studies

Not applicable.

6.4. Risk minimisation measures

6.4.1. Proposed risk minimisation measures

Table 43: Planned routine risk minimisation measures

Safety Concern	Routine Risk Minimization Activities
Serious and opportunistic infections including TB	Routine risk communication: • SmPC Section 4.4 summarizes the risk and provides guidance on ways to reduce the risk. • SmPC Section 4.4 includes a statement on dose dependency of upadacitinib on reports of serious infection. • SmPC Section 4.4 specifies a higher incidence of infections in the elderly and diabetic populations. • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq and describes the risk of viral reactivation.

	• The PL advises that patients do not take Rinvoq if they have active TB and warns that patients with a history of TB, or who have been in close contact with someone with TB should consult their doctor or pharmacist before and during treatment with Rinvoq. Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.2 outlines lymphocyte and neutrophil counts and when not to initiate upadacitinib dosing. • SmPC Section 4.2 outlines interruption guidelines based on ALC and ANC. • SmPC Section 4.3 indicates that upadacitinib is contraindicated in patients with active TB or active serious infections. • SmPC Section 4.4 states that patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with upadacitinib and that upadacitinib therapy should be interrupted if a patient develops a serious or opportunistic infection. • SmPC Section 4.4 advises to consider the risks and benefits of initiating upadacitinib in patients with chronic or recurrent infections. • A patient who develops a new infection during treatment with upadacitinib should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, the patient should be closely monitored, and upadacitinib should be interrupted if the patient is not responding to therapy. • Screening for TB prior to initiation is advised, and upadacitinib should not be given if active TB is diagnosed. Anti-TB therapy should be considered prior to initiation of upadacitinib in patients with untreated latent TB or in patients with risk factors for TB infection. • SmPC Section 4.4 specifies patient populations for which upadacitinib should be used with caution. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Other routine risk minimization measures: Prescription only medicine
Safety Concern	**Routine Risk Minimization Activities**
Herpes zoster	Routine risk communication: • SmPC Section 4.4 describes the risk of viral reactivation such as herpes zoster. • SmPC Section 4.8 describes findings from upadacitinib clinical trials. • The PL warns that patients who have an infection or who have a recurring infection should consult their doctor or pharmacist before and during treatment with Rinvoq and describes the risk of viral reactivation. • The PL warns that patients who have had a herpes zoster infection (shingles) should tell their doctor if they get a painful skin rash with blisters as these can be signs of shingles. Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 advises that prior to initiating upadacitinib patients be brought up to date with all immunizations including herpes zoster according to current immunization guidelines.

	• SmPC Section 4.4 advises that if a patient develops herpes zoster, interruption of upadacitinib therapy should be considered until the episode resolves. Other routine risk minimization measures: Prescription only medicine
Safety Concern	**Routine Risk Minimization Activities**
NMSC	Routine risk communication: • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.4 indicates that NMSCs have been reported in patients treated with upadacitinib and includes a statement on dose-dependency. • SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 advises on periodic skin examination. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Other routine risk minimization measures: Prescription only medicine
Safety Concern	**Routine Risk Minimization Activities**
GI perforation	Routine risk communication: • SmPC Section 4.4 informs on reports of diverticulitis and GI perforation in clinical trials and from post-marketing sources. • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq. Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 advises to use with caution in patients who may be at risk for GI perforation and prompt evaluation if specific signs/symptoms occur. Other routine risk minimization measures: Prescription only medicine
Safety Concern	**Routine Risk Minimization Activities**
Malignancies excluding NMSC	Routine risk communication: • SmPC Section 4.4 indicates that malignancies have been reported in patients receiving JAK inhibitors, including upadacitinib, and includes a statement on upadacitinib dose-dependency. • SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor).

	Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Other routine risk minimization measures: Prescription only medicine
Safety Concern	**Routine Risk Minimization Activities**
MACE	Routine risk communication: • SmPC Section 4.4 describes the effect of upadacitinib on lipids and describes that impact on CV morbidity and mortality has not been determined. • SmPC Section 4.4 indicates that events of MACE were observed in clinical trials for upadacitinib. • SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq. Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.2 describes monitoring of lipid parameters following initiation of upadacitinib. • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Other routine risk minimization measures: Prescription only medicine
Safety Concern	**Routine Risk Minimization Activities**
VTEs (deep venous thrombosis and pulmonary embolus)	Routine risk communication: • SmPC Section 4.4 indicates that events of deep vein thrombosis and pulmonary embolism have been reported in clinical trials for upadacitinib. • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq and advises that patients tell their doctor if they get certain symptoms. • SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 specifies in patients with VTE risk factors other than cardiovascular or malignancy risk factors, use upadacitinib with

	caution. Examples of the risk factors which may put a patient at higher risk for VTE are provided. • SmPC Section 4.4 on re-evaluation of VTE risk and to promptly evaluate patients with signs and symptoms of VTE and discontinue upadacitinib in patients with suspected VTE, regardless of dose. Other routine risk minimization measures: Prescription only medicine
Safety Concern	**Routine Risk Minimization Activities**
DILI	Routine risk communication: SmPC Section 4.4 describes the effect of upadacitinib on transaminases. Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 recommends prompt investigation of the cause of liver enzyme elevation to identify potential cases of DILI. • SmPC Section 4.4 advises that if increases in ALT or AST are observed during routine patient management and DILI is suspected, upadacitinib should be interrupted until this diagnosis is excluded. Other routine risk minimization measures: Prescription only medicine
Safety Concern	**Routine Risk Minimization Activities**
Fetal malformation following exposure in utero	Routine risk communication: • SmPC Section 4.6 describes the teratogenic effects observed in animals receiving upadacitinib and state that there are no or limited data from use of upadacitinib in pregnant women. • The PL advises that patients do not take Rinvoq if they are pregnant, that Rinvoq must not be used during pregnancy, and that patients who become pregnant while taking Rinvoq must consult their doctor straight away. Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.3 and Section 4.6 indicate that upadacitinib is contraindicated during pregnancy. • SmPC Section 4.6 and PL advise on use of effective contraception. • SmPC Section 4.6 advises that female pediatric patients and/or their caregivers should be informed about the need to contact the treating physician once the patient experiences menarche. • The PL informs caregivers to let their doctor know if their child has their first menstrual period while using Rinvoq. Other routine risk minimization measures: Prescription only medicine
Safety Concern	**Routine Risk Minimization Activities**
Fractures	Routine risk communication: None Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures: Prescription only medicine

Safety Concern	Routine Risk Minimization Activities
Use in very elderly (≥ 75 years of age)	Routine risk communication: • SmPC Section 4.2 states that there are limited data in patients 75 years of age and older. • SmPC Section 4.4 indicates that there is an increased risk of adverse reactions with upadacitinib 30 mg in patients 65 years of age and older. • SmPC Section 4.4 specifies increased risk of MACE, malignancies, serious infections, and all-cause mortality in patients 65 years of age and older, as observed in a large randomized study of tofacitinib (another JAK inhibitor). Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.2 specifies that upadacitinib 15 mg is recommended in patients 65 years of age and older. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Other routine risk minimization measures: Prescription only medicine
Safety Concern	**Routine Risk Minimization Activities**
Use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C	Routine risk communication: • SmPC Section 4.4 describes the risk of viral reactivation. • The PL warns that patients who have ever had hepatitis B or hepatitis C should consult their doctor or pharmacist before and during treatment with Rinvoq. Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 describes the need for screening and consultation with a hepatologist if HBV DNA is detected. Other routine risk minimization measures: Prescription only medicine
Safety Concern	**Routine Risk Minimization Activities**
Use in patients with moderate hepatic impairment	Routine risk communication: • SmPC Section 4.2 describes use in patients with hepatic impairment. Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.2 states that upadacitinib should not be used in patients with severe (Child-Pugh C) hepatic impairment. • SmPC Section 4.3 indicates that upadacitinib is contraindicated for use in patients with severe hepatic impairment. • The PL advises that patients do not take Rinvoq if they have severe liver problems and warns that patients should consult their doctor or pharmacist before and during treatment with Rinvoq if their liver does not work as well as it should. Other routine risk minimization measures: Prescription only medicine

Safety Concern	Routine Risk Minimization Activities
Use in patients with severe renal impairment	Routine risk communication: • SmPC Section 4.2 describes use in patients with renal impairment. Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.2 states that upadacitinib should be used with caution in patients with severe renal impairment. • SmPC Section 4.2 specifies that for RA, PsA, AS, nr-axSpA, AD, and GCA, the recommended dose is 15 mg QD for patients with severe renal impairment and that for UC and CD, the recommended dose is 30 mg QD for induction treatment and 15 mg QD for maintenance treatment for patients with severe renal impairment. Other routine risk minimization measures: Prescription only medicine.
Safety Concern	**Routine Risk Minimization Activities**
Long-term safety in adults	Routine risk communication: • SmPC Section 4.4 indicates that upadacitinib clinical data on malignancies are currently limited and long-term studies are ongoing. Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures: Prescription only medicine.
Long-term safety in adolescents with AD	Routine risk communication: None Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures: Prescription only medicine.
Long-term safety in children	Routine risk communication: None Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures: Prescription only medicine.

In addition, the MAH has proposed the following changes of the additional risk minimisation measures:

Annex 6. Details of Proposed Additional Risk Minimization Activities (If Applicable)

The additional risk minimization program will be an educational program targeted to both HCP and patients.

Key messages of the additional risk minimization measures

HCP Material

HCP Educational Guide:

- General introductory language that the HCP measure contains important information to assist the discussion with patients when prescribing upadacitinib. The guide also informs on steps which can be taken to reduce a patient's risk for key safety aspects of upadacitinib.
- Indication and posology statements provided to reinforce in whom upadacitinib should be used

Use in patients 65 years of age and older

- Language to reinforce risks in these patients and use of the 15 mg dose

Language for HCPs to inform patients of the importance of the patient card

Risk of serious and opportunistic infections including TB

- Language on the risk of infections during treatment with upadacitinib
- Language on increased risk of serious infections in patients 65 years of age and older
- Details on how to reduce the risk of infection with specific clinical measures (what laboratory parameters should be used to initiate upadacitinib, screening for TB, and getting patients immunised as per local guidelines, and interruption of upadacitinib if an infection develops)
- Language on contraindication in patients with active TB and on consideration of anti-TB therapy in patients with latent TB
- Language on avoidance of live vaccines (i.e., Zostavax) prior to and during upadacitinib treatment
- Details to advise patients on signs/symptoms of infection to be aware of, so that patients can seek medical attention quickly.

Risk of herpes zoster

- Language on the risk of herpes zoster during treatment with upadacitinib
- Details to advise patients on signs/symptoms of infection to be aware of, so that patients can seek medical attention quickly.

Risk of fetal malformation

- Language on teratogenicity of upadacitinib in animals
- Details on how to reduce the risk of exposure during pregnancy for female patients of childbearing potential based on the following: upadacitinib is contraindicated during pregnancy, female patients of childbearing potential should be advised to use effective contraception both during treatment and for 4 weeks after the final dose of upadacitinib treatment, and to advise patients to inform their HCP immediately if they think they could be pregnant or if pregnancy is confirmed.

Risk of MACE

- Reminder that in patients at high risk for MACE upadacitinib should only be used if no suitable treatment alternatives are available, with examples of who may be at high risk
- Language on the risk of hyperlipidaemia during upadacitinib therapy
- Details on monitoring of lipid levels and management of elevated lipid levels per clinical guidelines

Risk of VTE

- Examples of the risk factors which may put a patient at higher risk for VTE and in whom caution is needed when using upadacitinib
- Use of caution in patients at high risk during treatment with upadacitinib
- Language that patients should be periodically re-evaluated for changes in VTE risk
- Language on need for discontinuation of upadacitinib, evaluation, and appropriate treatment for VTE if clinical features of deep venous thrombosis or pulmonary embolism develop

Risk of malignancy

- In patients at high risk for malignancy upadacitinib should only be used if no suitable treatment alternatives are available, with examples of who may be at high risk
- Reminder about the need for periodic skin examination for patients

Risk of GI perforation

- Upadacitinib should be used with caution in patients at risk for GI perforation with examples of those who may be at risk
- Reminder that patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of diverticulitis or GI perforation

Information for upadacitinib use in moderate to severe AD

~~**The 30 mg upadacitinib dose in AD**~~

- Language on dose-dependent increase in serious infections and herpes zoster with upadacitinib
- Language on dose-dependent increase in NMSC and malignancy
- Language on dose-dependent increase in plasma lipids with upadacitinib
- Language that the 30 mg dose is not recommended in certain populations (patients with severe renal impairment and patients taking strong CYP3A4 inhibitors)
- Language to reinforce that the lowest effective dose of upadacitinib should be used for treatment

~~**Upadacitinib use in adolescents 12 years and older**~~

- ~~Reminder that live, attenuated vaccines (i.e., varicella; measles, mumps, and rubella [MMR]; bacilli Calmette-Guérin) which depending on local guidelines may be considered in adolescents. Language not to administer these vaccines immediately prior to or during upadacitinib treatment~~
- ~~Language to remind adolescents of the potential pregnancy risks and on the appropriate use of effective contraception~~
- ~~Language that if their adolescent patient has not experienced menarche, to inform their adolescent patient or caregiver to let them know when they do~~

Information for upadacitinib use in moderate to severe UC or CD

- Reminder to review induction and maintenance dosing in product labeling
- Language on dose-dependent increase in serious infections and herpes zoster with upadacitinib
- Language on dose-dependent increase in NMSC and malignancy
- Reminder about induction and maintenance dose in certain populations (patients taking strong CYP3A4 inhibitors and severe renal impairment)

- Language to reinforce that the lowest effective dose of upadacitinib should be used for maintenance treatment

Upadacitinib use in pediatric patients (children from 2 years and adolescents)

- Reminder that live, attenuated vaccines (i.e., varicella; measles, mumps, and rubella [MMR]; bacilli Calmette-Guérin) which depending on local guidelines may be considered in pediatric patients. Language not to administer these vaccines immediately prior to or during upadacitinib treatment
- Language to remind pediatric patients of the potential pregnancy risks and on the appropriate use of effective contraception
- Language that if their pediatric patient has not experienced menarche, to inform their pediatric patient or caregiver to let them know when they do

Instructions on where to report AEs will be included.

Instructions for how to access digital HCP information will be included, if applicable.

Patient Card:

- Contact details of the upadacitinib prescriber
- Language that the patient card should be carried by the patient at any time and to share it with HCPs involved in their care (i.e., non-upadacitinib prescribers, emergency room HCPs, etc.)
- Description of signs/symptoms of infections the patient needs to be aware of, so that they can seek attention from their HCP:
  - Language to advise patients and their HCPs about the risk of live vaccinations when given during upadacitinib therapy. Examples of live vaccines are provided.
  - Language to advise patients to tell their HCP if they have history of TB or have been in contact with TB.
- Description of targeted risks for awareness by the patient and for HCPs involved in their care including:
  - Risk of heart disease - Description of signs/symptoms of heart disease that the patient needs to be aware of, so that they can seek attention from their HCP
  - Reminder to use contraception, that upadacitinib is contraindicated during pregnancy, and to notify their HCPs if they become pregnant while taking upadacitinib
  - Reminder to inform their HCP if a child has her first menstrual period while taking upadacitinib
  - Description of signs/symptoms of deep venous thrombosis or pulmonary embolism which the patient needs to be aware of, so that they can seek attention from an HCP
  - Reminder of the risk of cancer. Regarding skin cancer reminder to let their doctor know if they notice any new growth on the skin.
  - Risk of a hole in the bowel – description of signs/symptoms which the patient needs to be aware of, so that they can seek attention from an HCP

6.4.2. Discussion on the risk minimisation measures

6.4.2.1. Routine risk minimisation measures

Routine risk minimisation measures were updated in line with changes to the safety specification. Long-term safety was renamed to Long-term safety in adults and Long-term safety in children was added as new safety concern. The proposed changes were agreed.

6.4.2.2. Additional risk minimisation measures

In Annex 6 Details of Proposed Additional Risk Minimization Activities, a change in the HCP material was introduced. The section concerning guidance for adolescent patients aged 12 years and older was updated to make it applicable to paediatric patients 2 years and older. In addition, a reminder for parents and patients to inform their HCP if a child has her first menstrual period while taking upadacitinib was added to the Patient Card. These updates were acceptable. The proposed risk minimisation measures were sufficient to minimise the risks of the product in the proposed indications.

6.5. RMP Summary and RMP Annexes overall conclusion

The RMP Summary has been updated in line with changes to other parts of the RMP.

The RMP Annexes are acceptable.

6.6. Overall conclusion on the Risk Management Plan

☒ The PRAC considers that the updated risk management plan version 21 is acceptable.

The MAH is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Protected Personal Data (PPD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

7. Pharmacovigilance

Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.1. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

8. Product information

8.1. Summary of Product Characteristics (SmPC)

8.1.1. SmPC section 4.1 justification

Since efficacy data were extrapolated from an adult population with similar disease, the wording of the indication for the paediatric population should be harmonized to the adult indication. The CHMP agreed that patients with RF-positive polyarticular JiA, RF-negative polyarticular JiA and also extended oligoarticular JiA were similar enough regarding pathophysiology, clinical manifestations and response to therapeutic interventions for extrapolation from adults with RA. Thus, the following indication was considered acceptable:

"Rinvoq is indicated for the treatment of active polyarticular juvenile idiopathic arthritis (polyarticular rheumatoid factor positive [RF+] or negative [RF-], extended oligoarticular), in patients 2 years of age and older who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). Rinvoq may be used as monotherapy or in combination with methotrexate"

8.1.2. SmPC section 5.1 justification

A study description regarding the phase 2 single armed open label paediatric study was included in SmPC Section 5.1. Descriptive data regarding two endpoints from this study; i.e the proportion of patients achieving an ACR paediatric 70 response and the proportion of patients achieving JADAS27-CRP remission at week 12 and week 48, reported using non responder imputation, was considered relevant to include in the SmPC to inform the prescriber and to put into context with the adult RA data. Since efficacy data were extrapolated from an adult population with similar disease, data from the adult RA studies were included in the SmPC 5.1 for the new paediatric formulation as well.

8.2. Labelling

8.2.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

8.2.2. Quick Response (QR) code

The www.Rinvoq.eu website for Rinvoq was approved during the initial Marketing Authorisation Application.

A request to update the approved QR code in the labelling and package leaflet (PL) for the purpose of accessing a website containing statutory information (PL and Patient Card as part of the Educational material outlined in the Risk Management Plan) has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through the QR code:

- URL of the platform hosting the information: www.Rinvoq.eu, updated with the addition of the polyarticular course juvenile idiopathic arthritis indication which introduces the 1 mg/ml oral solution presentation.

The website contains the PL in an interactive, easily navigable format which is broken down into tabs per section of the PL, plus one additional tab for the bottle opening instructions (as detailed within the PL). In addition, the contents of the PL or the Patient Card can be downloaded from the website as a pdf.

9. Benefit-risk assessment

9.1. Therapeutic context

9.1.1. Disease or condition, proposed therapeutic indication.

With this submission, the MAH applied to extend the clinical indications for Rinvoq to include polyarticular course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older and to register a new oral solution providing upadacitinib 1 mg/mL.

JIA is a chronic, severe disease with a global incidence estimated of 7.8/100,000 and a prevalence of 20.5/100,000 for children under 16 years of age.

The ILAR classification from 2001 identifies 7 JiA disease types: systemic arthritis, oligoarthritis, polyarthritis/RF negative, polyarthritis/RF positive, JPsA, ERA, and undifferentiated arthritis. The classification is based on the number of joints affected, the presence of specific serologic findings, and systemic manifestations of disease in the first 6 months of diagnosis. pcJIA is defined as arthritis of unknown etiology that begins before 16 years of age, persists for at least 6 weeks, and affects 5 or more joints during the course of the disease. pcJIA accounts for about 30% of all JIA cases. For several, but not all, of the JIA subtypes, there are adult variants of the disease that shares pathophysiology, clinical manifestations and response to therapeutic interventions.

The initially proposed indication was "*Rinvoq is indicated for the treatment of active polyarticular course juvenile idiopathic arthritis in patients 2 years of age and older. Rinvoq may be used as monotherapy or in combination with methotrexate.*"

Upon CHMP's request, the MAH agreed to revise the indication during the procedure, as follows: *Rinvoq is indicated for the treatment of active polyarticular juvenile idiopathic arthritis (polyarticular rheumatoid factor positive [RF+] or negative [RF-], extended oligoarticular), in patients 2 years of age and older who have responded inadequately to, or who are intolerant to one or more DMARDs. Rinvoq may be used as monotherapy or in combination with methotrexate.*

9.1.2. Available therapies and unmet medical need

For a detailed description, please see section 02 of this document.

Currently, there is no cure for JIA. The primary target for treatment of patients with JIA is clinical remission, with LDA as an alternative target, particularly in patients with long-standing disease. Per current treatment guidelines, MTX is recommended as the first-line treatment for pcJIA, with NSAIDs and intra-articular GCs recommended as adjunctive therapies. In patients who continue to have active disease despite MTX therapy, the addition of a bDMARD is recommended. There are several bDMARDs (TNF-α inhibitors, CTLA4-IG, IL-6 receptor inhibitor) approved for the treatment of JiA. In addition, 2 other JAK-inhibitors (tofacitinib and baricitinib) have been approved for different subtypes of JIA, including polyarticular JIA. Despite the availability of effective treatments, many patients still do not achieve clinical remission or LDA and some develop intolerance or lose response over time. In an analysis of long-term studies, less than half (11 to 47%) of patients were in clinical remission off medication in adulthood. While there has been significant progress in therapy for JIA, there is still an unmet need for additional effective and well-tolerated therapy options to treat JIA.

9.2. Main clinical studies

For a detailed description of the main clinical studies supporting this application, please refer to section 5.3.2. of this document.

This application included an efficacy extrapolation approach combined with PK and safety data from Study M15-340 and additional safety data from AD studies. The extrapolation approach is based on the 3 key criteria: 1) similarity of disease progression between children with pcJIA and adults with RA; 2) similar response to treatment intervention; and 3) a similar exposure-response or concentration-response relationship that is predictive of the clinical response. Upadacitinib plasma exposures which are identified to be optimally efficacious in adult patients with RA are expected to also be optimally efficacious in paediatric patients with pcJIA. A detailed description regarding the background of these assumptions is provided in section 5.3.3. of this document.

The application was further supported by a clinical study M15-340 in active polyarticular course JIA, a phase 1, multinational, single arm, open label study with the main focus on PK evaluation, tolerability and safety. The study was ongoing during the procedure and included 3 parts:

- In part 1 (7 days), extensive PK sampling was collected.
- Part 2 is a long-term extension of part 1 (155 weeks)
- Part 3 includes an additional safety cohort (156 weeks).

The study included patients 2-17 years with an active polyarticular course JIA, defined as 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, with 5 or more active joints at the time of screening). The patients received a QD extended-release tablet (15 mg) formulation or a twice daily immediate-release oral solution (1 mg/mL) formulation depending on the subject's body weight and ability to swallow tablets.

In total, 122 subjects received at least 1 dose of upadacitinib through the data cutoff date of 21 March 2025, including 27 subjects age 2 to < 6 years, 53 subjects age 6 to < 12 years, and 42 subjects age 12 to < 18 years. A total of 34 subjects has completed the study, 68 subjects were ongoing and 21 subjects (17.2%) has discontinued study drug.

9.3. Favourable effects

Two population PK models were used to simulate and compare the exposures in adults with RA given 15 mg QD ER tablets to paediatric patients with pcJIA (2 to 17 years of age) administered either oral solution or ER tablets according to the proposed posology, to support the extrapolation of efficacy from adults with RA to paediatric patients with pcJIA. The $AUC_{24h,ss}$ and $C_{max,ss}$ were compared:

- The simulated median (90% simulated prediction interval) target exposure range in adults with RA was 376 (186-780) hr*ng/mL and 42.1 (24-72.9) ng/mL for AUC24,ss and Cmax,ss.
- For children weighing 10 to <20 kg, 20 to <30 kg and ≥30 kg, the simulated $AUC24_{h,ss}$ ratio was 20% lower, 11% lower and 15% lower, respectively, compared to the simulated exposure in adults with RA. The 90% prediction intervals largely overlapped with the adult 90% prediction interval $AUC_{24h,ss}$ exposure with 15 mg ER tablets.
- For children weighing 10 to <20 kg, 20 to <30 kg and ≥30 kg, the simulated $C_{max,ss}$ ratio was 15% lower, 5% lower and 6% higher, respectively, compared to the simulated exposure in adults with RA. The upper 90% prediction interval was slightly higher compared to the adult 90% prediction interval.

The simulations indicated an overlapping C_{max} and $AUC_{24,ss}$ in children with pcJIA and adults with RA. The totality of the data indicated that the fluctuations in plasma concentration over time (and lower C_{trough}) were not expected to result in a reduced efficacy with the oral solution administered BID. Overall, upadacitinib plasma exposures ($C_{max,ss}$ and $AUC_{24,ss}$) in paediatric patients with pcJIA following the recommended weight-based paediatric dosing scheme were predicted to be similar to the target plasma exposure in adult RA patients receiving the recommended dose, hence, supporting the extrapolation of efficacy from adults with RA to paediatric patients with pcJIA.

In Study M15-340, at week 12 the proportions of patients achieving paediatric ACR 30/50/70/90/100 were 90.4%/86.8%/71.1%/41.2%/28.1% of the 114 evaluated patients. The proportions of patients with low disease activity and remission were 54% and 24%.

In Study M15-340, at week 48 the proportions of patients achieving paediatric ACR 30/50/70/90/100 were 96.3%/93.6%/89.0%/72.5%/57.8% of the 109 evaluated patients. The proportion of patients with low disease activity or remission was 79.4% and 49.5%.

Overall, the efficacy results from the uncontrolled, open label study M15-340 in paediatric patients with pcJIA provided support to the PK data for an effect in line with the adult RA population.

9.3.1. Uncertainties and limitations about favourable effects

Since efficacy data were extrapolated from an adult population with similar disease, the wording of the indication for the paediatric population needed to be harmonized with the adult approved indication. The CHMP agreed that patients with RF-positive polyarticular JiA, RF-negative polyarticular JiA and also extended oligoarticular JiA were similar enough regarding pathophysiology, clinical manifestations and response to therapeutic interventions for data extrapolated from adults with RA to these populations. However, systemic JiA are not regarded as a similar disease as RA and Rinvoq is not approved for adult-onset Stills disease (the adult variant of systemic JiA). Thus, upon CHMP's request, the MAH revised the wording of the therapeutic indication to the following: *"Rinvoq is indicated for the treatment of active polyarticular juvenile idiopathic arthritis (polyarticular rheumatoid factor positive [RF+] or negative [RF-], extended oligoarticular), in patients 2 years of age and older who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). Rinvoq may be used as monotherapy or in combination with methotrexate."*

9.4. Unfavourable effects

A total of 122 paediatric patients with pcJIA were exposed to at least one dose of upadacitinib in Study M15-340.

TEAEs per patient year were more frequent in the youngest children (2 to < 12 years) than in adolescents (12 to < 18 years). 98.4 % of patients had at least one TEAE and among these, infections were reported most frequently. Among these, nasopharyngitis (15.6 %), upper respiratory tract infection (7.4 %), abdominal pain (6.6 %), nausea (5.7 %), and headache (5.7 %) were the most common. Serious and opportunistic infections including TB are an important identified risk of upadacitinib and a warning regarding this risk is described in the current product labelling. The frequency of serious infections reported in children with pcJIA receiving upadacitinib (1.6 events per 100 PY) was in line with the known safety profile in adults with RA where the overall long-term rate of serious infections for the upadacitinib 15 mg group was 3.8 events per 100 PY.

Eleven events of bone fracture occurred in the 122 children exposed to upadacitinib in study M15-340, corresponding to 1.6 E/100 PYs in age group 2 to < 6 years, 6.3 E/100 PYs in age group 6 to < 12 years, and 3.7 E/100 PYs in age group 12 to < 18 years. The relatively high frequency of bone fractures observed in study M15-340 was at least partly considered attributed to the increased risk of bone fractures in the JIA population. Fractures is currently listed as an important potential risk in the RMP and will be further characterised from the ongoing Category 3 PASS as agreed in the RMP.

No deaths were reported in the study of upadacitinib in paediatric patients with pcJIA through the data cutoff date.

In the M15-340 study of upadacitinib in children with pcJIA, findings of reduced hight velocity (4.9%), reduced weight gain (23%) and delayed puberty (5 subjects) occurred at a frequency expected for the population.

No new ADRs beyond those currently listed in the upadacitinib product information were identified from the pcJIA clinical programme.

The safety profile of upadacitinib in children with pcJIA was generally consistent with the safety profile observed with upadacitinib in adult RA and adolescent AD.

9.4.1. Uncertainties and limitations about unfavourable effects

The assessment of the observed safety data from upadacitinib treatment in children with pcJIA was limited as it relied on one open uncontrolled Study M15-340. Importantly, the assessment of safety in children with pcJIA relied largely on extrapolation based on similar exposures in the paediatric population and the adult RA population in which a larger number of patients were exposed and placebo-controlled studies were performed. In the paediatric study, either the oral solution (BID) or the tablets (QD) were administered, whereas only tablets were administered in the adult studies.

Although the size of the safety database in children with pcJIA was limited, it was overall considered sufficient to support the proposed indication and dose in this application mainly based on extrapolation from adults from PK-matching. Further, the overall safety profile as observed in the pivotal paediatric study was generally consistent with the safety observed with upadacitinib in adult RA and adolescent AD. Long term safety in children was added as missing information in the RMP in order to further characterize potential long-term effects on growth and development. This safety concern will be further characterised in the Category 3 PASS Study M15-340 (final report expected in Q4 2027).

9.5. Effects Table

Assessment of favourable and unfavourable effects of upadacitinib in pcJIA relied primarily on extrapolation of efficacy and safety from adults with RA through PK-matching. Key favourable and unfavourable effects from the observed data in Study M15-340 in the current extension of indication application are listed in the effects table below.

Table 44: Effects Table for Rinvoq for the treatment of pcJIA

Effect (short description)	Treatment	Control	Uncertainties/ Strength of evidence	Ref
Favourable Effects				
Paediatric ACR 70 response v 12	71.1% (N=114)	No control group	**SoE:** **Unc:** Open label, uncontrolled	(1)
Paediatric ACR 100 response	28.1% (N=114)	No control group	**SoE:** **Unc:** Open label, uncontrolled	(1)
JADAS27 CRP ≤1 (remission)	24.6% (N=114)	No control group	**SoE:** **Unc:** Open label, uncontrolled	(1)
Paediatric ACR 70 response v 12	89.0% (N=109)	No control group	**SoE:** **Unc:** Open label, uncontrolled	(1)
Paediatric ACR 100 response	57.8% (N=109)	No control group	**SoE:** **Unc:** Open label, uncontrolled	(1)
JADAS27 CRP ⩽1 (remission)	49.5% (N=107)	No control group	**SoE:** **Unc:** Open label, uncontrolled	(1)
Unfavourable Effects				
Serious infections	1.6 E/100 PY	No control group	The current section 4.4 of the SmPC for Rinvoq includes a warning for serious infections. The corresponding frequency in adults with RA is 3.8 E/100 PY.	(1)
CPK elevation	3.5 E/100 PY	No control group	The current section 4.8 of the SmPC for Rinvoq includes 'Blood CPK increase' (common).	(1)
Hepatic disorder	7.5 E/100 PY	No control group	This included 17 events of transaminase ↑, 1 blood bilirubin ↑, 1 hepatosplenomegaly. The current section 4.8 of the SmPC for Rinvoq includes 'ALT increased' and 'AST increased' (common).	(1)
Anaemia	2.4 E/100 PY	No control group	The current section 4.8 of the SmPC for Rinvoq includes 'Anaemia' (common).	(1)
Neutropenia	2.7 E/100 PY	No control group	The current section 4.8 of the SmPC for Rinvoq includes 'Neutropenia' (common).	(1)
Lymphopenia	1.6 E/100 PY	No control group	The current section 4.8 of the SmPC for Rinvoq includes 'Lymphopenia' (common).	(1)
Bone fracture	4.3 E/100 PY	No control group	Fractures is currently listed as an important potential risk in the RMP.	(1)

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence; E: events; PY, patient years - Note: (1) Study M15-340

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

This extension of indication application to include pcJIA in patients 2 years of age and older and to register a new paediatric oral solution providing upadacitinib 1 mg/mL relied on extrapolation of clinical efficacy from adults with RA and of clinical safety from adults with RA and adolescents with AD.

The efficacy extrapolation approach was based on the following criteria: 1) similar pathophysiology and clinical manifestation between children with pcJIA and adults with RA; 2) similar response to treatment intervention between children with pcJIA and adults with RA; and 3) similar exposure-response or concentration-response relationship that is predictive of the clinical response. Upadacitinib plasma exposures which are identified to be optimally efficacious in adult patients with RA are expected to also be optimally efficacious in paediatric patients with pcJIA. The extrapolation concept was endorsed by the CHMP.

The population PK models were pivotal for the extrapolation of efficacy. Upadacitinib plasma exposures ($C_{max,ss}$ and $AUC_{24,ss}$) in paediatric patients with pcJIA following the recommended weight-based paediatric dosing scheme were predicted to be similar to the target plasma exposure in adult RA patients receiving the recommended dose. Hence, PK-matching between paediatric patients from 2 years of age with pcJIA and adults with RA was shown.

Regarding efficacy, the CHMP agreed that some JiA subtypes (RF-positive polyarticular JiA, RF-negative polyarticular JiA and also extended oligoarticular JiA) were similar enough regarding pathophysiology, clinical manifestations and response to therapeutic interventions to allow extrapolation from adults with RA. The wording of the therapeutic indication in pcJIA is aligned with the adult approved RA indication in terms of nomenclature and line of treatment.

Although the study M15-340 was conducted in an open-label manner, the observed paediatric ACR response rates were sufficiently high to be considered clinically relevant and in line with the results seen in the adult RA studies. In addition, although acknowledging the limitation of comparison between studies, the proportion of patients achieving inactive disease was no less than the proportion seen in JIA patients in studies with other JAK-inhibitors. However, the provided efficacy data were probably overestimated as they were derived from an uncontrolled, open-label, single-arm study. Thus, there was no self-standing data demonstrating robust efficacy in the paediatric pJIA population, but the results were considered supportive only for an effect with the suggested posology, with the PK-matching and extrapolation approach as the pivotal evidence.

Regarding safety, no new ADRs beyond those currently listed in the upadacitinib label were observed in the pcJIA clinical programme. The safety profile was generally consistent with the safety observed with upadacitinib in adult RA. There was a relatively high frequency of bone fractures observed in study M15-340, it was at least partly attributed to the increased risk of bone fractures in the JIA population. Fractures is an important potential risk listed in the RMP and will be further characterised from the ongoing Category 3 PASS as agreed in the RMP. Long term safety in children was added as missing information in the RMP in order to further characterize potential long-term effects on growth and development. This safety concern will be further characterised in the Category 3 PASS Study M15-340 (final report expected in Q4 2027).

9.6.2. Balance of benefits and risks

The concept of efficacy extrapolation between children with pcJIA and adults with RA based on 1) similar pathophysiology and clinical manifestation; 2) similar response to treatment intervention; and 3) similar exposure-response or concentration-response relationship that is predictive of the clinical response, was endorsed by the CHMP.

PK-matching between paediatric patients from 2 years of age with pcJIA and adults with RA was shown since upadacitinib plasma exposures in paediatric patients with pcJIA following the recommended weight-based paediatric dosing scheme were predicted to be similar to the target plasma exposure in adult RA patients receiving the recommended dose. In addition, the efficacy results achieved from the uncontrolled, open label study M15-340 in paediatric patients with pcJIA provided support to the PK

data for an effect in line with the adult RA population. Hence, the CHMP agreed that the efficacy of upadacitinib in paediatric patients with some subtypes of JIA (RF-positive polyarticular JiA, RF-negative polyarticular JiA and also extended oligoarticular JiA) was demonstrated based on the extrapolation of data in adults RA patients. The safety profile of upadacitinib was in general similar as already known.

Overall, the benefits of upadacitinib outweigh the risks for the treatment of active polyarticular juvenile idiopathic arthritis (polyarticular rheumatoid factor positive [RF+] or negative [RF-], extended oligoarticular), in patients 2 years of age and older who have responded inadequately to, or who are intolerant to one or more DMARDs.

9.7. Benefit-risk conclusions

9.7.1. At Day 180 - CHMP conclusions

The B/R balance of upadacitinib is positive for the treatment of active polyarticular juvenile idiopathic arthritis (polyarticular rheumatoid factor positive [RF+] or negative [RF-], extended oligoarticular), in patients 2 years of age and older who have responded inadequately to, or who are intolerant to one or more DMARDs. Rinvoq may be used as monotherapy or in combination with methotrexate.