14 September 2023
EMA/436396/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Olumiant

International non-proprietary name: baricitinib

Procedure No. EMEA/H/C/004085/II/0037

Note

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

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List of abbreviations

AA	Alopecia Areata
AD	Atopic Dermatitis
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transferase
ANA	Anti-nuclear antibodies
AST	Aspartate aminotransferase
ATE	Arterial thromboembolic even.
AUC	Area under the curve
BCS	Biopharmaceutics Classification System
BMI	Body Mass Index
CHAQ	Childhood Health Assessment Questionnaire
CHMP	Committee of Human Medicinal products
CPK	Creatine phosphokinase
CRP	C Reactive protein
CTCAE	Common Terminology Criteria for Adverse events
DBW	Double Blind withdrawal
DLP	Data lock point
DMARDs	Disease- modifying antirheumatic drugs
DVT	Deep vein thrombosis
EASI	Eczema Area and Severity index
EASI75	75% improvement from baseline in EASI
EASI90	90% improvement from baseline in EASI
EFD	Embryo-fetal Development
E-R	Exposure-response
ERA	Enthesitis related arthritis
ESR	Erythrocyre sedimentation rate
GCP	Good Clinical Practices
HPLC	High performance liquid chromatography
HRQoL	Health-related quality of life

ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	Identification
IGA	Investigator's global assessment
IL	Interleukin
ILAR	International League of Associations for Rheumatology
IR	Incidence rate
ITT	Intent-to-treat
JAK	Janus Kinase
JIA	Juvenile Idiopathic Arthritis
Lte	Long-term extension
MACE	Major adverse cardiovascular event
mg	milligram
mL	millilitre
MTX	Methotrexate
NRS	Numeric rating system
NSAIDs	Nonsteroidal anti-inflammatory drugs
OAT3	Organic Anion Transporter 3
OLLI	Open-label lead-in
PBT	Persistent, bioaccumulative and toxic
PDCO	Paediatric Committee
PDE	Permitted Daily Exposure
PEC	Predicted environmental Concentration
PedACR30	Paediatric 30% improvement in American College of Rheumatology criteria
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PIP	Paediatric Investigation Plan
PND	Postnatal day
PNEC	Predicted no-effect concentrations
PPND	Pre-and postnatal development
PRAC	Pharmacovigilance Assessment Committee
QC	Quality Control
QD	Once daily

QoL	Quality of Life
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
RMP	Risk Management Plan
SAE	Serious adverse event
SCORAD	scoring atopic dermatitis
SCORAD75	75% improvement from baseline in SCORAD
SmPC	Summary of Product Characteristics
SMQ	standard MedRA Query
SOC	Single organ class
STAT	Signal transducers and activators of transcription
TBL	Total bilirubin
TCNI	Topical calcineurin inhibitor
TCS	Topical corticosteroids
TE	Treatment emergent
TEAE	Treatment emergent adverse event
TNFα	Tumor Necrosis Factor alpha
TYK	Tyrosine Kinase
ULN	Upper limit of normal
USP/NF	United States Pharmacopoeia/National Formulary
vPvB	very Persistent and very Bioaccumulative
VTE	Venous Thromboembolic events

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eli Lilly Nederland B.V. submitted to the European Medicines Agency on 25 November 2022 an application for a variation.

The following variation was requested:

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

Extension of indication to include the treatment of paediatric patients (from 2 years of age and older) with moderate to severe atopic dermatitis for OLUMIANT, based on the final results from study I4V-MC-JAIP; this is a Phase III, multicentre, randomised, double blind, placebo controlled, parallel-group, outpatient study evaluating the pharmacokinetics, efficacy, and safety of baricitinib in paediatric patients with moderate-to-severe atopic dermatitis. As a consequence sections 4.1, 4.2, 4.4, 4.5, 4.8, 4.9, 5.1, 5.2 of the SmPC are updated. The Package Leaflet has been updated accordingly. Version 17.1 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0311/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0311/2021 was completed.

Information relating to orphan market exclusivity

Similarity

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.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Peter Mol

Timetable	Actual dates
Submission date	25 November 2022
Start of procedure:	31 December 2022
CHMP Rapporteur Assessment Report	24 February 2023
PRAC Rapporteur Assessment Report	3 March 2023
Updated PRAC Rapporteur Assessment Report	9 March 2023
PRAC Outcome	16 March 2023
CHMP members comments	20 March 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 March 2023
Request for supplementary information (RSI)	30 March 2023
CHMP Rapporteur Assessment Report	20 June 2023
PRAC Rapporteur Assessment Report	23 June 2023
PRAC members comments	28 June 2023
PRAC Outcome	6 July 2023
CHMP members comments	10 July 2023
Updated CHMP Rapporteur Assessment Report	13 July 2023
Request for supplementary information (RSI)	20 July 2023
PRAC Rapporteur Assessment Report	21 August 2023
CHMP Rapporteur Assessment Report	30 August 2023
PRAC Outcome	31 August 2023
CHMP members comments	4 September 2023
Updated CHMP Rapporteur Assessment Report	6 September 2023
Opinion	14 September 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Atopic dermatitis (AD) is a common, chronic, relapsing, symptomatic, inflammatory skin disease characterised by itch, dry skin, and eczematous lesions affecting children, adolescents and adults.

The clinical manifestations of AD are overall similar in adults and paediatric patients, although the location and type of skin lesions may differ[1,2,3]:

- eczematous, papulo-vesicular, and patchy lesions localised to the cheeks are common in infants,
- eczematous lesions typically involving flexural areas, nape of the neck, dorsum of the feet, and hands are common in children, and
- mostly lichenified plaques involving flexural areas as well as head and neck are common in adolescents and adults.

The claimed therapeutic indication

The proposed indication is: Baricitinib is indicated for the treatment of moderate to severe atopic dermatitis in adult and paediatric patients 2 years of age and older who are candidates for systemic therapy.

Epidemiology

AD is one of the most common chronic diseases in childhood. The prevalence of AD is higher in children than in adults. The prevalence of AD ranges from approximately 9% in teenagers to 14% in children 0 to 4 years of age[4]. In addition, the distribution of severity tends to shift to higher severities at older ages, with older children being more likely to have moderate-to-severe disease[5].

Clinical presentation

Itch is the key symptom of AD and is one of the most bothersome symptoms of AD. The itch-scratch cycle can lead to the worsening of AD by increasing inflammation and the potential for infection[6]. Furthermore, severe itch is associated with decreased Quality of Life (QoL) affecting emotional wellbeing and leading to sleep problems [7,8]. Family life can also be severely impaired because of sleep deprivation by the affected child as well as by disruption of school and social interactions, including interaction with peers and family members [9,10,11,12].

[1] Bieber T. (2010). Atopic dermatitis. *Annals of dermatology*, *22*(2), 125–137. https://doi.org/10.5021/ad.2010.22.2.125

[2] Silverberg J. I. (2019). Comorbidities and the impact of atopic dermatitis. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology*, *123*(2), 144–151. https://doi.org/10.1016/j.anai.2019.04.020

[3] Langan, S. M., Irvine, A. D., & Weidinger, S. (2020). Atopic dermatitis. *Lancet (London, England)*, *396*(10247), 345–360. https://doi.org/10.1016/S0140-6736(20)31286-1

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[11] Leung D. Y. (2000). Atopic dermatitis: new insights and opportunities for therapeutic intervention. *The Journal of allergy and clinical immunology*, *105*(5), 860–876. https://doi.org/10.1067/mai.2000.106484

[12] Ben-Gashir, M. A., Seed, P. T., & Hay, R. J. (2004). Quality of life and disease severity are correlated in children with atopic dermatitis. *The British journal of dermatology*, *150*(2), 284–290. https://doi.org/10.1111/j.1365-2133.2004.05776.x

Management

AD is standardly treated with emollients and topical corticosteroids (TCS) to address barrier dysfunction and immune abnormalities: low-potency TCS for mild AD and medium and high-potency TCS for moderate-to-severe AD. However, the continuous long-term use of TCS is not recommended because of the risk of local side effects like skin atrophy, dyspigmentation and systemic exposure, especially in children with a proportionately greater body surface area to weight ratio[13]. Topical calcineurin inhibitors (TCNI) are approved for the treatment of AD in paediatric patients from the age of 2 years with inadequate response or intolerance to TCS or where treatment with TCS is either inadvisable or not possible. In addition, the use of TCNI's is commonly restricted to sensitive areas of skin, such as eyelids.

Ciclosporin is approved only in some countries for paediatric patients with AD, restricted to treating patients ⩾16 years old with severe AD when systemic therapy is required. However, since 2020, several systemic treatments (dupilumab, upadacitinib, and tralokinumab) have been authorised in the EU:

- Dupilumab is indicated for the treatment of moderate-to-severe AD in adults and adolescents 12 years and older who are candidates for systemic therapy and for severe AD in children aged 6 to 11 years who are candidates for systemic therapy.
- Upadacitinib is indicated for the treatment of moderate-to-severe AD in adults and adolescents 12 years and older who are candidates for systemic therapy.
- Tralokinumab is indicated for the treatment of adolescent patients of 12 years and older who are candidates for systemic therapy.

Despite the recent approval of newer systemic treatments, there remains an unmet medical need for AD paediatric patients who do not respond to currently approved systemic therapies. Further, oral JAK inhibitors (abrocitinib and upadacitinib) have shown a relatively fast response in adults with AD compared to dupilumab [14,15].

2.1.2. About the product

Baricitinib is an orally available, selective JAK inhibitor with potency and selectivity for JAK1 and JAK2, and less potency for JAK3 or tyrosine kinase 2 [16]. JAK1, JAK2, JAK3, and tyrosine kinase 2, along with the STAT pathway, play an important role in signal transduction following cytokine and growth factor binding to their receptors [17].

The fundamental pathophysiology of AD, with excessive T cell activation, is similar among adults,

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[14] Blauvelt, A., et. al. (2021). Efficacy and Safety of Upadacitinib vs Dupilumab in Adults With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial. *JAMA dermatology*, *157*(9), 1047–1055. https://doi.org/10.1001/jamadermatol.2021.3023

[15] Reich, K., et.al. (2022). Efficacy and safety of abrocitinib versus dupilumab in adults with moderate-to-severe atopic dermatitis: a randomised, double-blind, multicentre phase 3 trial. *Lancet (London, England)*, *400*(10348), 273–282. https://doi.org/10.1016/S0140-6736(22)01199-0

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[17] Pesu, M., Laurence, A., Kishore, N., Zwillich, S. H., Chan, G., & O'Shea, J. J. (2008). Therapeutic targeting of Janus kinases. *Immunological reviews*, *223*, 132–142. https://doi.org/10.1111/j.1600-065X.2008.00644.x

adolescents, and children[18,19]). The JAK-STAT pathway plays a critical role in the pathogenesis of AD by upregulating epidermal chemokines, proinflammatory cytokines, and proangiogenic factors as well as by downregulating antimicrobial peptides and factors responsible for skin barrier function[20]. The JAK-STAT signalling pathway is functional from infancy, and aberrations in JAK-STAT signalling are implicated in other rare autoinflammatory diseases with onset within the first year of life[21,22].

Baricitinib has been shown to improve AD disease severity in adults [23,24] and has received regulatory authorisation in the EU (Olumiant SmPC), for the treatment of adult patients with moderate-to-severe AD who are candidates for systemic therapies. Baricitinib also is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to or who are intolerant to one or more disease-modifying anti-rheumatic drugs, for the treatment of severe alopecia areata (AR) in adults and for the treatment of juvenile idiopathic arthritis (JIA). Olumiant is available as 1, 2 and 4 mg film-coated immediate-release tablet either as monotherapy or in combination with non-biologic disease-modifying anti-rheumatic drugs.

2.1.3. The development programme

The baricitinib clinical development programme for paediatric AD includes one global clinical study (I4V-MC-JAIP) to evaluate the pharmacokinetics (PK), efficacy, and safety of baricitinib in paediatric patients with moderate-to-severe AD. The design of the Phase 3 registration programme was agreed upon with the PDCO as laid down in the PIP and its modification (EMEA-001220-PIP03-16-M01).

Study **JAIP** included a 2 week, open-label PK lead-in in a small number of patients to confirm baricitinib exposure at the high dose that was planned to be used in the double-blind part of the study. Following the results, the high dose used in the randomised, double-blind part of the study was 4 mg QD for older participants (10 to <18 years) and 2 mg QD for younger participants (2 to <10 years). Medium and low doses were consequently selected at 2 mg QD and 1 mg QD (10 to <18 years) and 1 mg QD and 0.5 mg QD (2 to <10 years). Participants enrolled in the open-label PK lead-in part of the study (N = 33) contributed to safety analyses but not efficacy analyses. The primary objective of the placebo-controlled, double-blind, parallel-dose part of the study was to demonstrate the superiority of each dose of baricitinib (low, medium, high) versus placebo in the proportion of participants achieving IGA of 0 or 1 with a $\geqslant$2-point improvement at week 16. Patients were allowed to use low or medium-potency TCS, which could be tapered down when lesions disappeared. Patients who participated in the double-blind treatment period and completed through week 16 were eligible to continue in the long-term treatment extension period for up to 4 additional years of treatment.

The long-term extension phase is ongoing. At the time of the data cut-off of 20 June 2022, all participants had completed at least 24 weeks of treatment in study JAIP, results up to the 24-week

[18] Czarnowicki, T., et.al. (2015). Early pediatric atopic dermatitis shows only a cutaneous lymphocyte antigen (CLA)(+) TH2/TH1 cell imbalance, whereas adults acquire CLA(+) TH22/TC22 cell subsets. *The Journal of allergy and clinical immunology*, *136*(4), 941–951.e3. https://doi.org/10.1016/j.jaci.2015.05.049

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[21] Liu, Y., et. al. (2012). Mutations in proteasome subunit β type 8 cause chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature with evidence of genetic and phenotypic heterogeneity. *Arthritis and rheumatism*, *64*(3), 895–907. https://doi.org/10.1002/art.33368

[22] Liu, Y., et.al. (2014). Activated STING in a vascular and pulmonary syndrome. *The New England journal of medicine*, *371*(6), 507–518. https://doi.org/10.1056/NEJMoa1312625

[23] Reich, K., et.al. (2020). Efficacy and Safety of Baricitinib Combined With Topical Corticosteroids for Treatment of Moderate to Severe Atopic Dermatitis: A Randomized Clinical Trial. *JAMA dermatology*, *156*(12), 1333–1343. https://doi.org/10.1001/jamadermatol.2020.3260

[24] Simpson, E. L., et.al. (2020). Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. *The British journal of dermatology*, *183*(2), 242–255. https://doi.org/10.1111/bjd.18898

timepoint for efficacy and up to 3 years for safety were submitted.

The PDCO adopted an opinion on 11 November 2022, confirming the compliance of all studies in the agreed paediatric investigation plan as set out in the latest Agency's Decision (P/0311/2021) of 11 August 2021. PIP compliance for study JAIP, denoted as study 4 in the PIP, was concluded in an earlier decision (EMEA-C3-001220-PIP03-16-M02). The submitted article 46 paediatric study I4V-MC-JAIP (EMEA/C/004085/46/014) is combined with this extension application. The MAH did not ask for CHMP Scientific Advice. There is no EMA guidance for clinical investigation of medicinal products indicated for the treatment of AD.

2.1.4. General comments on compliance with GCP

According to the MAH, all studies were conducted in accordance with Good Clinical Practices (ICH 2016) and applicable local laws and regulations.

2.2. Non-clinical aspects

2.2.1. Ecotoxicity/environmental risk assessment

An updated environmental risk assessment has been provided. Since the estimations of exposure to the environment in previous ERAs were age agnostic, those previous predicted environmental concentrations will not change with the addition of paediatric AD patients. Therefore, the submitted ERA is based on the AA submission updated to reflect that all 3 indications RA, AD and AA are now registered but the conclusions have not changed. The environmental data previously submitted with the initial dossier serves as the basis for the updated environmental risk assessment.

Physical-chemical properties and fate characteristics indicate that baricitinib will not persist in the aqueous environmental compartment since it undergoes some removal by binding to sludge biosolids during sewage treatment and by partitioning to sediment once in the water column. The concentration of baricitinib in sediment are predicted to be very low. Baricitinib is subject to some removal from the sediment compartment through biodegradation and irreversible binding to sediment particles. The rate of removal is slow and there is some potential for persistence of low concentrations in aquatic sediment. Using assumptions of no metabolism, no removal during sewage treatment, and 1% of the European population taking the maximum dose for each indication, the maximum predicted environmental concentration of total baricitinib residue in surface water is 0.06 µg/L and in sediment is 230 µg/kg (dry weight).

Studies to evaluate both acute and chronic effects on environmental species have been conducted with baricitinib. Fish were the most sensitive species tested. The predicted no-effect concentrations (PNECs) of baricitinib for surface water, groundwater, and sewage microorganisms were 60, 210, and 100000 µg/L, respectively. The PNEC for sediment was 27150 µg/kg. The predicted environmental concentrations of total residues of baricitinib are significantly lower than the PNEC values. Therefore, excretion by humans of baricitinib and its metabolites is not expected to result in a significant environmental risk. Additionally, baricitinib is not expected to bioaccumulate in aquatic organisms based on a log Kow less than 4.5. Therefore, baricitinib is not classified as a PBT or a vPvB molecule.

The initial estimate of the PEC surface water is based on the maximum recommended daily dose of the active ingredient, a default market penetration of 1% of the total population, 200 L of wastewater discharge per capita, and an average dilution factor of 10 for discharge into surface water. For drug

substances used for multiple indications, the PECs for each indication are summed. PEC surface water calculated for each indication of baricitinib is 0.02 µg/L and the total PEC surface water is 0.06 µg/L.

2.2.2. Discussion on non-clinical aspects

No new non-clinical studies were submitted which was considered acceptable to the CHMP.

The conclusion by the Applicant that excretion by humans of baricitinib and its metabolites is not expected to result in a significant environmental risk is endorsed.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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.

- Tabular overview of clinical study I4V-MC-JAIP

Number of participants	516 (total enrolled) 33 (open-label PK lead-in) 483 (intent-to-treat population [double blind])
Population	Paediatric patients aged 2 to less than 18 years, with moderate-to-severe AD, who have had an inadequate response to TCS and/or TCNIs, where applicable.
Ages enrolled	**PK lead-in (open label)** 10 to <18 years (N = 20) 6 to <10 years (N = 7) 2 to <6 years (N = 6) **Intent-to-treat population (double blind)** 10 to <18 years (N = 350) 2 to <10 years (N = 133)
Phase *Status*	Phase 3 *Ongoing*
Primary endpoint	**Primary endpoint for double-blind treatment period** • Proportion of patients achieving IGA of 0 or 1 with a ≥2-point improvement at Week 16.
Key secondary endpoints	• Proportion of patients achieving EASI75 at 16 weeks • Proportion of patients achieving EASI90 at 16 weeks • Proportion of patients achieving SCORAD75 at 16 weeks • Mean change from baseline in EASI score at 16 weeks, and

	• Proportions of patients achieving a 4-point improvement in Itch NRS at 1 week, 2 weeks, 4 weeks, and 16 weeks for patients ≥10 years old.
Study periods	• 5-week screening period (Study Period 1) • 2-week, open-label PK lead-in period (Study Period 2) • 16-week, double-blind treatment period (Study Period 3) • up to 4-year, long-term extension period (Study Period 4), and • 4-week, posttreatment follow-up period (Study Period 5).

2.3.2. Pharmacokinetics

In the current application, the Applicant is requesting an extension for the treatment of paediatric patients aged 2 to <18 years with atopic dermatitis with a dose of 2 mg once daily in patients with a body weight <30 kg and a dose of 4 mg once daily in patients with a body weight of ≥30 kg. Patients with renal impairment or on OAT3 inhibitors should reduce the recommended dose by half. One clinical studied was conducted to evaluate the PK and PD of baricitinib in paediatric patients with AD (study JAIP). Furthermore, PopPK and exposure-response analysis were performed to support the extension of indication.

Analytical methods

Plasma

Baricitinib plasma samples obtained during the studies were analysed using a validated liquid-liquid extraction followed by liquid chromatography with tandem mass spectrometry detection method. Labcorp Bioanalytical Services LLC (previously called Covance Bioanalytical Services LLC) located in Indianapolis, Indiana, USA, performed the bioanalytical methods. The lower limit of quantification was 0.20 ng/mL, and the upper limit of quantification was 200.00 ng/mL. Samples above the limit of quantification were diluted to yield results within the calibrated range. Validation results are shown in Table 1.

Table 1. Analytical method used for the analysis of baricitinib in plasma

method	linear range	accuracy	precision	dilution integrity	stability
8232103	0.20-2000 ng/mL	100.7-103.3%	2.0-3.8%	10×	RT = 48 h -20°C = 380 d -70°C = 1290 d freeze-thaw-cycles = 5

A total of 2063 samples were analysed within 595 days of collection. 27 samples (1.3% of the total number of samples) were reanalysed due to high internal standard response (n =21), above the limit of quantitation (n=3), insufficient sample (n=1), and poor chromatography (n=2). During the bioanalysis of study samples, inter-assay accuracy (%relative error) and inter-assay precision (%relative standard deviation) ranged from 97.7 to 103.2% and -2.3% to 3.2%, respectively. A total of 156 samples were reanalysed to assess incurred sample reproducibility. 99.4% of repeat and original results were within 20% of each other.

Whole blood

Baricitinib whole dried bloodspot samples (Mitras® VAMS) were analysed using a validated impact-assisted extraction method followed by reversed-phase liquid chromatography with tandem mass spectrometry detection. Altasciences Company Inc. (Laval, Quebec, Canada) performed the bioanalytical analysis using method ELL-W6-652(R2). The lower limit of quantification was 0.20 ng/mL, and the upper limit of quantification was 200.00 ng/mL. Validation results are shown in Table 2.

Table 2. Analytical method used for the analysis of baricitinib in whole blood

method	linear range	accuracy	precision	dilution integrity	stability
ELL-W6-652(R2)	0.20-200 ng/mL	99.4-112.2%	2.7 to 10.7%	5×	22°C = 710 days autosampler = 120 h extraction plate = 138 h

A total of 214 samples were analysed within 702 days of collection. One sample (0.4% of the total number of samples) was reanalysed due to unexpected internal standard response. During bioanalysis of study samples, inter-assay accuracy (% relative error) and inter-assay precision (% relative standard deviation) ranged from 101.1 to 107.2 and 3.9 to 7.9%, respectively. A total of 25 samples were reanalysed to assess incurred sample reproducibility. 84.0% of repeat and original results were within 20% of each other.

Population PK model

The objective of the population pharmacokinetic analysis for baricitinib in atopic dermatitis patients aged 2 to <18 years is to support the posology. Specifically, the analyses aimed to:

- characterize the population PK of baricitinib and estimate the magnitude of interpatient variability in baricitinib exposure.
- confirm whether baricitinib exposure in paediatric patients receiving baricitinib 4 mg equivalent once daily doses is comparable to the exposure in adults receiving baricitinib 4 mg once daily during the PK lead-in period

A total of 2257 baricitinib concentrations from 392 patients were used to characterise the PK in paediatric patients with atopic dermatitis. The PK data were analysed using population pharmacokinetic (PopPK) methodology with NONMEM (Version 7.4.2) and Perl-Speaks NONMEM (Version 4.8.1). The model was validated using standard methods, including visual predictive checks and bootstrap analyses to verify that the model predictions matched the observed data. Whole blood samples were collected from all participants in the lead-in period. Plasma concordance samples with time-matched whole blood samples were collected from a subset of participants in the older age group. A total of 15 plasma concordance samples were available from 15 participants. The blood-to-plasma ratio was determined as the slope of the regression line using time-matched blood and plasma samples. The slope (1.32) was used to convert the blood data to plasma equivalents. A total of 214 whole blood samples were collected from 33 participants enrolled in the lead-in period and converted to plasma equivalents. Samples below the quantitative limit (N=8) and outliers (N=1) were excluded. The plasma equivalents were used to perform the PK analyses for the open-label PK lead-in period. From the final 2257 samples, samples below the quantitative limit (N=212), samples collected prior to the first dose or within the lag time (N=9) or outliers (N=1) were excluded from the analysis from 156 participants.

The final PopPK model used the same model structure as the previously developed PK model in adult patients. It was a 2-compartment model with zero-order absorption, including lag time and a semi-mechanistic partitioning of CL/F into an eGFR-dependent CLr/F and CLnr/F. An allometric relationship was used for the effect of weight on clearance-related parameters (CL/F, CLr/F, and

intercompartmental clearance) with the allometric exponent fixed to 0.75, and for the effect of weight on central and peripheral volume of distribution with the exponent fixed to 1. The absorption duration (D1) parameter included a Box-Cox-transformed BSV. There is no clinically relevant effect of gender, race, or ethnicity on baricitinib PK. The data do not suggest the need for any dose adjustment in patients with atopic dermatitis on the basis of these factors. Age was not retained as a covariate once body weight and renal function were added to the model. PK parameters from the final PK model are provided in *Table 3*.

The prediction-corrected VPC plot for the 0.5, 1, 2, and 4 mg doses is shown in Figure 1.

Table 3. Pharmacokinetic and covariate parameters in final PopPK model for baricitinib in patients with atopic dermatitis

Model Parameter (Unit)	Population Mean (%SEE)	BSV[a] (%SEE)	Mean (95% CI) from Bootstrap Analysis
D_1 (hr)	0.263 (8.86)	164 (13.9)	0.253 (0.232 – 0.295)
Box-Cox transformation parameter for D_1	0.311 (6.85)	—	0.395 (0.167 – 0.481)
CLnr/F(L/hr)[b]	2.76 (15.4)	58.4 (4.54)	2.68 (2.51 – 3.03)
CLr/F (L/hr)[b]	7.9 (12.1)	62.3 (16.5)	8.02 (7.44 – 8.38)
V_1/F (L)[c]	119 (4.12)	12.7 (19.9)	119 (116 – 122)
Q (L/hr)[d]	2.4 (9.17)	15.1 (FIX)	2.52 (2.19 – 2.63)
V_2/F (L)[e]	46.8 (14.7)	117 (44.3)	46.5 (34.3 – 60.5)
LAG (hr)	0.144 (1.73)	—	0.146 (0.135 – 0.151)
Allometric scaling CL[b]	0.75 (FIX)	—	—
Allometric scaling V[c,e]	1 (FIX)	—	—
Covariate for change in eGFR on CLr/F[f]	0.00778 (42.5)	—	0.00738 (0.00462 – 0.0115)
Covariance for CLnr/F and CLr/F[g]	0.303 (10.4)	—	—
Covariance for CLr and V_1/F[g]	-0.0265 (15.8)	—	—
Proportional error[h]	0.427 (13.9)	—	0.426 (0.411 – 0.441)

Abbreviations: AD = atopic dermatitis; BSV = between-subject variability; CI = confidence interval; CL = total body clearance of drug calculated after intravenous administration; CLnr/F = apparent non-renal clearance; CLr/F = apparent renal clearance; CV = coefficient of variation; D_1 = absorption duration; ΔeGFR = change in eGFR from baseline; eGFR = estimated glomerular filtration rate; EXP = exponential; FIX = fixed; LAG = absorption lag; PopPK = population pharmacokinetics; Q = intercompartmental clearance, SEE = standard error of estimate; SQRT = square root; V = volume of distribution; V_1/F = apparent central volume of distribution; V_2/F = apparent peripheral volume of distribution; WTE = weight at entry.

[a] BSV reported as, %CV = (SQRT(EXP(OMEGA(N))-1))*100.

[b] CL/F=(CLnr/F+CLr/F)*((WTE/74)^0.75).

[c] V1/F=119*((WTE/74)^1.00).

[d] Q=2.4*((WTE/74)^0.75).

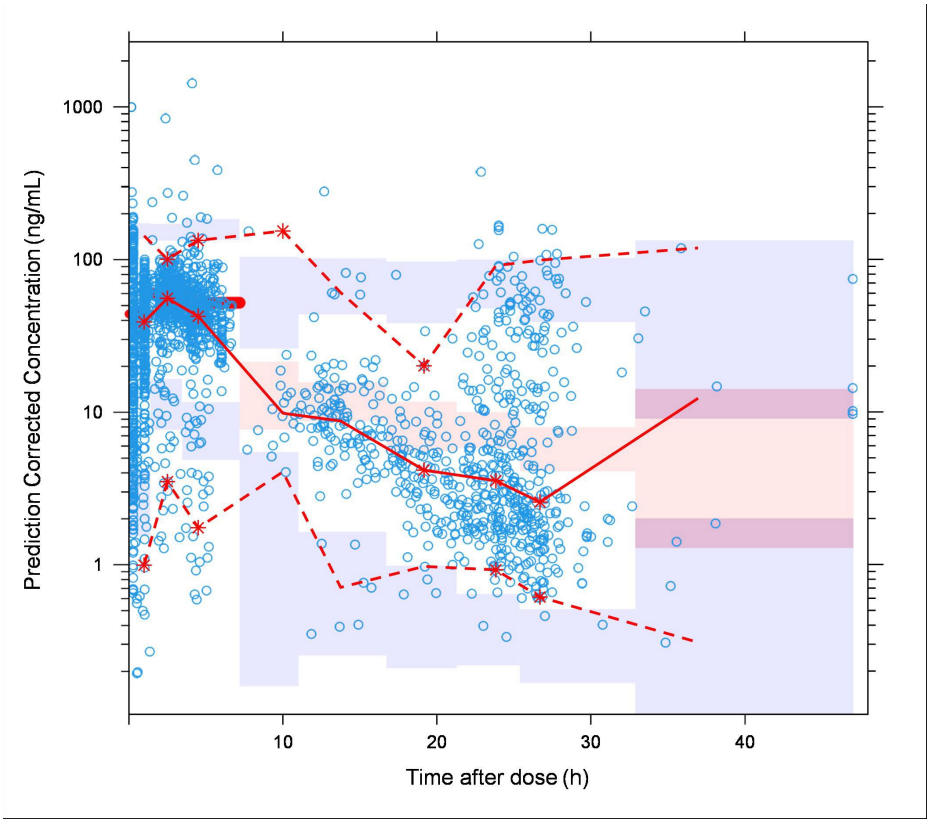
[e] V2/F=46.8*((WTE/74)^1.00).

[f] eGFR was estimated using the Bedside Schwartz equation. CLr/F = (apparent renal clearance*((baseline eGFR/93) + covariate for change in eGFR on apparent eGFR-dependent clearance * (ΔeGFR)), where 93 is median eGFR in mL/min/1.73 m^2 from the previous PopPK analysis.

[g] Covariance between ω2.

[h] Standard deviation.

Figure 1. Prediction-corrected visual predictive check for 0.5, 1, 2 and 4mg doses for the final pharmacokinetic model in paediatric patients with atopic dermatitis



Patients were dosed by age group in study JAIP. Since weight is a more physiologically relevant patient factor, the effect of weight on the C_{max} and AUC was further evaluated to identify an optimal weight cut-off value for dosing.

Absorption

After oral administration of baricitinib, C_{max} levels are reached ~1h after dosing (0.5-3.0 h). The absolute oral bioavailability of baricitinib from the commercial tablet is ~79% in healthy volunteers.

In healthy adult volunteers, the C_{max} is 41.6 nM, and the $AUC_{0-\infty}$ is 275 nM × h at the clinical dose of 4 mg.

In adult subjects with rheumatoid arthritis, the C_{max} is 53.2 ng/mL, and AUC_{τ} is 483 ng × h/mL, which are higher compared to healthy volunteers. In addition, CL/F is ~46% lower and $t_{½}$ ~25% shorter in rheumatoid arthritis patients relative to that in heathy subjects.

In adult patients with atopic dermatitis, the C_{max} and AUC at steady state are 45.9 ng/mL and 415 ng × h/mL, respectively, at the clinically relevant dose of 4 mg. The exposure tends to be lower in patients with atopic dermatitis compared to patients with rheumatoid arthritis (factor 0.86) and higher compared to healthy volunteers at the clinically relevant dose of 4 mg.

In adult patients with alopecia areata, the C_{max} and AUC at steady state are 47.5 ng/mL and 435 ng × h/mL, respectively, at the clinically relevant dose of 4 mg. The exposure tends to be lower in patients

with alopecia areata compared to patients with rheumatoid arthritis (factor 0.89) and higher compared to healthy volunteers and patients with atopic dermatitis.

In healthy volunteers, the intra-individual variability in AUC and C_{max} is low (<14%), and the inter-individual variability is moderate (17-26%). The inter-individual variability in rheumatoid arthritis patients was 41% for the AUC and 22% for the C_{max}. The inter-individual variability was 50% for the AUC and 21% for the C_{max} in patients with atopic dermatitis.

Distribution

The plasma protein binding of baricitinib is ~50% and was independent of the concentration (including clinically relevant concentrations). The blood-to-plasma ratio is 1.14, indicating a weak/moderate association with the blood cell compartment.

The volume of distribution is ~1.1 L/kg, indicating that baricitinib distributes from the plasma compartment into tissues. The Vd is 2.0 L/kg in patients with rheumatoid arthritis and 2.3 L/kg in patients with atopic dermatitis.

Metabolism

Only baricitinib was detected circulating in human plasma. Metabolites accounted for 4-7% of the dose in urine and ~1% in faeces. In addition, baricitinib is metabolised to a limited extent *in vitro*. Overall, these data indicate that metabolism does not significantly contribute to the clearance of baricitinib. The enzymes involved in the limited metabolism of baricitinib were not identified, but this was also considered not warranted.

Transporters

In vitro studies indicate that baricitinib is a substrate for P-glycoprotein, BCRP, OAT3 and MATE2-K. Baricitinib is not a substrate for OATP1B1, OATP1B3, OAT1, OCT1, OCT2, and MATE1. The transporters P-glycoprotein, OAT3 and MATE2-K are most likely involved in the active excretion into urine. BCRP may be involved in the excretion via faeces. However, excretion via faeces is limited; therefore, the *in vivo* contribution of BCRP to the excretion of baricitinib is most likely limited. Genetic polymorphisms in P-glycoprotein will most likely not have a clinically relevant effect on the PK of baricitinib. For MATE-2K, a conclusion on whether SNPs in MATE-2K would lead to clinically significant changes in the PK of baricitinib cannot be drawn as current information is too limited. A higher clearance of baricitinib due to the rs12943590 variant in MATE-2K will most likely not lead to a clinically relevant effect since a good response was observed in non-renal patients to a 2 mg dose.

Excretion

Baricitinib is mainly excreted via urine and predominately as the parent. Around 20% of the dose is excreted via faeces. This is most likely mainly unabsorbed baricitinib since the bioavailability is ~79%.

The total clearance is ~17 L/h, and the renal clearance is ~13.4 L/h in healthy subjects. These results indicate that baricitinib is actively excreted into the urine, which is confirmed by the transporter studies. The CL is 11.9 L/h in patients with rheumatoid arthritis and ~14.2 L/h in patients with atopic dermatitis. The elimination half-life of baricitinib is ~10 h in healthy volunteers and 12.5 h in patients with rheumatoid arthritis, and 12.9 h in patients with atopic dermatitis.

Dose proportionality and time dependencies

The C_{max} and $AUC_{0-\infty}$ increase dose-proportionally in healthy subjects over a single dose range of 1 to 30 mg (slightly more over the dose range 30 to 40 mg).

After multiple once-daily dosing, a steady state was reached between the second and third dose. Accumulation after repeated dose administration of baricitinib is minimal; the accumulation ratio ranged from 0.89- to 1.25-fold and 1.02- to 1.24-fold based on C_{max} and AUC, respectively.

Pharmacokinetics in target population

Study **JAIP** is a Phase 3, multicentre randomized, double-blind, placebo-controlled, parallel-group, outpatient study evaluating the pharmacokinetics, efficacy, and safety of baricitinib in paediatric patients with moderate to severe atopic dermatitis. This study was conducted at 78 centres in 17 countries and was conducted between May 2019 and April 2022. In the two-week open-label period in which the PK was investigated, patients aged 2 to <10 years received a dose of 2 mg once daily as oral suspension and patients aged 10 to <18 years received a dose of 4 mg once daily as a tablet. During the double-blind treatment period, patients received 0.5 mg (lowest dose for patients aged 2 to <10 years), 1 mg (lowest dose for patients aged ≥10 years), 2 mg (highest dose for patients aged 2 to <10 years) or 4 mg (highest dose for patients aged ≥10 years). A total of 32 patients were 2 to <6 years, 79 patients were 6 to <10 years and 281 patients were 10 to <18 years. The body weight ranged from 12 to 104 kg (mean was 46.6 kg).

Whole blood samples were collected in the lead-in period to determine if paediatric exposure to baricitinib was consistent with baricitinib exposure in adults at 4 mg once daily. Plasma samples were collected in the lead-in and double-blind treatment period from patients that received placebo and baricitinib for approximately 16 weeks from baseline. Samples were collected during the lead-in period pre-dose and at 0.25, 0.5, 1, 2, 4, 6 hours post-dose and during the double-blind treatment period pre-dose and at 0.25, 1, 2 to 4, 4 to 6 hours post-dose.

The PK parameters are summarised in Table 4. Population PK analysis showed that CL/F and apparent volume of distribution decrease with decrease in body weight and age.

Table 4. PopPK parameter estimates in paediatric patients with atopic dermatitis based on study JAIP per age category

age (years)	dose (mg)	$C_{max,ss}$ (ng/mL)	$AUC_{\tau,ss}$ (ng × h/mL)	V/F (L)	$t_{½}$ (h)	CL/F (L/h)
2 to<6	0.5 mg (n=9)	18.9 (CV%=29)	94.3 (CV%=108)	37.4 (CV%=23)	12.6 (CV%=29)	5.29 (CV%=108)
	1 mg (n=8)	35.1 (CV%=21)	200 (CV%=63)	38.2 (CV%=15)	11.1 (CV%=45)	4.98 (CV%=63)
	2 mg (n=15)	64.8 (CV%=22)	298 (CV%=51)	38.9 (CV%=16)	10.7 (CV%=36)	6.69 (CV%=51)
6 to<10	0.5 mg (n=24)	11.6 (CV%=29)	74.8 (CV%=64)	61.9 (CV%=23)	14.2 (CV%=21)	6.67 (CV%=64)

	1 mg (n=26)	23.1 (CV%=23)	155 (CV%=65)	61.5 (CV%=24)	14.1 (CV%=39)	6.42 (CV%=65)
	2 mg (n=29)	45.7 (CV%=35)	279 (CV%=77)	63.4 (CV%=31)	13.2 (CV%=56)	7.14 (CV%=77)
10to<18	1 mg (n=87)	13.2 (CV%=34)	109 (CV%=63)	121 (CV%=29)	17.9 (CV%=39)	9.16 (CV%=63)
	2 mg (n=86)	27.8 (CV%=34)	222 (CV%=66)	111 (CV%=30)	16.4 (CV%=43)	8.98 (CV%=66)
	4 mg (n=108)	50.7 (CV%=29)	383 (CV%=61)	119 (CV%=29)	16.0 (CV%=41)	10.4 (CV%=61)

In addition, PopPK was used to predict the PK with dosing based on body weight. The results are shown in Table 5.

*Table 5. PopPK parameter estimates in paediatric patients with atopic dermatitis based on study JAI*P per body weight category

body weight (kg)	dose (mg)	$C_{max,ss}$ (ng/mL)	$AUC_{T,ss}$ (ng × h/mL)	V/F (L)	$t_{½}$ (h)	CL/F (L/h)
<30	2 mg (n=35)	57.1 (CV%=22)	298 (CV%=59)	47.1 (CV%=25)	11.7 (CV%=45)	6.70 (CV%=59)
≥30	4 mg (n=106)	50.3 (CV%=28)	383 (CV%=62)	120 (CV%=28)	16.1 (CV%=41)	10.4 (CV%=41)

Special populations

The effect on the pharmacokinetics of baricitinib on renal function, hepatic function, age, weight, race, gender, and Erythrocyte Sedimentation Rate (ESR) were investigated.

Moderate hepatic impairment, age (age range of 19 to 83 years) and ERS (measure of disease state in Rheumatoid Arthritis patients) did not have a clinically significant effect on the exposure to baricitinib. No clinical studies with baricitinib were performed in patients with severe hepatic impairment. Patients with severe hepatic impairment often have serious co-morbidities, which calls for caution when considering pharmacological treatment. Therefore, the use of baricitinib in patients with severe hepatic impairment is not recommended, which is acceptable.

A reduction in baricitinib renal clearance and an increase in the AUC were observed with increased severity of renal impairment. In patients with rheumatoid arthritis, a less pronounced effect of renal function on the exposure of baricitinib was observed. This is consistent with a reduced fraction of excretion out of the total elimination pathways of baricitinib in patients with rheumatoid arthritis compared to healthy subjects. In addition, renal function had a significant effect on the $AUC_{T,ss}$, but not on $C_{max,ss}$ of baricitinib in patients with juvenile idiopathic arthritis, similar to adult patients with

rheumatoid arthritis. The estimated mean ratios (lower renal function: normal renal function) for $AUC_{T,ss}$ were 2.06 and 1.56 for moderate and mild renal impairment, respectively.

In addition, C_{max} decreased with increasing body weight. However, the effect of body weight on baricitinib PK is not considered clinically relevant in adults. Gender and race (American versus Japanese) were shown to have an effect on the PK of baricitinib, but this is most likely due to differences in body weight.

Pharmacokinetic interaction studies

Baricitinib as victim

In vitro and *in vivo* data indicate that >10% of the baricitinib dose is metabolised. Baricitinib is actively excreted by the transporters P-glycoprotein, BCRP, OAT3 and MATE2-K. In clinical drug-drug interaction (DDI) studies, the potential of other drugs to affect the PK of baricitinib was investigated. A clinically significant interaction was observed when baricitinib was co-administered with probenecid (a strong OAT3 inhibitor). No other clinical DDI studies have been conducted with OAT3 inhibitors with less inhibition potential. Co-administration of ketoconazole (strong CYP3A inhibition), fluconazole (strong CYP2C19 inhibition and moderate CYP2C9 and 3A inhibition), rifampicin (inducer via CAR/PXR of, among others CYP3A and P-glycoprotein) and cyclosporine (P-glycoprotein inhibition) with baricitinib did not have a clinically relevant effect on the pharmacokinetics of baricitinib. No *in vivo* studies were performed for the inhibition of BCRP and MATE2-K. Complete inhibition of BCRP may lead to a bioavailability of 100% which may result in an AUC increase of 1.25-fold. This increase is not considered clinically relevant. Furthermore, the clinical significance of an interaction at MATE2-K would be minimal, given the multiple exit routes of baricitinib from the proximal tubule cell. Maximal inhibition of MATE-2K will lead to a less than 2-fold increase in the AUC of baricitinib because other transporters can compensate for the lack of function. Therefore, inhibition of MATE-2K is likely not clinically relevant. An increase in gastric pH does not affect the overall exposure to baricitinib. Therefore, baricitinib may be co-administered with drugs that are gastric pH-modifying agents.

Baricitinib as perpetrator

Baricitinib is not an inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, and 3A5 at clinically relevant concentrations. In addition, baricitinib is not an inducer via AhR, PXR and CAR at clinically relevant maximal plasma concentrations, portal vein concentrations and maximal intestinal concentrations. Therefore, it is unlikely that baricitinib will lead to clinically relevant DDIs due to CYP inhibition or induction. Furthermore, baricitinib is not an inhibitor of the transporters P-glycoprotein, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, OAT2, OAT3, MATE-1 and MATE2-K at clinically relevant concentrations. Baricitinib may be an inhibitor of OCT1 at maximal portal vein concentrations. Concomitant administration of baricitinib with drugs for which the rate-limiting step is hepatic uptake by OCT1, may lead to an increase in Cmax.

In clinical DDI studies, the potential of baricitinib to affect the PK of oral contraceptives (via CYP3A), simvastatin (via CYP3A and OATP1B1), and digoxin (via P-glycoprotein) was investigated. The clinical DDI studies confirm the *in vitro* data that baricitinib is not an inhibitor or inducer of CYP3A and not an inhibitor of P-glycoprotein. Concomitant administration with simvastatin led to a (not clinically significant) decrease in AUC and Cmax of simvastatin. The underlying mechanism of action is unknown. Furthermore, baricitinib does not have an effect on the PK of methotrexate, a commonly concomitant prescribed medicine in RA patients.

In the clinical safety studies, an effect on the creatinine clearance was observed (decrease in creatinine clearance). Creatinine is cleared by the following transporters OCT2, OAT2, MATE1 and MATE2-K.

Baricitinib was not an inhibitor of OCT2, OAT2, MATE1 and MATE2-K at clinically relevant concentrations. The cause for this observed decreased creatinine clearance is unknown.

Exposure relevant for safety evaluation

In paediatric patients with atopic dermatitis weighing <30 kg, the C_{max} is 57.1 ng/mL, and the AUC_T is 298 ng × h/mL.

In paediatric patients with atopic dermatitis weighing ≥30 kg, the C_{max} is 50.3 ng/mL, and the AUC_T is 383 ng × h/mL.

2.3.3. Pharmacodynamics

Mechanism of action

Baricitinib is an orally available, selective JAK inhibitor with potency and selectivity for JAK1 and JAK2, and less potency for JAK3 or tyrosine kinase 2[16]. JAK1, JAK2, JAK3, and tyrosine kinase 2, along with the STAT pathway, play an important role in signal transduction following cytokine and growth factor binding to their receptors[7]. In the pathogenesis of AD, the JAK-STAT pathway plays a critical role by upregulating epidermal chemokines, proinflammatory cytokines, and proangiogenic factors as well as by downregulating antimicrobial peptides and factors responsible for skin barrier function[20]. The fundamental pathophysiology of AD, with excessive T cell activation, is similar among age groups (adults, adolescents, and children) [18,19]. The JAK-STAT signalling pathway is functional from infancy, and aberrations in JAK-STAT signalling are implicated in other rare autoinflammatory diseases with onset within the first year of life[21,22].

2.3.4. PK/PD modelling

Exposure-response relationship

In the study JAIP patients were treated with placebo or 0.5 mg, 1 mg, 2 mg, or 4 mg in the double-blind treatment period. Sparse blood samples were collected, and PopPK modelling was used to determine the PK of baricitinib for the different dosages. The $C_{avg,ss}$ was used as a measure for exposure.

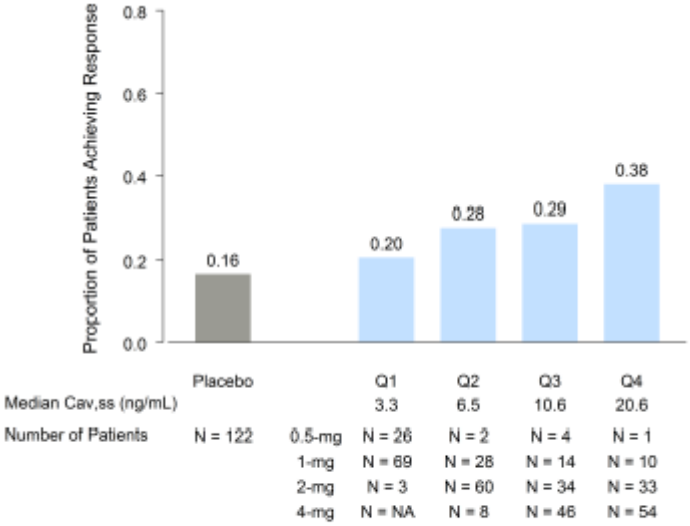
Using the data of study JAIP, efficacy endpoints from 514 patients were used for exposure quartile analyses for the primary endpoint, IGA 0 or 1 at week 16, and for the secondary endpoint, EASI75 at week 16. For the secondary endpoint, Itch NRS at Week 16, data were collected from patients aged 10 to <18 years; thus, 242 patients were included in that analysis.

An exposure-response relationship was observed for the overall group of patients when dosed with 0.5 mg (lowest dose for patients aged 2 to <10 years), 1 mg (lowest dose for patients aged ≥10 years), 2 mg (highest dose for patients aged 2 to <10 years) or 4 mg (highest dose for patients aged ≥10 years) on the primary and key secondary endpoints at week 16:IGA score of 0 or 1 (Figure 2); EASI75 (Figure 3); Itch NRS (Figure 4).

The dose applied in the study JAIP was stratified by age; the high dose used in the randomised, double-blind part was 4 mg QD for older participants (10 to <18 years) and 2 mg QD for younger participants (2 to <10 years). When the exposure-response analyses were stratified by weight class (<30 kg or ≥30 kg), results differed per outcome. For IGA 0 or 1 at week 16 (primary outcome), the

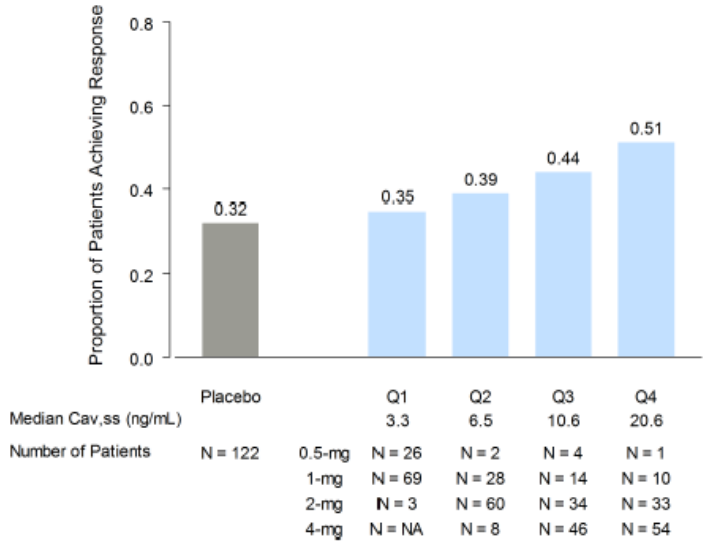
exposure-response relationship for patients <30 kg and ≥30 kg were numerically similar to the overall results (as in Figure 2). For EASI75 at week 16 (secondary outcome), the exposure-response relationship for patients <30 kg and ≥30 kg was numerically dissimilar to the overall results. Notably, in the patients weighing <30 kg, the response in Q4 was lower than the responses of placebo, Q2 and Q3 (Figure 3).

Figure 2. Observed IGA 0 or 1 at week 16 by baricitinib average plasma concentration at steady state ($C_{av,ss}$) quartiles for patients receiving placebo, 0.5-, 1-, 2-, or 4-mg baricitinib once-daily doses in study JAIP



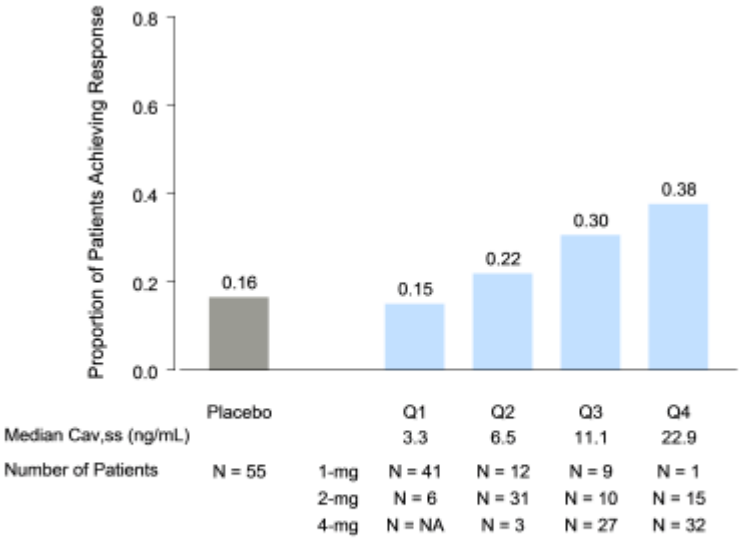
Abbreviations: $C_{av,ss}$ = average concentration during a dosing interval at steady state; IGA = Investigator's Global Assessment; N = number of subjects analysed; NA = not applicable; Q = quartile.
Note: Light blue bars indicate response rate.

Figure 3. Observed EASI75 response rates at week 16 by baricitinib average plasma concentration at steady state ($C_{av,ss}$) quartiles for patients receiving 0.5-, 1-, 2- or 4-mg baricitinib once-daily doses in study JAIP



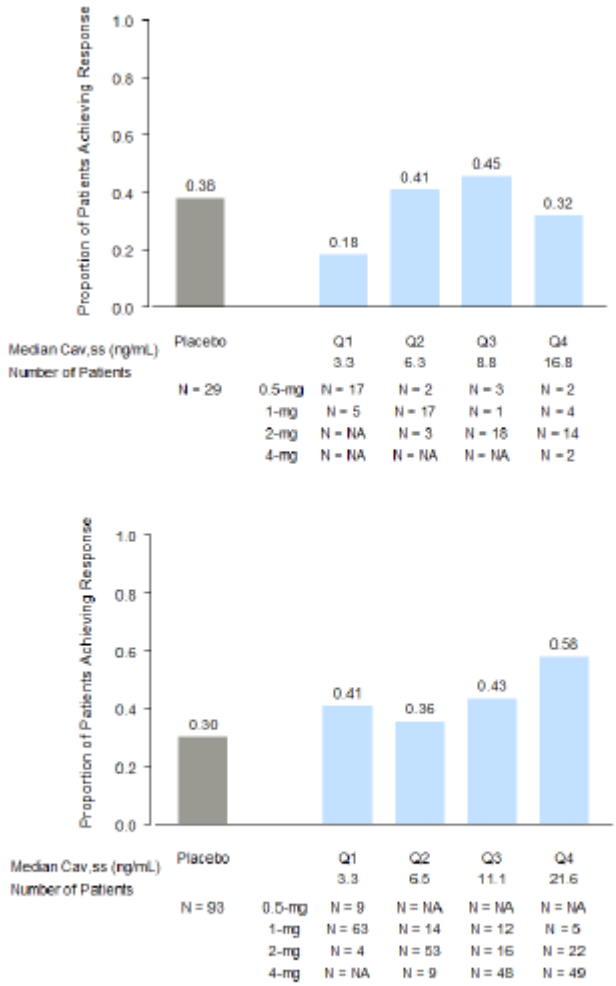
Abbreviations: EASI = Eczema Area and Severity Index; $C_{av,ss}$ = average concentration during a dosing interval at steady state; N = number of subjects analysed; NA = not applicable; Q = quartile.
Note: Light blue bars indicate response rate.

Figure 4. Observed Itch NRS values at week 16 by baricitinib average plasma concentration at steady state (Cav,ss) quartiles for patients receiving 0.5-, 1-, 2- or 4-mg baricitinib once-daily doses in study JAIP



Abbreviations: $C_{av,ss}$ = average concentration during a dosing interval at steady state; N = number of subjects analysed; NA = not applicable; NRS = Numeric Rating Scale; Q = quartile.
Note: Light blue bars indicate response rate.

Figure 5. Observed EASI75 response rates at week 16 for patients <30 kg (upper panel) and ≥30 kg (lower panel) by baricitinib average plasma concentration at steady state (Cav,ss) quartiles for patients receiving 0.5-, 1-, 2- or 4-mg baricitinib once-daily doses in study JAIP



Abbreviations: EASI = Eczema Area and Severity Index; $C_{av,ss}$ = average concentration during a dosing interval at steady state; N = number of subjects analysed; NA = not applicable; Q = quartile.
Note: Top panel: <30 kg: bottom panel: ≥30 kg. Light blue bars indicate response rate.

2.3.5. Discussion on clinical pharmacology

Pharmacokinetics

The Applicant is requesting an extension of indication for the treatment of paediatric patients aged 2 to <18 years with atopic dermatitis with a dose of 2 mg once daily in patients with a body weight <30 kg and a dose of 4 mg once daily in patients with a body weight of ≥30 kg. One clinical study evaluated the PK and PD of baricitinib in paediatric patients (study JAIP). It should be noted that patients treated with an OAT3 inhibitor or who have renal impairment are to be treated with half the dose; thus 1 mg in patients weighing <30 kg and 2 mg in patients weighing ≥30 kg. The 1 mg tablet was assessed and approved in the extension procedure EMEA/H/C/004085/X/0035/G. The tablet can be dissolved in water for patients who cannot swallow tablets, as reflected in section 4.2 of the SmPC.

A clinical study was conducted to evaluate the PK of baricitinib in paediatric patients with atopic dermatitis (study JAIP). In the two-week open-label period, the PK was investigated in patients aged 2

to <10 years receiving a dose of 2 mg once daily as oral suspension and patients aged 10 to <18 years receiving a dose of 4 mg once daily as a tablet. During the double-blind treatment period, patients received 0.5 mg (lowest dose for patients aged 2 to <10 years), 1 mg (lowest dose for patients aged ≥10 years), 2 mg (highest dose for patients aged 2 to <10 years) or 4 mg (highest dose for patients aged ≥10 years). The PK aim of the study was to find a paediatric dose leading to similar exposure in paediatric patients as to that seen in the adult pivotal studies. The PK was determined per age category (2 to <6 years, 6 to <10 years and ≥10 years) and with a body weight cut-off (<30 kg and ≥30 kg). As a principle, the weight-based posology is endorsed.

The same validated analytical method was used to determine the plasma concentrations in studies JAIP as in the initial MAA. However, the Applicant used an additional new analytical technique for the analysis of baricitinib in whole dried bloodspot samples for study JAIP. Upon CHMP's request, the Applicant provided information that the plasma and dried blood samples matched. Overall, the analytical methods appear sufficiently validated.

The blood-to-plasma ratio in study JAIP was slightly higher than observed at MAA. The reason for the higher observed blood-to-plasma ratio is not known. However, since the number of dried blood samples is limited, the effect on the PK is most likely negligible and CHMP agrees that the difference is not meaningful.

Baricitinib is mainly excreted via urine and predominately as the parent compound. Furthermore, C_{max} and AUC increase dose-proportionally over the clinical dose range of 1 to 4 mg following single and multiple dosing. No effect of age is expected in children aged 2 years and older; therefore, the approach of the Applicant to use the already developed PopPK model to determine the PK in juvenile idiopathic arthritis patients aged 2 to <18 years is acceptable. The model appears to be able to predict the PK in atopic dermatitis patients aged 2 to <18 years. However, the model appeared not to be able to capture the elimination accurately. Upon CHMP's request, the Applicant showed that observed and predicted PopPK data for greater than or equal to 30 kg are reasonably concordant from 0 to 16 hours. There is a slight over-prediction of concentration from 16 to 30 hours. This is most likely due to a high number of trough samples with high observed concentrations, which the CHMP accepts. Therefore, the PopPK model can be used to predict the PK in paediatric patients with atopic dermatitis.

A total of 32 subjects were aged 2 to <6 years, 79 subjects were aged 6 to <10 years, and 281 subjects were aged 10 to <18 years. The body weight ranged from 12 to 104 kg (mean was 46.6 kg). A total of 84 subjects had a body weight of <30 kg. The subjects had a mean body weight of 21.6 kg (range is 12.0-29.9 kg). A total of 308 subjects had a body weight of >30 kg with a mean body weight of 53.4 kg (range of 30.0-104 kg).

The Applicant assumes that the disease is similar in adults and paediatric patients with atopic dermatitis and a similar exposure-response relationship is expected. Based on PopPK data, the C_{max} is higher in paediatric patients with atopic dermatitis weighing <30 kg and ≥30 kg compared to adult patients with atopic dermatitis. In contrast, the AUC is lower in paediatric patients with atopic dermatitis weighing <30 kg and ≥30 kg compared to adults. Thus, the exposure does not appear to be similar in paediatric patients and adults. The higher C_{max} in paediatric patients with atopic dermatitis could lead to additional safety issues. In contrast, the lower AUC could lead to decreased efficacy.

The exposure in paediatric patients weighing 10 to <20 kg is higher compared to adults with the proposed posology, and the probability of developing adverse events could increase. From modelling data, it appears that reducing the dose to 1 mg once daily would lead to too low exposure and could compromise efficacy in paediatric patients weighing 10 to <20 kg. However, due to the higher exposure of baricitinib 2 mg in these low weight children, the probability of developing adverse events could increase. Therefore, based on the available data the posology paediatric patients with AD

weighing <30 kg is acceptable, as reflected in the section 4.2 of the SmPC. To follow-up the safety of AD paediatric patients weighing <30 kg, the Applicant agreed to include Study I4V-MC-JAIP (JAIP) (paediatric AD) as a category 3 study in the RMP. The Applicant also agreed to routinely monitor events reported from post-marketing sources and that any significant findings will be reported in Periodic Safety Update Reports (PSURs).

Pharmacodynamics

PD analyses using biomarkers for efficacy or safety have not been performed. For efficacy, biomarkers are not considered needed, in the presence of (descriptive) exposure-response analyses with main clinical outcomes (IGA 0/1, EASI75, Itch NRS). The wide dose range used in the study JAIP (placebo, 0,5 mg, 1 mg, 2 mg, 4 mg) leads to a wide range in exposure, which facilitates the interpretation of exposure-response analyses.

For the total group of patients, there was a clear exposure-response relationship between quartiles of baricitinib plasma concentrations ($C_{av,ss}$) and IGA 0 or 1, EASI75, and Itch NRS, at week 16. Based on PK results, the proposed dose recommendations for the SmPC are 2 mg for patients <30 kg and 4 mg if ≥30 kg. However, results differed per outcome when the exposure-response analyses were stratified by weight class (<30 kg or ≥30 kg). However, for the patients <30 kg only the IGA0/1 results (primary outcome) are clearly supportive. The results on EASI75 in the children <30 kg does not show a clear dose-response relationship, mainly due to a relatively high probability for response in the placebo group and a relatively low probability to reach response in the highest quartile of exposure. These EASI75 results in the <30 kg group may be caused by chance, due to the relatively low number of children <30 kg. Results on Itch were not available in the low weight class, because in younger patients (<10 years of age) another instrument was used (PRISM). Because of the absence of a clear dose-response relation for EASI75 and because there are no data on Itch NRS, there is a lack of supportive efficacy data in the <30 kg weight group. This lack of data is however mitigated by the results on IGA 0/1 (primary outcome) and by the fact that the concern about exposure in children <30 kg is a relatively high dose, rather than too low a dose that could lead to reduced efficacy. Previous PK/PD analyses in adults with RA showed that AUC rather than C_{max} drives efficacy, and in children weighing <30 kg the AUC was considered more similar to the adult exposure than C_{max}. Therefore, the exposure-response relationships support the dose in children <30 kg from the efficacy point of view.

2.3.6. Conclusions on clinical pharmacology

The pharmacokinetics of baricitinib in paediatric patients with AD have been sufficiently characterised. The following posology in AD patients 2 years and older is endorsed by the CHMP: 2 mg dose once daily in patients weighing 10 kg to <30 kg and a dose of 4 mg once daily in patients with a body weight of ≥30 kg. Further safety data in paediatric patients weighing <30 kg will be provided as a Category 3 PASS of the RMP and through routine monitoring by the Applicant.

2.4. Clinical efficacy

2.4.1. Dose response studies

No separate dose-response study has been performed. The dosing strategy for the 'high dose' (4 mg equivalent exposure to adults) was assessed using the PK lead-in period of study JAIP, and doses below the 'high dose' were tested in the subsequent randomised controlled period of study JAIP. This strategy had been agreed upon with PDCO.

2.4.2. Main study

Title of Study

A phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group, outpatient study evaluating the pharmacokinetics, efficacy, and safety of baricitinib in paediatric patients with moderate to-severe Atopic Dermatitis (I4V-MC-JAIP).

Design

Study I4V-MC-JAIP was designed as a 'phase 3', multicentre, randomised, double-blind, placebo controlled, parallel-group, outpatient study evaluating the PK, efficacy, and safety of baricitinib compared with placebo in paediatric participants 2 to <18 years of age with moderate-to-severe AD.

The study was divided into 5 periods:

- 5-week screening period (Period 1)
- 2 week, open-label PK lead-in period (Period 2)
- 16-week, double-blind treatment period (Period 3)
- up to 4-year long-term extension period (Period 4)
- 4-week post-treatment follow-up period (Period 5)

Patients were enrolled in the randomised, double-blind study period (period 3), not until the results of the PK lead-in period (period 2) had confirmed the appropriate dose selection for the age group. For the double-blind part of the study, it was planned that at least 440 participants with moderate-severe AD would be enrolled, with at least n=320 aged 10 to <18 years and n=120 participants aged 2 to <10 years old. Participants were randomised (1:1:1:1) to placebo, baricitinib low-dose QD, medium-dose QD, or high-dose QD. Accordingly, the daily doses for participants 10 to <18 years old were 4 mg, 2 mg, and 1 mg; the doses for participants 2to <10 years old were 2 mg, 1 mg, and 0.5 mg. For patients <10 years of age, oral suspension was used, and patients ≥10 years of age were supplied with tablets. Randomisation was stratified according to disease severity (IGA 3 versus 4). Background therapy with medium-potency and/or low-potency TCS and topical TCNI was permitted for use on active lesions until lesions were under control. The primary outcome was IGA 0 or 1 at week 16, EASI75 at week 16, and improvement ≥4 points in Itch NRS (patients ≥10 years only) at week 16, which were among the secondary outcomes adjusted for multiplicity.

Patients who had completed study periods 2 or 3 were eligible to continue in the long-term extension period for up to 4 additional years of treatment (period 4). Period 5 was applied for patients who discontinued the study early or completed/will complete study period 4.

Study participants

The inclusion and exclusion criteria were designed to include paediatric patients with moderate-to-severe AD who were candidates for systemic treatments.

The main **inclusion** criteria were:

- Children aged 2 to <18 years with moderate-to-severe AD for 12 months or more in participants 6 years and older, and at least 6 months in children aged 2 to <6 years.

- Moderate-to-severe AD at screening and baseline as evidenced by all of: an EASI score ≥16; IGA score of ≥3; ≥10% of BSA involvement.
- Documented history of inadequate response to TCS, and inadequate response or history of intolerance to TCNI (not in regions were TCNI are not available or are not recommended).

  Inadequate response is defined as failure to achieve stable long-term disease control (for example, IGA ≤2):

  - after use of at least a moderate-potency TCS for at least 4 weeks or for the maximum duration recommended by the product prescribing information within 6 months of screening.
  - after use of TCNI for at least 4 weeks of treatment or for the maximum duration recommended by the product prescribing information.
  - after use of systemic therapies intended to treat AD within 6 months preceding screening, such as cyclosporine, methotrexate, azathioprine, systemic corticosteroids, or mycophenolate mofetil.

  Intolerance to TCNI is defined as:

  - a documented history of clinically significant adverse reactions that in the opinion of the investigator outweigh the benefits of re-treatment (e.g., skin burning).
- Applied emollients daily for at least 14 days prior to baseline and agreed to use emollient daily throughout the study.
- Provision of informed consent and age-appropriate assent as required.

The main **exclusion** criteria were:

- Have active, or had a history of, other concomitant skin conditions (e.g., psoriasis or lupus erythematosus) that would interfere with evaluations of the treatment effect.
- Had a history of erythrodermic, refractory, or unstable skin disease requiring frequent hospitalisations or intravenous treatment for skin infections.
- Had a history of eczema herpeticum within 12 months prior to screening or had a history of 2 or more episodes of eczema herpeticum in the past.
- Had any serious concomitant illness that is anticipated to require the use of systemic corticosteroids or otherwise interfere with study participation, or require active frequent monitoring (e.g., unstable chronic asthma).
- Had a positive test for viral hepatitis (B and C) as defined in the protocol.
- Have uncontrolled arterial hypertension; be immunocompromised; have had VTE, myocardial infarction (MI), unstable ischemic heart disease, stroke, or New York Heart Association Stage III/IV heart failure within 12 weeks before screening; have had VTE or be at high risk; have a history of lymphoproliferative disease or be suspected for that, have active primary or recurrent malignant disease; have a current or recent clinically serious viral, bacterial, fungal, or parasitic infection, have active or latent TB.
- Have abnormalities on screening laboratory tests: AST or ALT ≥2x upper limit of normal (ULN); alkaline phosphatase (ALP) ≥2x ULN; total bilirubin ≥1.5x ULN; haemoglobin <10.0 g/dL (100.0 g/L); total white blood cell count <2500 cells/µL (<2.50x10^3/µL or <2.50 GI/L); neutropenia (absolute neutrophil count [ANC] <1200 cells/µL) (<1.20x10^3/µL or

<1.20 GI/L); lymphopenia (lymphocyte count <750 cells/µL) (<0.75x10^3/µL or <0.75 GI/L); thrombocytopenia (platelets <100,000/µL) (<100x10^3/µL or <100 GI/L); estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (eGFR, calculated using Bedside Schwartz 2009 formula).

Treatments

Experimental treatment
In the study, baricitinib (high, medium, and low) doses QD were compared to placebo, as tablets for patients aged 10 years and older, and as oral suspension formulation in patients of 2 to <10 years. In addition, dose strength was stratified by the age cut-off of 10 years.

Patients 10 to <18 years old allocated to the high dose received baricitinib 4 mg QD tablets and placebo tablets matching 2 mg and 1 mg baricitinib. Likewise, patients allocated to the medium dose received baricitinib 2 mg QD and matching placebo for 4 mg and 1 mg, and patients allocated to the low dose received baricitinib 1 mg and matching placebo tablets for 4 mg and 2 mg. Patients allocated to placebo received three placebo tablets matching the baricitinib strengths. Tablets for blinded treatment were packed in blister packs with 3 tablets a day. Open-label investigational product tablets were provided in bottles.

Patients 2 to <10 years old allocated to the high dose received 2mg QD oral suspension formulation (1 ml per day). Likewise, patients allocated to the medium dose received 1 mg oral suspension (0.5 ml a day), and patients allocated to the low dose received 0.5 mg oral suspension (0.25 ml a day). Accordingly, patients allocated to placebo received 1 ml, 0.5 ml, or 0.25 ml of placebo oral suspension formulation, matching baricitinib oral suspension. Baricitinib oral suspension (2-mg/mL baricitinib) or matching placebo was supplied as a ready-to-use oral suspension in a bottle to be administered using an oral syringe.

Treatment compliance
Patient compliance with study medication was assessed at each visit after baseline. Patients treated with baricitinib or placebo were considered noncompliant if they missed >20% of the prescribed doses during the study (unless the investigator withheld the study medication for safety reasons). Patients found to be non-compliant were assessed to determine the reason for noncompliance and educated and/or managed as deemed appropriate to improve compliance.

Concomitant treatment
Daily use of emollients was required. However, when daily applications were missed, it was not considered a protocol violation.

Stable use of antihistamines was allowed, and downward dose adjustments or discontinuation of antihistamines was permitted.

Patients received sponsor-provided TCS (triamcinolone 0.1% cream or equivalent-potency TCS and hydrocortisone 2.5% ointment or equivalent-potency TCS) at screening. TCS was to be used on active lesions as prescribed by the investigator. After baseline, TCS should continue to be applied to affected areas as clinically indicated until lesions are under control (clear or almost clear). TCS was then tapered and stopped as clinically indicated. In the long-term extension period (period 4), TCS was permitted in all potencies.

The use of TCNIs (e.g., tacrolimus and pimecrolimus) or a topical PDE-4 inhibitor (i.e., crisaborole, where approved) were permitted in areas where the application of TCS is considered inappropriate by the investigator (e.g., face, neck, skin folds, genital areas, etc.). Like for TCS, TCNI was tapered and stopped as clinically indicated.

To allow for adequate assessment of skin dryness, patients were asked not to apply emollients or TCS (TCNI, PDE-4i) on the day of their study visit prior to the procedures.

If lesions reappeared, the patients should resume the application of TCS, TCNI or PDE-4 inhibitor as described above.

Rescue treatment
In the randomised, double-blind period (Period 3), patients whose lesions persisted or worsened despite the use of emollients and low- and/or medium-potency TCS were eligible for topical rescue with high- or ultra-high-potency TCS. Patients whose disease was still not controlled could be rescued to systemic therapies (conventional systemics or biologics), which required discontinuation of experimental treatment (continuing the study was encouraged).

Prohibited treatment
The treatment with investigational product should be discontinued when prohibited treatments were started: live vaccines, systemic corticosteroids, any systemic therapy used as AD rescue, probenecid.

Treatment discontinuation
For abnormal laboratory findings and clinical events (regardless of relatedness), specific guidance was provided for **temporarily** interrupting treatment and when treatment may be restarted Table 6.

Table 6. Criteria for the temporary interruption and resumption of investigational treatment.

Hold Investigational Product if the Following Laboratory Test Results or Clinical Events Occur:	Investigational Product May Be Resumed When:
WBC count <2000 cells/μL (<2.00x10^3/μL or <2.00 GI/L)	WBC count ≥2500 cells/μL (≥2.50x10^3/μL or ≥2.50 GI/L)
ANC <1000 cells/μL (<1.00x10^3/μL or <1.00 GI/L)	ANC ≥1200 cells/μL (≥1.20x10^3/μL or ≥1.20 GI/L)
Lymphocyte count <500 cells/μL (<0.50x10^3/μL or <0.50 GI/L)	Lymphocyte count ≥750 cells/μL (≥0.75x10^3/μL or ≥0.75 GI/L)
Platelet count <75,000/μL (<75x10^3/μL or <75 GI/L)	Platelet count ≥100,000/μL (≥100x10^3/μL or ≥100 GI/L)
eGFR <50 mL/min/1.73 m^2 (from serum creatinine)	eGFR ≥60 mL/min/1.73 m^2
ALT or AST >5x ULN	ALT and AST return to <2x ULN, and IP is not considered to be the cause of enzyme elevation
Hemoglobin <8 g/dL (<80.0 g/L)	Hemoglobin ≥10 g/dL (≥100.0 g/L)
Symptomatic herpes zoster (shingles or chicken pox)	All skin lesions have crusted and are resolving
Infection that, in the opinion of the investigator, merits the IP being interrupted	Resolution of infection
Clinical features of VTE (such as deep vein thrombosis or pulmonary embolism) are present[a]	After ruling out event of VTE

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; GI = billion; IP = investigational product; ULN = upper limit of normal; VTE = venous thromboembolic event; WBC = white blood cell.

[a] Evaluate promptly and institute appropriate treatment. If upon evaluation VTE is ruled out and no other temporary or permanent discontinuation criteria are met, then IP may be resumed.

Investigational treatment should be **permanently** discontinued when there is suspicion for liver damage based on laboratory values (e.g. ALT or AST >8× ULN or ALT or AST >5× ULN for more than 2 weeks), and in case of other abnormalities in laboratory values (white blood cell count <1000 cells/μL (1.00x103/μL or 1.00 GI/L); ANC <500 cells/μL (0.50x103/μL or 0.50 GI/L); lymphocyte count <200 cells/μL (0.20x103/μL or 0.20 GI/L); haemoglobin <6.5 g/dL (<65.0 g/L). Also in case of pregnancy, malignancy, HBV positivity, VTE, investigational treatment was permanently discontinued.

Objectives

The efficacy objective of the randomised placebo-controlled period was to analyse whether there was superiority of each dose of baricitinib versus placebo in the treatment of paediatric patients >2 years of age with moderate-to-severe AD.

Further objectives were to: characterise the PK profile of baricitinib in paediatric participants with AD; assess the participant acceptability and palatability of baricitinib tablets and oral suspension; evaluate the potential effects of baricitinib on the cellular and humoral immune system; assess the efficacy of baricitinib during longer-term treatment; assess growth and bone safety of baricitinib during longer-term treatment.

Outcomes/endpoints

The **primary endpoint** was the proportion of patients with a **vIGA-AD score of 0 or 1** (clear or almost clear skin) with at least a 2-point improvement at 16 weeks. The IGA is a commonly used scale in clinical trials in adult and paediatric patients[25,26]. The score is based on an overall assessment of the degree of erythema, papulation/induration, oozing/crusting, and lichenification, and is scored from 4 (severe disease) to 0 (clear skin).

Table 7. Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD)

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

Source: www.eczemacouncil.org

The **key secondary endpoints**, adjusted for multiplicity, were:

- The proportion of patients achieving 75% improvement on the EASI (**EASI75**) at 16 weeks, the proportion of patients achieving a 90% improvement on the EASI (**EASI90**) at 16 weeks, the mean change from baseline in **EASI** score at 16 weeks. The investigator-rated EASI assesses the extent of disease at 4 body regions for erythema, induration/papulation,

[25] Langley, R. G., Feldman, S. R., Nyirady, J., van de Kerkhof, P., & Papavassilis, C. (2015). The 5-point Investigator's Global Assessment (IGA) Scale: A modified tool for evaluating plaque psoriasis severity in clinical trials. *The Journal of dermatological treatment*, *26*(1), 23–31. https://doi.org/10.3109/09546634.2013.865009

[26] Futamura, M., Leshem, Y. A., Thomas, K. S., Nankervis, H., Williams, H. C., & Simpson, E. L. (2016). A systematic review of Investigator Global Assessment (IGA) in atopic dermatitis (AD) trials: Many options, no standards. *Journal of the American Academy of Dermatology*, *74*(2), 288–294. https://doi.org/10.1016/j.jaad.2015.09.062

excoriation, and lichenification, each on a scale of 0 to 3 (Hanifin et al. 2001). The EASI is a validated scale in patients down to 2 months of age (Barbier 2004).

- The proportion of patients achieving a 75% improvement on the SCORAD (**SCORAD75**) at 16 weeks. The SCORing Atopic Dermatitis (SCORAD) index is an investigator-rated assessment that uses the rule of nines to assess disease extent and evaluates 6 clinical characteristics: erythema, oedema/papulation, oozing/crusts, excoriation, lichenification, and dryness. The SCORAD index also includes patient-assessed symptoms of pruritus and sleep loss (VAS). (Stalder and Taieb 1993; Oranje 2007)
- The proportion of patients with an improvement of **≥4-points in Itch NRS** at 1 week, 2 weeks, 4 weeks, and 16 weeks for patients ≥10 years old. The Itch NRS is a patient-assessed, 11-point horizontal scale anchored at 0 ('no itch') and 10 ('worst itch imaginable') (Naegeli 2015; Kimball 2016).

Other **secondary endpoints**, not adjusted for multiplicity, included:

- Mean change from baseline in **BSA** affected at 16 weeks. The BSA is derived from the EASI assessment.
- The proportion of participants developing **skin infections** requiring antibiotic treatment by Week 16.
- Mean change in the **PRISM** at 1 week, 2 weeks, 4 weeks, and 16 weeks for participants <10 years old. The Parent-Reported Itch Severity Measure (PRISM) is a single-item, parent/caregiver-administered scale on the overall severity of their child's itching. Assessment is based on observed actions of the child in the past 24 hours. Response options range from 'No Itch', over 'Mild', 'Moderate' and 'Severe' to 'Very Severe'.
- The mean number of days without the use of background **TCS** over 16 weeks and mean gram quantity of TCS used over 16 weeks (tube weights). The use of TCS is assessed using a daily diary to record if a patient has applied a TCS to the skin in the last 24 hours.
- Mean change from baseline in the total score of the **POEM** at 16 weeks. The Patient-Oriented Eczema Measure (POEM) is a 7-item, patient-administered scale to assess disease severity in children and adults. Items ask about the frequency of 7 symptoms (itching, sleep disturbance, bleeding, weeping/oozing, cracking, flaking, and dryness/roughness) over the last week (Charman et al. 2004). Response categories include 0 ('no days'), 1 ('2 days'), 2 ('3-4 days'), 3 ('5-6 days'), 4 'every day'). The POEM is a validated scale in patients down to 1 year of age (Charman et al. 2004).
- Mean changes from baseline in the **PROMIS**-paediatric depression and the PROMIS-paediatric anxiety at 16 weeks. The PROMIS Depression Short Form and the Anxiety Short Form are available in a paediatric self-report(ages 8 to <18 years) and for parents/caregivers serving as proxy reporters for their children(youth ages ≥5 years). Children aged <5 years will not complete this assessment. Both versions assess depression/anxiety "in the past seven days." Response options range from 1 ('Never') to 5 ('Almost always'). Total raw scores are converted to T-Scores with higher scores representing greater depression or anxiety.
- Mean change in **CDLQI/IDQOL** scores at 16 weeks. The Children's Dermatology Life Quality Index (CDLQI) is a patient-administered, 10-question, validated, quality-of-life questionnaire that is designed for use in children ≥4 years old that covers 6 domains including symptoms and feelings, leisure, school or holidays, personal relationships, sleep, and treatment (Lewis-Jones and Finlay 1995). The recall period is over the last week. Response categories range from 0

('not at all') to 3 ('very much'). A CDLQI total score of 0 to 1 is considered as having no effect on a child's life (Waters et al. 2010). The Infant's Dermatitis Quality of Life Index (IDQOL) is a caregiver-administered, 11-question, validated, quality-of-life questionnaire that is designed for use in paediatric patients <4 years old with AD (Lewis-Jones et al. 2001; Basra et al. 2013).

- **Acceptability** and tolerability of the baricitinib tablet and oral suspension were assessed in the PK lead-in period, at baseline (visit 2, after dosing) and after about 2 weeks of dosing (visit 4). Tablet acceptability was assessed using a self-completed questionnaire to assess the study participant's ability to swallow the tablet in patients of 10 years and older, who received tablets in the trial. The questionnaire for suspension acceptability and palatability assessed the study participant's experience of taste and smell of the suspension and ease of administering and taking the suspension [27,28]. The questionnaire was completed by parents or caregivers for children 2 to <10 years of age who received the suspension formulation.

Sample size

For the randomised placebo-controlled period of study **JAIP**, it was aimed to enrol at least 440 patients 2 to <18 years of age; at least n=320 patients (10 to<18 years) and at least n=120 patients (2 to <10 years). The proposed sample size (N=440) will ensure a >95% power to detect any difference between the baricitinib high dose and placebo treatment groups or the baricitinib medium dose and placebo treatment groups, each using a 2-sided alpha of 0.05, assuming a 10% placebo, 25% medium dose, and 30% high dose response rate for the primary endpoint using a chi-squared test. The assumptions are based on the effects in the adult phase 2 study (JAHG) for the primary endpoint of IGA 0 or 1at week 16. IGA 0 or 1 represents an AD outcome of clear or almost clear skin, coming from a baseline of moderate or severe disease. The anticipated effect size represents 3 times more patients achieving this benefit compared to placebo.

In older paediatric patients (≥10 years of age), the sample size of 320 is sufficient to detect that the baricitinib high or medium dose is superior to placebo at least 80% of the time.

Sample size estimates were calculated using nQuery® Advisor 7.0 for the older subgroup of patients, and power estimates were obtained from R 3.5.0 and JAGS 4.2.0 for the younger subgroup of patients.

Randomisation

For the randomised placebo-controlled part of the study (Period 3), assignment to treatment groups was determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS was used to assign blister packs or bottles containing double-blind investigational product to each patient. Site personnel had to confirm that the correct blister packs or bottles were located, by entering a confirmation number found on the blister packs or bottles into the IWRS.

Randomisation was stratified by disease severity at baseline (IGA 3 versus 4) and by region.

[27] Davies, E. H., & Tuleu, C. (2008). Medicines for children: a matter of taste. *The Journal of pediatrics*, *153*(5), 599–604.e6042. https://doi.org/10.1016/j.jpeds.2008.06.030

[28] Kozarewicz P. (2014). Regulatory perspectives on acceptability testing of dosage forms in children. *International journal of pharmaceutics*, *469*(2), 245–248. https://doi.org/10.1016/j.ijpharm.2014.03.057

Blinding (masking)

The experimental treatment was provided to the patient/caregivers by the investigator. For patients 10 to <18 years old, the double-blind investigational product included 3 tablets per day provided in blister packs. Each tablet (4-mg versus 2-mg versus 1-mg) has a distinctive shape and colour, and each strength tablet has a matching placebo. For patients 2 to <10 years old, baricitinib oral suspension (containing 2-mg/mL baricitinib) or matching placebo was supplied as a ready-to-use oral suspension in a bottle to be administered using an oral syringe.

Statistical methods

Efficacy analyses

The tests of treatment effects were generally conducted at a 2-sided alpha level of 0.05.

Treatment comparisons between baricitinib and placebo of discrete efficacy variables, including the primary outcome, were made using logistic regression analysis with region, disease severity, age, treatment group, and treatment group-by-age interaction in the model. The percentages, difference in percentages, and 95% confidence interval (CI) of the difference in percentages were reported. Treatment-by-age interaction was added to the logistic regression model of the primary and key secondary variables as a sensitivity analysis. If this interaction is significant at a 2-sided 0.1 level, further inspection was used to assess whether the interaction is quantitative (i.e., the treatment effect is consistent in direction but not size of effect) or qualitative (the treatment is beneficial for some but not all age groups). The p-value from the Fisher exact test will also be produced.

For analysing treatment effects of continuous outcomes over time, a restricted maximum likelihood-based mixed-effects model of repeated measures (MMRM) was used. The model included treatment, age cohort, region, baseline severity, visit, and treatment-by-visit interaction, and treatment-by-age cohort interaction as fixed categorical effects and baseline score and baseline score-by-visit interaction as fixed continuous effects. An unstructured (co)variance structure will be used to model the between- and within-patient errors. If this analysis fails to converge, other structures were tested. The Kenward–Roger method was used to estimate the degrees of freedom. Type III sums of squares for the least squares means (LSMs) was used for the statistical comparison; 95% CI were also reported. Contrasts were set up within the model to test treatment groups at specific time points of interest.

Treatment comparisons of continuous efficacy and health outcome variables could also be made using analysis of covariance (ANCOVA) with region, disease severity, treatment group, and baseline value in the model. Type III tests for LSM were used for statistical comparison between treatment groups. The LSM difference, standard error, p-value, and 95% CI were reported.

Safety analyses

Fisher's exact test was used for the AEs, discontinuation, and other categorical safety data for between-treatment group comparisons. Continuous vital signs, body weight, and other continuous safety variables, including laboratory variables, were analysed by an ANCOVA with treatment and baseline value in the model.

Missing data imputation

1. Non-responder imputation (NRI) was used for all patients who discontinued the study or the study treatment at any time for any reason for analysis for categorical variables such as IGA 0/1 or EASI 50/75/90 after discontinuation and onward.

2. Continuous variables such as EASI and SCORAD scores were assumed to be missing after rescue or discontinuation, and then an MMRM analysis was performed.

3. Last observed carried forward (LOCF) was performed, using the last observed value on or prior to discontinuation or rescue therapy. This was analysed using a logistic model for categorical variables or ANCOVA for continuous variables, as described above.

Censoring

The efficacy analyses used 3 prespecified censoring rules:

- Primary censoring
  - o censored efficacy data after rescue
  - o censored efficacy data after permanent discontinuation of the study treatment
- Secondary censoring
  - o did not censor efficacy data after rescue
  - o censored efficacy data after permanent discontinuation of the study treatment
- Tertiary censoring
  - o censored efficacy data after any using any medication considered rescue medication even if not used for AD rescue (e.g., oral prednisone used for allergic reaction).
  - o censored efficacy data after permanent discontinuation of the study treatment.

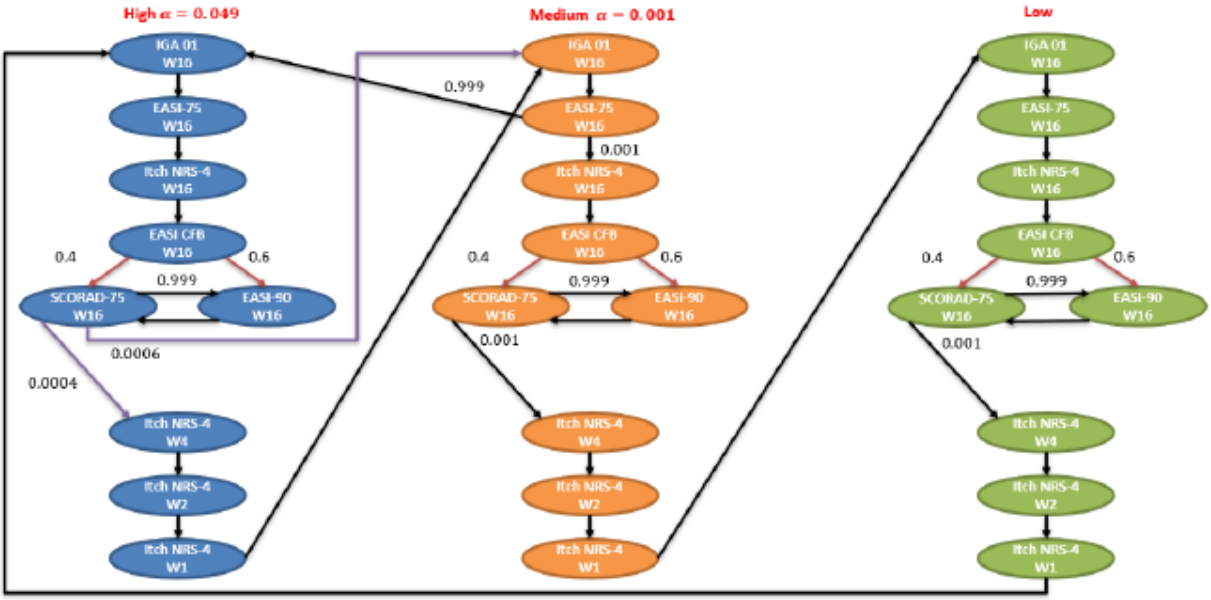
All efficacy endpoints were analysed using the primary censoring rule. The secondary censoring rule was applied to primary and key secondary efficacy endpoints as a sensitivity analysis. The tertiary censoring rule was used as an additional sensitivity analysis and was applied to selected primary and secondary categorial endpoints (IGA 0/1, EASI75, SCORAD75, Itch NRS 4-pointreduction).

Adjustment for Multiple Comparisons

Multiplicity controlled analyses were performed on the primary and key secondary endpoints to control the overall family-wise Type I error rate at a 2-sided α level of 0.05, using a graphical multiple testing procedure[29]. For the primary objective, the alpha was split, with baricitinib high dose receiving 0.049 and baricitinib medium dose receiving 0.001 to start, and baricitinib low dose receiving recycled alpha based on prior results in the testing scheme. This procedure made no multiplicity adjustments for other secondary endpoints.

Figure 6. Multiplicity-adjusted testing scheme for primary and key secondary endpoints

[29] Bretz, F., Posch, M., Glimm, E., Klinglmueller, F., Maurer, W., & Rohmeyer, K. (2011). Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests. *Biometrical journal. Biometrische Zeitschrift*, *53*(6), 894–913. https://doi.org/10.1002/bimj.201000239



Abbreviations: CFB = change from baseline; EASI = Eczema Area and Severity Index; EASI-75/-90 = at least 75%/90% improvement from baseline in Eczema Area and Severity Index; IGA = Investigator's Global Assessment; NRS= numeric rating scale; SCORAD = SCORing Atopic Dermatitis; SCORAD-75 = at least 75% improvement from baseline in SCORing Atopic Dermatitis; W =week.

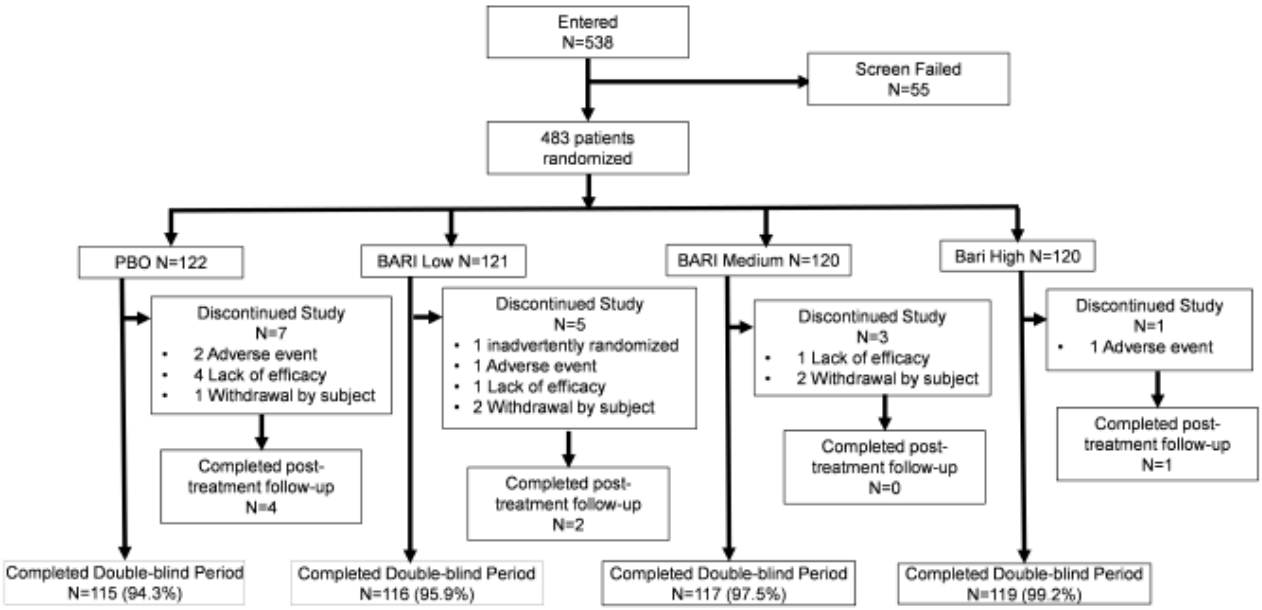
Results

Participant flow

ITT population

For the randomised placebo-controlled part of the study (Period 3), 538 potential study participants were screened, and 483 were randomised to investigational treatment (Figure 7). (One participant allocated to baricitinib low-dose was inadvertently randomised and discontinued from the study prior to the first dose.) The participants were equally divided into four treatment groups: high dose, medium dose, low dose, and placebo.

Figure 7. Participant flow in the randomised placebo-controlled part of study JAIP



Abbreviation: N = number of participants in the analysis population.

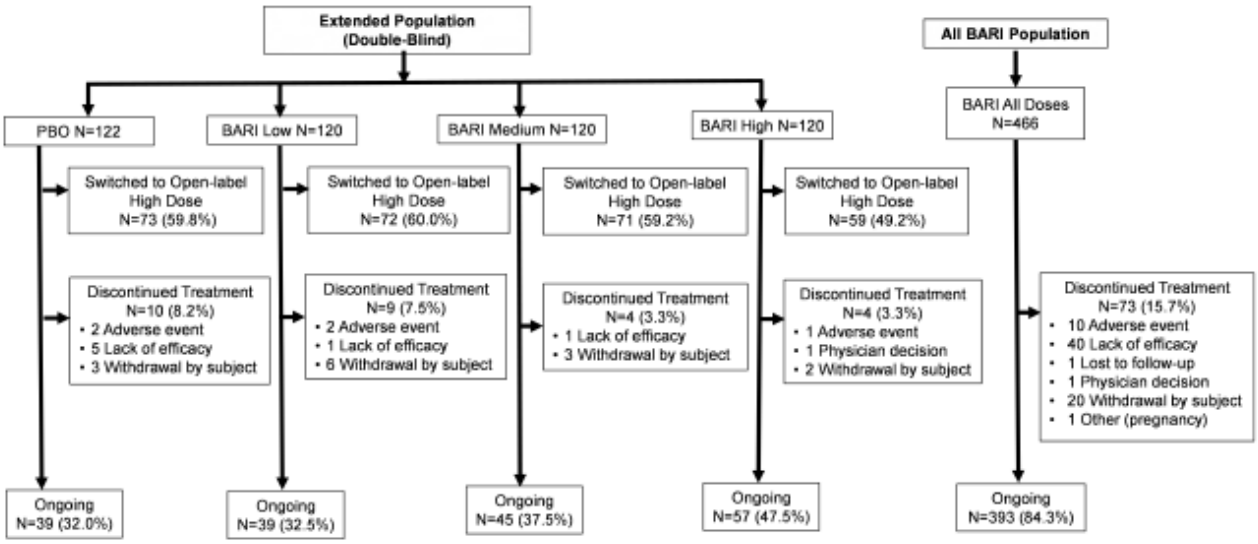
The completion rates range from 94% in the placebo group to 99% in the high-dose group. In the high-dose group, there was one withdrawal due to an AE; in the placebo group there were most (n=4) withdrawals due to lack of efficacy. Of the 16 study discontinuations, 6 were in patients <10 years old, spread over treatment groups. The numbers of treatment discontinuations by treatment group before end of the randomised phase (week 16), without discontinuing the study, were not reported.

Extended population

Patients who had at least some response (IGA 0, 1 or 2) at week 16, continued on their allocated treatment (high dose, medium dose, low dose, placebo). Patients with an insufficient response or with rescue treatment switched to open-label treatment with baricitinib high dose. At the interim data cut-off (20 June 2022), 48% of participants randomly assigned to high dose were ongoing on their initial treatment, compared with 38% for medium dose, 33% for low dose, and 32% for placebo (Figure 8).

Among participants in the Extended population, a lower proportion of participants randomly assigned to baricitinib high dose (3.3%) and medium dose (3.3%) discontinued study treatment compared with low dose (7.5%) and placebo (8.2%).

Figure 8. Participant flow following the randomised placebo-controlled part of study JAIP



Abbreviations: BARI = baricitinib; N = number of participants in the analysis population; PBO = placebo.

Recruitment

Enrolment in study JAIP started on 24 May 2019 (first patient first visit) and was completed for the randomised part on 24 April 2022 (last patient last visit). The extension study is still ongoing and will continue for 4 years.

Of the 483 patients enrolled in the placebo-controlled part of the study, 38% were recruited in European centers (Austria, Czech Republic, France, Germany, Hungary, Poland, Russia, Spain, United Kingdom), 7.8% were recruited in Japan, and 55% in the rest-of-the world (Australia, India, Israel, Taiwan, Argentina, Brazil and Mexico).

Conduct of the study

Protocol changes

The initial protocol was approved in September 2018 and changed two times: on 12 June 2019 (version a) and 6 August 2020 (version b). The main changes in version a were: instead of monotherapy of experimental treatment on top of emollients, low- and medium-potency TCS would additionally be used as background treatment in study periods 3 and 4; instead of needing IGA 0 or 1 to remain on the interventional treatment from period 3 in period 4 a IGA 0,1 or 2 would qualify. The main changes in version b were: the addition of knee imaging and increased frequency of hand x-ray requirements for monitoring bone growth, and clarification of assessment of any symptomatic areas of bones/joints were included based on regulatory feedback. The duration of the long-term follow-up study was extended from 2 years to 4 years.

Protocol violations

Among study participants randomised in the double-blind treatment period, 98 (20%) participants had at least 1 important protocol deviation. There were 29 participants with eligibility violations, most often body weight below 5th percentile of age (n=11) and missing laboratory data prior to randomisation (n=12). There were 18 violations concerning investigational product: incorrect randomisation (n=1) and significant non-compliance (n=17). There was 1 safety violation, a SAE was not reported <24

hours. There were 63 violations concerning study procedures, most often missing baseline values of imaging procedures (n=23), missing DFI questionnaire by caregivers (n=32), e-diary non-compliance (n=11).

Impact of COVID-19

Study enrolment was delayed due to the COVID-19 pandemic. Prior to the primary endpoint at week 16, disruptions due to COVID-19 were primarily delayed visits or the need for telephone visits resulting in missing procedures. No participants discontinued from the study due to a COVID-19 infection or had to be excluded from the PP set due to COVID-19 induced protocol violations.

Inspections and audits

GCP audits have been performed by the sponsor in 4 centers (in Taiwan, Poland, Russia, Japan). It was not declared whether or not GCP inspections have been performed.

Baseline data

At baseline of the placebo-controlled period, demographic characteristics (age, sex, Caucasian-ness, height and weight, region), time since AD diagnosis, and baseline disease severity (IGA, EASI, BSA, Itch) were numerically equal across the 4 treatment groups (Table 8). In the youngest age group (2 to <10 years of age), there were n=34 patients randomised to placebo and n=32 to the 'high dose'. In the oldest age group (10 to <18 years of age), there were n=88 patients randomised to placebo and n=88 to the 'high dose'.

Also when stratified by age (2 to <10 years and 10 to <18 years), baseline variables were similar over treatment groups.

A small majority of participants (62%) had an IGA score of 3, while the others (38%) had an IGA of 4. The mean (SD) EASI score was 26 (9.7), BSA affected was 41% (18%), and Itch NRS was 5.4 (2.6).

The most common pre-existing disorders were allergic rhinitis (41%), food allergy (33%), hypersensitivity (30%), asthma (28%), seasonal allergy (23%), drug hypersensitivity (20%), and allergic conjunctivitis (13%), equally divided over treatment groups.

Table 8. Baseline characteristics of the placebo-controlled period of study JAIP

Attribute	PBO N = 122	BARI Low Dose N = 121	BARI Medium Dose N = 120	BARI High Dose N = 120
Age (years), mean (SD)	11.8 (4.01)	12.4 (4.05)	11.8 (3.66)	11.9 (3.83)
Female, n (%)	64 (52.5)	62 (51.2)	63 (52.5)	53 (44.2)
Male, n (%)	58 (47.5)	59 (48.8)	57 (47.5)	67 (55.8)
Race				
White, n (%)	94 (77.0)	94 (77.7)	93 (77.5)	88 (73.3)
Height percentile (SD)	46.2 (29.95)	47.2 (27.51)	46.8 (30.31)	51.2 (29.26)
Weight percentile (SD)	58.8 (31.94)	57.1 (31.23)	56.1 (30.14)	66.4 (28.46)
BMI percentile (SD)	63.4 (30.65)	60.3 (32.09)	61.4 (28.34)	70.0 (26.38)
Duration since AD diagnosis (years), mean (SD)	9.2 (4.35)	9.8 (5.07)	9.4 (4.15)	9.0 (4.08)
Geographic region				
Europe	46 (37.7)	46 (38.0)	43 (35.8)	46 (38.3)
Japan	9 (7.4)	10 (8.3)	10 (8.3)	9 (7.5)
Rest of World	67 (54.9)	65 (53.7)	67 (55.8)	65 (54.2)
IGA Score				
IGA = 3	74 (60.7)	75 (62.5)	74 (61.7)	75 (62.5)
IGA = 4	48 (39.3)	45 (37.5)	46 (38.3)	45 (37.5)
EASI, mean (SD)	26.99 (10.290)	26.59 (9.955)	26.78 (9.025)	25.31 (9.466)
BSA, mean (SD)	41.28 (19.067)	42.38 (19.492)	41.16 (16.846)	40.37 (17.729)
Itch NRS in participants 10 to <18 years old, mean (SD)	4.86 (2.512)	5.65 (2.378)	5.65 (2.633)	5.69 (2.661)
PRISM in participants 2 to <10 years old, mean (SD)	3.16 (0.864)	2.88 (0.890)	2.94 (1.097)	2.94 (1.011)

Abbreviations: AD = atopic dermatitis; BSA = body surface area; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; N = number of participants in the analysis population; n = number of participants in the specified category; NRS = numeric rating scale; PRISM = Parent-Reported Itch Severity Measure.

Source: Table JAIP.8.6 and Table JAIP.8.7

Before baseline, virtually all (99%) of patients had used TCS and usually (89%) had an insufficient response, while 2.9% had an intolerance to TCS (Table 9). Most (87%) of the patients had used TCNI, with 83% having an insufficient response and 14% having had an intolerance to TCNI. The 4 patients who did not use TCS before baseline, had used systemic treatments.

Table 9. Treatment history at baseline of the placebo-controlled period of study JAIP

Prior Therapy, n (%)	PBO N = 122	BARI Low Dose N = 121	BARI Medium Dose N = 120	BARI High Dose N = 120	Total N = 483
Topical therapies	**122 (100)**	**121 (100)**	**120 (100)**	**117 (97.5)**	**480 (99.4)**
Topical corticosteroid therapy	122 (100)	119 (98.3)	120 (100)	117 (97.5)	478 (99.0)
Topical calcineurin inhibitor use	98 (80.3)	107 (88.4)	102 (85.0)	104 (86.7)	411 (85.1)
Topical JAK inhibitors	2 (1.6)	0	1 (0.8)	0	3 (0.6)
Topical PDE 4 inhibitors – Crisaborole	0	3 (2.5)	3 (2.5)	2 (1.7)	8 (1.7)
Systemic therapies	**53 (43.4)**	**47 (38.8)**	**56 (46.7)**	**49 (40.8)**	**205 (42.4)**
Systemic JAK inhibitors	0	0	0	0	0
Systemic corticosteroids	30 (24.6)	31 (25.6)	33 (27.5)	29 (24.2)	123 (25.5)
Systemic immunosuppressants	28 (23.0)	21 (17.4)	27 (22.5)	29 (24.2)	105 (21.7)
Ciclosporin	14 (11.5)	12 (9.9)	16 (13.3)	22 (18.3)	64 (13.3)
Methotrexate	16 (13.1)	11 (9.1)	13 (10.8)	13 (10.8)	53 (11.0)
Azathioprine	2 (1.6)	0	2 (1.7)	1 (0.8)	5 (1.0)
Mycophenolic acid	1 (0.8)	0	1 (0.8)	0	2 (0.4)
Calcineurin inhibitors	0	0	0	1 (0.8)	1 (0.2)
Immunotherapy	1 (0.8)	0	1 (0.8)	0	2 (0.4)
Phototherapy	**7 (5.7)**	**11 (9.1)**	**10 (8.3)**	**8 (6.7)**	**36 (7.5)**
Biologic therapies	**2 (1.6)**	**3 (2.5)**	**3 (2.5)**	**2 (1.7)**	**10 (2.1)**
Dupilumab	2 (1.6)	2 (1.7)	3 (2.5)	2 (1.7)	9 (1.9)
Nemolizumab	0	1 (0.8)	0	0	1 (0.2)

Abbreviations: JAK = Janus kinase; N = number of participants in the analysis population; n = number of participants in the specified category; PDE = phosphodiesterase.

Source: Table JAIP.8.12

Numbers analysed

In the ITT population of the placebo-controlled study, N=483 participants were included; with n=133 participants (28%) of 2 to <10 years and n=350 participants of 10 to <18 years. In the PP set, N=462 participants were included due to not having any important protocol violation, n=21 participants were excluded from the PP set (n=4 on placebo, n=7 on low dose, n=6 on medium dose, n=4 on high dose).

There were N=7 patients entering the 4 week follow-up period (Period 5), while they did not enter the long term extension study.

Exposure, compliance, and rescue

Exposure

In the 16 weeks placebo-controlled period (112 days), the exposure was similar across the baricitinib treatment groups (~114 days) and on average 2 days less in the placebo group (Table 10).

Table 10. Exposure by treatment group in the placebo-controlled period of study JAIP

All Study Participants	PBO N = 122	BARI Low Dose N = 120	BARI Medium Dose N = 120	BARI High Dose N = 120
Mean days of exposure (SD)	110.4 (16.00)	113.6 (11.49)	113.5 (10.84)	113.7 (6.52)
Total patient-years	36.87	37.33	37.30	37.37
10 to <18 years	**N = 88**	**N = 87**	**N = 86**	**N = 88**
Mean days of exposure (SD)	109.1 (18.34)	113.2 (11.65)	114.5 (7.84)	114.3 (3.25)
Total patient-years	26.29	26.97	26.96	27.54
2 to <10 years	**N = 34**	**N = 33**	**N = 34**	**N = 32**
Mean days of exposure (SD)	113.7 (6.06)	114.7 (11.17)	111.1 (16.03)	112.2 (11.41)
Total patient-years	10.58	10.37	10.34	9.83

Abbreviation: N = number of participants in the analysis population.
Source: Table JAIP.8.16, Table JAIP.8.17, and Table JAIP.8.18

Compliance

Compliance that was less than 80% of the treatment regimen over the placebo-controlled period (0-16 weeks) was defined as non-compliance. Overall, treatment compliance was >95%. The proportions of patients with non-compliance was 2.3% in the placebo group (tablets only, compliance to placebo solution not given), 5.0% in the low dose group, and 3.3% in each of the medium dose and high dose groups.

Rescue

During the placebo-controlled period, there were 10 (8.2%) patients who got rescue therapy in the placebo group, as compared to 7 (5.8%) patients in the low dose group, 3 (2.5%) in the medium dose group, and 4 (3.3%) in the high dose group. Six patients were rescued within 2 weeks, 2 of them in the placebo group, 2 in the low dose group, and 1 in each of the medium dose and high dose groups.

Outcomes and estimation

Graphical testing procedure

Within the framework of the graphical testing procedure, treatment effects of baricitinib high dose were statistical significantly different as compared with placebo, on all 16-week key efficacy endpoints as well as the Itch NRS 4-point improvement at 4 weeks (Figure 9). Treatment effects of the baricitinib medium and low doses versus placebo, were not statistically significant on any of the study endpoints.

Figure 9. Results of the graphical testing procedure showing nominal p-values for all endpoints included in the procedure

Abbreviations: CFB = change from baseline; EASI = Eczema Area and Severity Index; EASI-75/-90 = at least 75%/90% improvement from baseline in Eczema Area and Severity Index; IGA = Investigator's Global Assessment; NRS= numeric rating scale; SCORAD = SCORing Atopic Dermatitis; SCORAD-75 = at least 75% improvement from baseline in SCORing Atopic Dermatitis; W =week.

Primary endpoint

At week 16, the proportion of patients with IGA 0 or 1 was 42% in the high dose (4 mg equivalent) group, as compared to 16% in the placebo group (p<0.0001) in the ITT population (Table 11). Treatment effects in the medium and low-dose groups were not statistically significantly different from the placebo group. In the medium dose group, there were 26% patients with IGA 0 or 1 (p=0.072), and in the low dose group, there were 18% (p=0.73) responders with IGA 0 or 1.

Table 11. IGA 0 or 1 with a ≥2 point improvement at week 16 (primary outcome) in the placebo-controlled phase of study JAIP

	PBO N = 122	BARI Low Dose N = 121	BARI Medium Dose N = 120	BARI High Dose N = 120
Response, n (%)	20 (16.4)	22 (18.2)	31 (25.8)	50 (41.7)
Difference vs. PBO (95% CI)	N/A	1.8 (-7.8, 11.4)	9.4 (-0.9, 19.6)	25.3 (13.9, 35.8)
p-Value	N/A	0.7261	0.0718	<0.0001

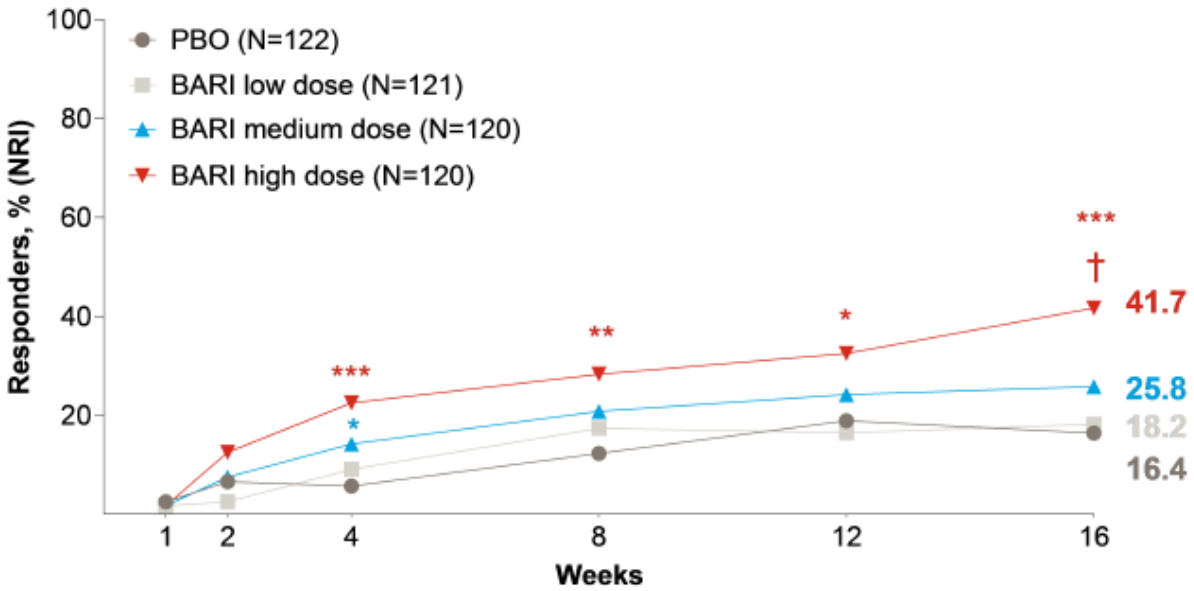
Abbreviations: IGA = Investigator's Global Assessment; N/A = not applicable; N = number of participants in the analysis population; n = number of participants in the specified category.

Source: Table JAIP.8.20

In the 4 planned sensitivity analyses, the treatment effect in IGA 0 or 1 of the high dose as compared to placebo remained statistically significant: in the ITT population with secondary censoring and non-responder imputation (p<0.0001); the ITT population with tertiary censoring and non-responder imputation (p<0.0001); the PP-set with primary censoring and non-responder imputation (p<0.0001); in the IIT population with primary censoring and placebo multiple imputation (p=0.001).

Over time, from baseline to week 16, the treatment effects in the high dose group were larger than in the medium dose group and the low dose and placebo groups (Figure 10).

Figure 10. IGA 0 or 1 with a ⩾2 point improvement from baseline to week 16, in the placebo-controlled phase of study JAIP



Abbreviations: BARI = baricitinib; IGA = Investigator's Global Assessment; N = number of participants in the analysis population; NRI = nonresponder imputation; PBO = placebo.
*p<.05.
**p<.01.
***p<.001 vs. PBO (nominal p-value; logistic regression analysis).
†Statistically significant with multiplicity adjustment.

Key secondary outcomes

At week 16, there was a (multiplicity adjusted) statistically significant treatment effect of baricitinib high dose (4 mg equivalent), as compared to placebo, in EASI75, EASI90, SCORAD75, EASI change from baseline, and Itch NRS ≥4 points improvement (Table 12).

Table 12. Primary and key secondary endpoints at week 16 in the placebo-controlled phase of study JAIP

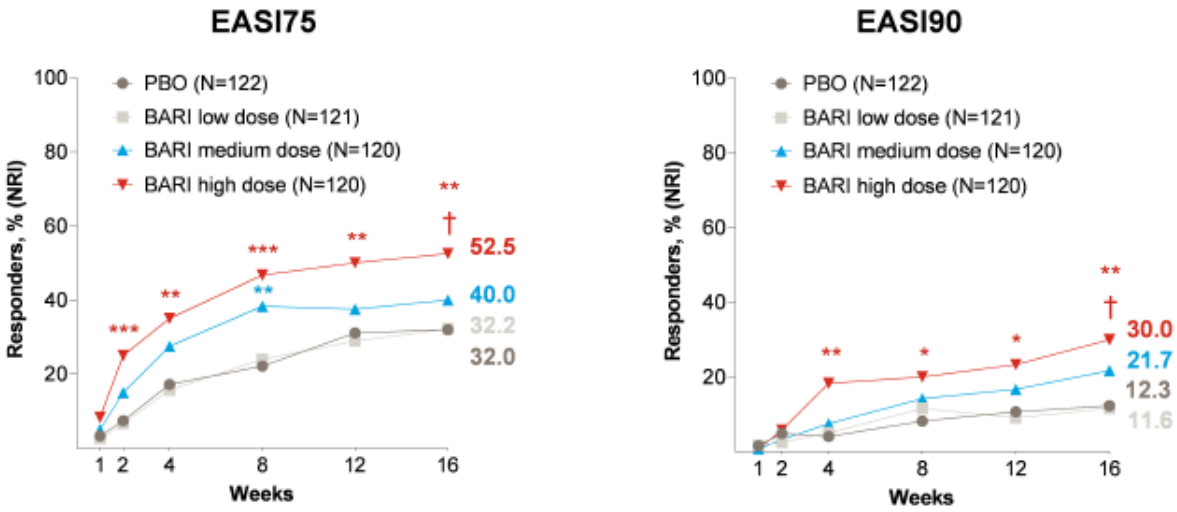
Endpoints at Week 16	PBO N = 122	BARI Low Dose N = 121	BARI Medium Dose N = 120	BARI High Dose N = 120
Primary endpoint				
IGA 0/1, n (%) (95% CI)	20 (16.4) (10.9, 24.0)	22 (18.2) (12.3, 26.0)	31 (25.8) (18.8, 34.3)	50 (41.7)*** (33.2, 50.6)
Key secondary endpoints				
EASI75, n (%) (95% CI)	39 (32.0) (24.4, 40.7)	39 (32.2) (24.6, 41.0)	48 (40.0) (31.7, 48.9)	63 (52.5)** (43.6, 61.2)
EASI90, n (%) (95% CI)	15 (12.3) (7.6, 19.3)	14 (11.6) (7.0, 18.5)	26 (21.7) (15.2, 29.9)	36 (30.0)** (22.5, 38.7)
SCORAD75, n (%) (95% CI)	12 (9.8) (5.7, 16.4)	9 (7.4) (4.0, 13.5)	19 (15.8) (10.4, 23.4)	24 (20.0)* (13.8, 28.0)
EASI change from baseline Least-squares mean change (SE)	-14.16 (1.001)	-15.67 (0.990)	-15.83 (0.978)	-16.88 (0.984)*
Itch ≥4-point improvement in participants 10 to <18 years old n/N (%) (95% CI)	9/55 (16.4) (8.9, 28.3)	11/63 (17.5) (10.0, 28.6)	16/62 (25.8) (16.6, 37.9)	22/62 (35.5)* (24.7, 47.9)

Abbreviations: BARI = baricitinib; CI = confidence interval; EASI = Eczema Area and Severity Index; EASI90 = 90% improvement from baseline in EASI; IGA = Investigator's Global Assessment; n = number of participants in the specified category; N = number of participants in the analysis population; PBO = placebo; PDE = phosphodiesterase; SCORAD75 = 75% improvement from baseline in SCORAD; SE = standard error.

Note: * = p<.05; ** = p<.01; *** = p<.001 vs. PBO (nominal p-value; logistic regression analysis).

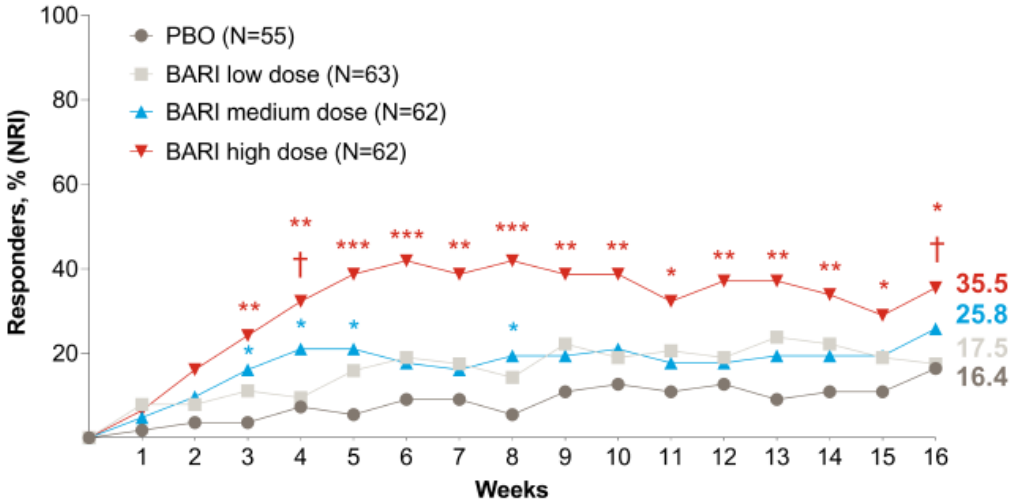
Over time, from baseline to week 16, the proportions of responders in **EASI75, EASI90** (Figure 11) and **SCORAD75** (not shown) in the high dose group were higher than the responses in the medium, low dose and placebo groups. At week 4, the difference in ≥4 points improvement in **Itch NRS** was (multiplicity adjusted) statistically significant (p=0.0026), with 7.3% in the placebo group and 32% in the high dose group (Figure 12). The results of the pre-planned sensitivity analyses of the key secondary outcomes (EASI75, EASI90, SCORAD75, change in EASI, Itch NRS response≥4) were in line with the results from the primary analyses.

Figure 11. EASI75 and EASI90, from baseline to week 16in the placebo-controlled phase of study JAIP



Abbreviations: BARI = baricitinib; EASI = Eczema Area and Severity Index; EASI75/90 = 75%/90% improvement from baseline in EASI score; N = number of participants in the analysis population; NRI = nonresponder imputation; PBO = placebo.
*p<.05.
**p<.01.
***p<.001 vs. PBO (nominal p-value; logistic regression analysis).
†Statistically significant with multiplicity adjustment.

Figure 12. Itch NRS improvement ≥4 points in patients ≥10 years, from baseline to week 16 in the placebo-controlled phase of study JAIP



Abbreviations: BARI = baricitinib; N = number of participants in the analysis population; NRI = nonresponder imputation; NRS = numeric rating scale; PBO = placebo.
[a]Patients aged ≥10 years with baseline Itch NRS Score ≥4 points.
*p<.05.
**p<.01.
***p<.001 vs. PBO (nominal p-value; logistic regression analysis).
†Statistically significant with multiplicity adjustment.

Other secondary outcomes

The other secondary outcomes were not adjusted for multiplicity.

The mean change in **%BSA affected** was statistically significantly (p=0.014) larger in the 'high dose' group with -26% as compared to placebo with -20%. The BSA is integrated in the EASI.

The **PRISM** is a single-item, parent- or caregiver-administered scale to rate the overall severity of their child's itching, completed for participants <10 years old. At week 16, the LS mean (SE) change from baseline in PRISM score was -0.28 (0.16) in the high dose group and 0.02 (0.15) in the placebo group (p=0.12). At week 16, the mean (SE) change in the medium dose group was -0.44 (p=0.015) and -0.19 (p=0.27) in the low dose group.

At week 16, 3 (2.5%) of patients on 'high dose' had skin infections requiring antibiotic treatment versus 7 (5.7%) on placebo, which was not a statistically significant (p=0.30) difference.

TCS use, calculated as the median (P25 – P75) number of days that TCS was not used during the 16 weeks (112 days) of the placebo-controlled period, was 11 (1 – 55) days in the placebo group, and 25 (2 – 78) in the high dose group (p=0.16, based on parametric testing). TCS use was also calculated as the amount of drug used during the placebo-controlled period. The median difference in TCS use for baricitinib high dose versus placebo was -82 gr (p=0.014), mainly due to a reduction in medium-potency corticosteroids in the high dose group.

The **POEM** is a 7-item, participant-reported scale (0-28) to assess symptom severity. At baseline, the mean (SD) POEM score was 14 (6.8) in the placebo group and 15 (6.9) in the baricitinib high dose group. At week 16, the mean (SD) change from baseline in POEM was -3.6 (7.5) in the placebo group, as compared to – 5.3 (8.4) in the baricitinib high dose group (p=0.0496).

The **IDQOL and CDLQI** are, respectively caregiver reported and self-reported questionnaires to assess the impact on the patient's daily living due to skin disorders. There were no statistically significant differences in change from baseline for the PROMIS depression and anxiety subscales between placebo and baricitinib high dose.

The **PROMIS** has a subscale for depression and for anxiety and is self-completed or by care-givers. There were no statistically significant differences in change from baseline for the PROMIS depression and anxiety subscales, between placebo and baricitinib high dose.

Maintenance

Patients with at least some response (IGA 0, 1 or 2) at week 16 of the placebo-controlled randomised period, continued on the treatment they were originally allocated to (Table 13). More patients from the high dose group continued on their original dose (n=81) as compared to the lower dose groups and placebo (n=57). At week 20 the proportion of responders (IGA 0 or 1) was 43% in the placebo group, and 51% in the high dose group. At week 52 the proportion of responders was 40% in the placebo group and 47% in the high dose group. Similar trends were seen when analysing EASI-75.

The non-responders (IGA 3 or 4) at week 16 who were originally allocated to high dose, remained on high dose while being transferred to the open-label phase. Of these non-responding patients, no (0/38) patients had a response at week 20, 8% had a response (IGA 0 or 1) at week 24, and 17% at week 52.

Table 13. IGA 0 or 1 at weeks 20 to 52, in patients with at least some response (IGA 0, 1 or 2) at week 16 in the placebo-controlled phase of study JAIP

	PBO N = 58	BARI Low Dose N = 65	BARI Medium Dose N = 64	BARI High Dose N = 81
Results using NRI				
Week 16 (NRI)				
Response, n (%)	20 (34.5)	22 (33.8)	31 (48.4)	51 (63.0)
(95% CI)	(23.6, 47.3)	(23.5, 46.0)	(36.6, 60.4)	(52.1, 72.7)
Week 20 (NRI)				
Response, n (%)	25 (43.1)	29 (44.6)	28 (43.8)	41 (50.6)
(95% CI)	(31.2, 55.9)	(33.2, 56.7)	(32.3, 55.9)	(40.0, 61.2)
Week 24 (NRI)				
Response, n (%)	29 (50.0)	29 (44.6)	30 (46.9)	46 (56.8)
(95% CI)	(37.5, 62.5)	(33.2, 56.7)	(35.2, 58.9)	(45.9, 67.0)
Week 28 (NRI)				
Response, n (%)	28 (48.3)	25 (38.5)	25 (39.1)	44 (54.3)
(95% CI)	(35.9, 60.8)	(27.6, 50.6)	(28.1, 51.3)	(43.5, 64.7)
Week 40 (NRI)				
Response, n (%)	22 (37.9)	24 (36.9)	20 (31.3)	41 (50.6)
(95% CI)	(26.6, 50.8)	(26.2, 49.1)	(21.2, 43.4)	(40.0, 61.2)
Week 52 (NRI)				
Response, n (%)	23 (39.7)	25 (38.5)	23 (35.9)	38 (46.9)
(95% CI)	(28.1, 52.5)	(27.6, 50.6)	(25.3, 48.2)	(36.4, 57.7)

Abbreviations: IGA = Investigator's Global Assessment; ITT = intent-to-treat; mLOCF = modified last observation carried forward; n = number of participants in the specified category; N = number of participants in the analysis population; NRI = nonresponder imputation.
Source: Table 7.1 and Table 7.2

Ancillary analyses

Subgroups

The predefined subgroup analysis using the IGA 0 or 1 at week 16 (primary outcome) as an endpoint, showed that none of the interaction terms were statistically significant ($p<0.10$); (Table 14). Also, when EASI75 at week 16 was used as an endpoint, none of the interaction terms were significant ($p<0.10$), which includes age.

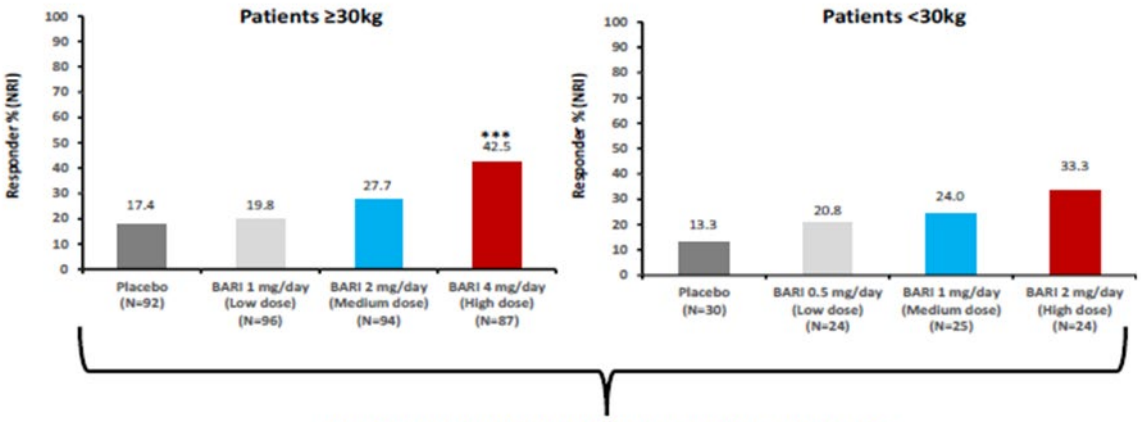
Table 14. Subgroup analysis of IGA 0 or 1 at week 16 in the placebo-controlled phase of study JAIP

Subgroup	Categories	Treatment/Subgroup Interaction p-Value
Age (years)	<10, ≥10	.9264
	2 to <6, 6 to <10, 10 to <18	.7630
Baseline weight (kg)	<20, ≥20 to <60, ≥60	.3610
Geographic region	Europe, Japan, Rest of World	.7654
Geographic region	Europe, Other	.9807
Geographic region	Japan, Other	.3883
Prior inadequate response to TCNI	Yes, No	.2556
Prior intolerance to TCNI	Yes, No	.3253
Prior inadequate response to TCS	Yes, No	.5266
Prior intolerance to TCS	Yes, No	.6406
Prior use of systemic therapy	Yes, No	.3525
Baseline disease severity	3, 4	.3857
Other atopic conditions	Yes, No	.1436

Abbreviations: IGA = Investigator's Global Assessment; TCNI = topical calcineurin inhibitor; TCS = topical corticosteroids.

Dose was stratified by age (cut-off 10 years) in the trial, but the MAH proposed a weight-based (cut-off 30 kg) dose stratification for the SmPC. The treatment effect in IGA 0 or 1 in the high dose group, as compared to placebo, was numerically smaller in children weighing 30 kg who were on 2 mg, as compared to children and adolescents weighing ≥30kg who were on 4 mg (Figure 13). In both weight groups there was a visible dose-response relationship.

Figure 13. IGA 0 or 1 at week 16, stratified by weight group, in the placebo-controlled phase of study JAIP



[a]Treatment-by-weight subgroup interaction term: P=0.9535

Abbreviations: IGA = Investigator's Global Assessment; N = number of participants in the analysis population; NRI = nonresponder imputation.

[a] Logistic regression analysis.

*** p<0.001 vs. PBO (nominal p-value, Fisher's exact test).

Acceptability and palatability

Acceptability and tolerability of the baricitinib tablet and oral suspension were assessed in the PK lead-in period, at baseline (visit 2, after dosing) and after about 2 weeks of dosing (visit 4).

For participants in the PK lead-in period 10 years of age and older who received tablets (N=20), the majority of responses (95%) reported that the study medication (4 mg tablet) was 'very easy' to swallow.

For participants in the PK lead-in period <10 years of age who received the oral suspension (N=13), all of the parent or caregiver responses (100%) reported that the study medication was 'easy' or 'very easy' for the parent or caregiver to administer and the participant to take. The majority of parent or caregiver responses (73%) reported that the participant 'liked' or 'liked very much' the taste of the oral suspension whereas 58% reported that the participant 'liked' or' liked very much' the smell of the oral suspension and 42% 'neither liked or disliked' the smell of the oral suspension.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 15. Summary of Efficacy for trial JAIP

Title: A PHASE 3, MULTICENTRE, RANDOMISED, DOUBLE BLIND, PLACEBO CONTROLLED, PARALLEL-GROUP, OUTPATIENT STUDY EVALUATING THE PHARMACOKINETICS, EFFICACY, AND SAFETY OF BARICITINIB IN PAEDIATRIC PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS		
Study Identifier	I4V-MC-JAIP	
Design	Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group, outpatient	
	Screening period (study period 1)	5 weeks
	PK lead-in period (study period 2)	2 weeks
	Double-blind treatment period (study period 3)	16 weeks
	Long-term extension period (study period 4)	Up to 4 years
	Posttreatment follow-up period (study period 5)	4 weeks
Treatment Groups	Study Period 1 • No treatment groups (screening period) Study Period 2: • 2 to <10 years o Baricitinib high dose (2 mg QD) • 10 to <18 years o Baricitinib high dose (4 mg QD) Study Periods 3 and 4: • 2 to <10 years o Baricitinib high dose (2 mg QD) o Baricitinib medium dose (1 mg QD) o Baricitinib low dose (0.5 mg QD) o Placebo QD • 10 to <18 years o Baricitinib high dose (4 mg QD) o Baricitinib medium dose (2 mg QD) o Baricitinib low dose (1 mg QD) o Placebo QD	
Hypothesis	Superiority	

Double-Blind Treatment Period	Baricitinib QD 2 to <10 years, oral suspension 10 to <18 years, tablets		Randomized N: 361 Baricitinib low dose, N = 121 Baricitinib medium dose, N = 120 Baricitinib high dose, N = 120		
	PBO QD 2 to <10 years, oral suspension 10 to <18 years, tablets		Randomized N: 122		
Endpoints **Double-Blind Treatment Period**	Primary endpoint	IGA 0, 1, W16	Proportion of participants with IGA of 0 or 1 with a ≥2-point improvement at Week 16		
	Key secondary endpoint	EASI75, W16	Proportion of participants achieving EASI75 (≥75% reduction from baseline in EASI) at Week 16		
	Key secondary endpoint	EASI90, W16	Percentage of participants achieving EASI90 (≥90% reduction from baseline in EASI) at Week 16		
	Key secondary endpoint	SCORAD75, W16	Proportion of participants achieving SCORAD75 (≥75% reduction from baseline in SCORAD) at Week 16 Weeks		
	Key secondary endpoint	EASI mean change, W16	Mean change in EASI score at Week 16 Weeks		
	Key secondary endpoint	Itch NRS, W1	Proportions of participants achieving a 4-point improvement in Itch NRS at Week 1		
	Key secondary endpoint	Itch NRS, W2	Proportions of participants achieving a 4-point improvement in Itch NRS at Week 2		
	Key secondary endpoint	Itch NRS, W4	Proportions of participants achieving a 4-point improvement in Itch NRS at Week 4		
	Key secondary endpoint	Itch NRS, W16	Proportions of participants achieving a 4-point improvement in Itch NRS at Week 16		
Multiplicity Adjustment	The SAP prespecified a graphical multiple testing procedure for the primary objective and key secondary objectives. This procedure controlled the family-wise type I error rate at a 2-sided alpha level of 0.05				
Database lock	01 June 2022				
Double-Blind Treatment Period– Results and Analysis – IGA 0,1 at Week 16					
Analysis description	**Primary endpoint:** Proportion of participants with IGA of 0 or 1 with a ≥2-point improvement at Week 16				
Statistical model	Logistic regression using NRI in the ITT population[a]				
Descriptive statistics and estimate variability	Treatment Group	PBO	BARI		
			Low Dose	Medium Dose	High Dose
	Number of participants (Nx)	122	121	120	120
	Response, n (%)	20 (16.4)	22 (18.2)	31 (25.8)	50 (41.7)
Effect estimate per comparison	Comparison groups	BARI QD versus PBO			
	Difference vs. PBO (95% CI)	N/A	1.8 (-7.8, 11.4)	9.4 (-0.9, 19.6)	25.3 (13.9, 35.8)
	p-value	N/A	0.7261	0.0718	<0.0001
Double-Blind Treatment Period– Results and Analysis – EASI75 at Week 16					

Analysis description	**Key secondary endpoint:** Percentage of participants achieving EASI75 (≥75% reduction from baseline in EASI) at Week 16				
Statistical model	Logistic regression using NRI in the ITT population				
Descriptive statistics and estimate variability	Treatment group	PBO	BARI		
			Low Dose	Medium Dose	High Dose
	Number of participants (Nx)	122	121	120	120
	Response, n (%)	39 (32.0)	39 (32.2)	48 (40.0)	63 (52.5)
Effect estimate per comparison	Comparison groups	BARI QD versus PBO			
	Difference vs. PBO (95% CI)	N/A	0.3 (-11.3, 11.9)	8.0 (-4.0, 19.8)	20.5 (8.1, 32.1)
	p-value	N/A	0.9615	0.2010	0.0017
Double-Blind Treatment Period– Results and Analysis – EASI90 at Week 16					
Analysis description	**Key secondary endpoint:** Percentage of participants achieving EASI90 (≥90% reduction from baseline in EASI) at Week 16				
Statistical model	Logistic regression using NRI in the ITT population				
Descriptive statistics and estimate variability	Treatment group	PBO	BARI		
			Low Dose	Medium Dose	High Dose
	Number of participants (Nx)	122	121	120	120
	Response, n (%)	15 (12.3)	14 (11.6)	26 (21.7)	36 (30.0)
Effect estimate per comparison	Comparison groups	BARI QD versus PBO			
	Difference vs. PBO (95% CI)	N/A	-0.7 (-9.1, 7.6)	9.4 (-0.1, 18.8)	17.7 (7.5, 27.6)
	p-value	N/A	0.8544	0.0561	0.0012
Double-Blind Treatment Period – Results and Analysis – SCORAD75 at Week 16					
Analysis description	**Key secondary endpoint:** Proportion of participants achieving SCORAD75 (≥75% reduction from baseline in SCORAD) at Week 16				
Statistical model	Logistic regression using NRI in the ITT population				
Descriptive statistics and estimate variability	Treatment group	PBO	BARI		
			Low Dose	Medium Dose	High Dose
	Number of participants (Nx)	122	121	120	120
	Response, n (%)	12 (9.8)	9 (7.4)	19 (15.8)	24 (20.0)
Effect estimate per comparison	Comparison groups	BARI QD versus PBO			
	Difference vs. PBO (95% CI)	N/A	-2.4 (-9.8, 5.0)	6.0 (-2.5, 14.6)	10.2 (1.1, 19.2)
	p-value	N/A	0.4943	0.1677	0.0336
Double-Blind Treatment Period – Mean Change in EASI Score at Week 16					
Analysis description	**Key secondary endpoint:** Mean change in EASI Score at Week 16				

Statistical model	MMRM in the ITT population[b]				
Descriptive statistics and estimate variability	Treatment group	PBO	BARI		
			Low Dose	Medium Dose	High Dose
	Number of participants (Nx)	122	121	120	120
	Least squares mean change (SE)	-14.16 (1.001)	-15.67 (0.990)	-15.83 (0.978)	-16.88 (0.984)
Effect estimate per comparison	Comparison groups	BARI QD versus PBO			
	LSM difference (SE) vs. placebo	N/A	-1.51 (1.349)	-1.67 (1.342)	-2.72 (1.347)
	p-value	N/A	0.2627	0.2135	0.0443
Double-Blind Treatment Period – Results and Analysis – Proportion of Participants Achieving a 4-Point Improvement in Itch NRS for Participants ≥10 Years Old at Weeks 1, 2, 4, and 16					
Analysis description	**Key secondary endpoint:** Proportion of participants achieving a 4-point improvement in Itch NRS for participants ≥10 years old at Weeks 1, 2, 4, and 16				
Statistical model	Logistic regression using NRI in the ITT population				
Descriptive statistics and estimate variability	**Week 1**	Treatment group	PBO	BARI	
				Low Dose	Medium Dose	High Dose
		Number of participants (Nx)	55	63	62	62
		Response, n (%)	1 (1.8)	5 (7.9)	3 (4.8)	4 (6.5)
Effect estimate per comparison		Comparison groups	BARI QD versus PBO			
		Difference vs. PBO (95% CI)	N/A	6.1 (-2.9, 15.6)	3.0 (-5.4, 11.6)	4.6 (-4.1, 13.8)
		p-value	N/A	0.1742	0.3855	0.2736
Descriptive statistics and estimate variability	**Week 2**	Treatment group	PBO	BARI		
				Low Dose	Medium Dose	High Dose
		Number of participants (Nx)	55	63	62	62
		Response, n (%)	2 (3.6)	5 (7.9)	6 (9.7)	10 (16.1)
Effect estimate per comparison		Comparison groups	BARI QD versus PBO			
		Difference vs. PBO (95% CI)	N/A	4.3 (-5.5, 14.0)	6.0 (-4.1, 16.3)	12.5 (1.3, 23.9)
		p-value	N/A	0.3672	0.2194	0.0533
Descriptive statistics and estimate variability	**Week 4**	Treatment group	PBO	BARI		
				Low Dose	Medium Dose	High Dose
		Number of participants (Nx)	55	63	62	62
		Response, n (%)	4 (7.3)	6 (9.5)	13 (21.0)	20 (32.3)
Effect estimate per comparison		Comparison groups	BARI QD versus PBO			
		Difference vs. PBO (95% CI)	N/A	2.3 (-9.0, 12.9)	13.7 (0.7, 26.2)	25.0 (10.6, 38.1)
		p-value	N/A	0.7046	0.0478	0.0026
		Treatment group	PBO	BARI		

Descriptive statistics and estimate variability	**Week 16**			Low Dose	Medium Dose	High Dose
		Number of participants (Nx)	55	63	62	62
		Response, n (%)	9 (16.4)	11 (17.5)	16 (25.8)	22 (35.5)
Effect estimate per comparison		Comparison groups	BARI QD versus PBO			
		Difference vs. PBO (95% CI)	N/A	1.1 (-12.9, 14.5)	9.4 (-5.6, 23.7)	19.1 (3.1, 33.6)
		p-value	N/A	0.8866	0.2316	0.0328

Analyses

aThe study was carried out using an ITT population defined as all randomly assigned participants for the efficacy analyses. The primary efficacy measure was the binary outcome of response defined as an IGA score of 0 or 1 (clear or almost clear) with a ≥2-point improvement at Week 16. Given the sample size and a nonresponder imputation method for missing data, the planned sample size (N = 440 with 1:1:1:1 randomisation) would ensure a >95% power to detect any difference between the baricitinib high dose and placebo groups or the baricitinib medium dose and placebo groups, each using a 2-sided alpha of 0.05, assuming a 10% placebo, 25% medium dose, and 30% high dose response rate for the primary endpoint. Participants who were rescued or discontinued treatment were considered nonresponders. Treatment group comparisons for binary efficacy response measures were analysed using a logistic regression.

bMMRM in the ITT population: continuous secondary measures of efficacy were analysed using MMRM methodology.

Abbreviations: BARI = baricitinib; EASI = Eczema Area and Severity Index; EASI50/75/90 = at least 50%/75%/90% improvement from baseline in Eczema Area and Severity Index; IGA = Investigator's Global Assessment; NRS = Numeric Rating Scale; ITT = intention-to-treat; MMRM = mixed model for repeated measures; N = number of subjects; N/A = not applicable; NRI = nonresponder imputation; PBO = placebo; QD = once daily; SAP = statistical analysis plan; SCORAD = SCORing Atopic Dermatitis; SCORAD75/90 = at least 75%/90% improvement from baseline in SCORing Atopic Dermatitis; SE = standard error; vs = versus; W= week.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical study

Clinical program

The baricitinib clinical development programme for paediatric AD includes one global clinical study (I4V-MC-**JAIP**) for evaluating the PK, efficacy, and safety of baricitinib in paediatric patients 2 to <18 years with moderate-to-severe AD.

No separate dose-response study has been performed. The dosing strategy for the 'high dose' (4 mg equivalent exposure to adults) was assessed using the PK lead-in period of study JAIP, and doses below the 'high dose' were tested in the subsequent randomised controlled period of study JAIP. This strategy had been agreed with PDCO in the PIP. The dosing in the study JAIP was based on an age cut-off of 10 years. Based on the PK results of the study JAIP, the proposed dose recommendations for the SmPC are 2 mg for patients <30 kg and 4 mg if ≥30 kg (see PK discussion).

Study JAIP included a 2-week, open-label PK lead-in period, a 16-week, double-blind treatment period, and an up to 4-year long-term extension period. In the placebo-controlled part of the study JAIP, participants were randomised (1:1:1:1) to placebo, baricitinib low-dose QD, medium-dose QD, or high-dose QD. Accordingly, the daily doses for participants 10 to <18 years old were 4 mg, 2 mg, and 1

mg; the doses for participants 2 to <10 years old were 2 mg, 1 mg, and 0.5 mg. For patients <10 years of age, oral suspension was used, and patients ≥10 years of age were supplied with tablets.

In practice, patients <10 years may also be able to swallow tablets. However, for patients not able to swallow tablets, the oral solution used in the clinical programme is not available. In the X-35-G line extension submission, the MAH demonstrated the bioequivalence of the 2 mg/mL oral solution versus the 4 mg commercial tablet together with the option of tablet dispersion in water for patients who are not able to swallow tablets.

Study design

The basic design elements of study JAIP, including selection strategy for the 'high dose' regimen, the inclusion of a low dose and a moderate baricitinib dose and the use of placebo, the 16 week timing of the placebo-controlled phase, adopting IGA 0 or 1 as the primary outcome, and EASI75, SCORAD75 and Itch NRS as (multiplicity adjusted) key secondary outcomes, allowance for concomitant TCS, the follow-up with an open-label extension phase, was agreed with PDCO as laid down in the PIP and its modification.

Patient population

The selected study population is in line with the target population of *'moderate to severe atopic dermatitis in paediatric patients 2 years of age and older who are candidates for systemic therapy'*. The inclusion criteria follow expectations and were agreed upon with the PDCO as laid down in the PIP. The exclusion criteria are essentially in line with the posology and warnings in section 4.2 of the SmPC.

Endpoints and outcomes

The primary outcome was IGA 0 or 1 at week 16, EASI75 at week 16, and improvement ≥4 points in Itch NRS (patients ≥10 years only) at week 16, were among the secondary outcomes adjusted for multiplicity. The main efficacy outcomes are established assessment instruments for use in AD. These outcomes and the 16-week duration of the trial were also used in the adult trials for moderate-severe AD. The Itch NRS was used in children of 10 years and older, which is endorsed. In younger patients, itch was assessed by the caregiver using the PRISM instrument, which is not fully validated yet and therefore was not considered a key secondary outcome.

Treatment

Background therapy with medium-potency and/or low-potency TCS and topical TCNI was permitted for use on active lesions until lesions were under control. Use of TCS background treatment is acceptable, as this will be close to the practical use that can be envisaged and was agreed by PDCO (EMEA-C-001220-PIP03-16-M01).

Sample size and randomisation

For the randomised placebo-controlled period of study JAIP, it was aimed to enrol at least 440 patients 2 to <18 years of age; at least n=320 patients (10 to <18 years) and at least n=120 patients (2 to <10 years). The sample size estimations were based on the available information of the adult phase 2 trial, which is reasonable. The younger age group may not be large enough for the treatment effects reaching statistical significance within that stratum, but that is considered not needed.

The stratified randomisation procedure methods to preserve blinding were appropriately designed. While baricitinib tablets of 4 mg, 2 mg and 1 mg differ in colour, shape and size, matching placebos were made, and each participant in the placebo-controlled phase took 3 tablets a day. For the oral solution, a matching placebo solution was provided.

Statistical analysis

The approach for statistical analysis is standard and acceptable and is similar to the approach followed in earlier studies (JAHL, JAHM, JAIY, etc.). The primary censoring rule is agreed upon for primary analyses, and the secondary and tertiary rules are sensitivity analyses. The treatment comparisons for the primary secondary outcomes are adjusted for multiple comparisons, which is agreed. However, almost all alpha is spent on the high dose, which assumes an a priori large trust in the efficacy of the high dose over the medium dose and gives a small a priori probability for the medium dose to reach statistical significance (not pursued). A posteriori, the high dose showed larger treatment effects versus placebo, as compared to the medium dose.

Performance

Although important protocol changes have been performed shortly after first-patient-first-visit, regarding including TCS as background treatment and regarding eligibility to the continuation of randomised treatment after week 16 of IGA 0,1 or 2, the influence on overall results is considered minimal. The timing of protocol change b will have caused the missing imaging data at baseline, which consider monitoring of growth and bone safety. The telephone visits performed due to Covid19 did not include the week 16 visit, in which the primary outcome was assessed through physical examination. Therefore, Covid-19 did not appear to have influenced the main results of the study. Among study participants randomised in the double-blind treatment period, 98 (20%) participants had at least 1 important protocol deviation. Most of the important protocol violations concerned missing data, not necessarily of the main outcomes. It is endorsed that not all patients with an important protocol violation are excluded from the PP-set. The MAH informed that 4 routine investigator site audits had been performed, of which summary data were submitted and assessed. There were no audit findings with major consequences for the submitted data. The results of 2 routine inspections of sites in France were not yet available.

Similarity at baseline

At baseline of the placebo-controlled period, demographic characteristics (age, sex, Caucasian-ness, height and weight, region), time since AD diagnosis, and baseline disease severity (IGA, EASI, BSA, Itch) were similar across the 4 treatment groups. Baseline differences in sex (~8% less females in the high dose group) and Itch NRS (~0.9 points lower in placebo group) are of no concern. The baseline disease characteristics were in line with a target population with moderate to severe AD, who are candidates for systemic treatment: Overall, a small majority of participants (62%) had an IGA score of 3, while the others (38%) had an IGA of 4; the mean (SD) EASI score was 26 (9.7), BSA affected was 41% (18%), and Itch NRS was 5.4 (2.6); many patients had atopic/allergic comorbidities. With one exception for EASI (protocol violation), all patients had scores above the inclusion criterion. Virtually all patients (99%) had used TCS, and a large majority (87%) had used TCNI before, usually with an insufficient response. A considerable proportion of patients had used systemic corticosteroids (26%) or immunosuppressants (22%), biologics were infrequently used before (2.1%).

Patient flow

In the 16-week placebo-controlled phase, more patients in the placebo (8.2%) and low dose (5.8%) groups needed rescue, as compared to the medium (2.5%) and high dose (3.3%) groups.

Efficacy data and additional analyses

Overall effects

In the study JAIP, the primary endpoint and the key secondary endpoints (multiplicity adjusted) were met when comparing the high baricitinib dose to placebo. No endpoints were met for the medium dose as compared to placebo. The alpha was unequally spent, favouring the high dose over the medium

dose. Given the numerical results of the medium dose in primary and key secondary outcomes, lying roughly between the high dose and placebo treatment effects (see below), it is a posteriori acceptable that the medium dose is not favoured from the efficacy point of view.

Dose

While overall, the 'high dose' is more effective than the moderate and low doses and placebo, initially it is not clear whether the proposed posology is well justified. The 'high dose' in the study was based on age: 2 mg for patients <10 years and 4 mg for patients ≥10 years. The proposed posology, however, is weight-based and recommends 2 mg QD for patients <30 kg and 4 mg for patients ≥30 kg. As discussed in the PK section, higher exposure in paediatric patients weighing <30 kg was observed and theoretically the probability of developing adverse events could increase. However, reducing the dose to 1 mg once daily would lead to too low exposure and could compromise efficacy. Therefore, based on the available data the posology paediatric patients with AD weighing <30 kg is acceptable. This weight-based posology is in line with the posology for JIA patients assessed in the procedure EMEA/H/C/004085/X/0035/G.

Primary outcome

The proportion of patients with IGA 0 or 1 at week 16 was 42% in the high dose group, as compared to 16% in the placebo group (p<0.0001). The IGA 0 or 1 responses in the high dose group (42%) were higher than the responses on the medium dose (26%), while responses were similar in the low dose (18%) and placebo (16%) groups. The result for the primary endpoint was supported by the planned sensitivity analyses, using several types of censoring and imputation and including the PP-set. Over time, from baseline to week 16, the treatment effects in the high dose group were larger than the treatment effects in the medium dose group and the low dose and placebo groups. A difference with placebo started to emerge from weeks 2-4, with at week 4 a IGA 0 or 1 response of 23% in the high dose group as compared to 5.7% in the placebo group (nominal p<0.05).

Secondary outcomes

The result in the primary endpoint is supported by the results of the key secondary outcomes. At week 16, there was a (multiplicity adjusted) statistically significant treatment effect of baricitinib high dose, as compared to placebo, in EASI75, EASI90, SCORAD75, EASI change from baseline, and Itch NRS ≥4 points improvement. A statistically significant difference in response in Itch NRS from high dose with placebo, occurred at week 4. This is relevant, as itch is the main symptom of AD. Similarly, from baseline to week 16, the high dose had a more favourable course than placebo and the lower two dose groups, in EASI75 and 90 and SCORAD75.

Itch NRS was not assessed in children <10 years of age. Instead, the caregiver assessed PRISM was used. In that subgroup, the treatment effect in PRISM was not statistically significant at week 16 for high dose versus placebo (p=0.12), though the mean (SD) treatment effect was numerically larger in the high dose group: -0.28 (0.16) in the high dose group and 0.02 (0.15) in placebo; the treatment effect happened to be -0.44 in the medium dose group. Therefore, the PRISM results support the hypothesis that baricitinib will also be effective on itch in younger patients with AD.

Of the several other secondary outcomes that were assessed (not multiplicity adjusted), TCS use, POEM on patient-assessed symptom severity and IDQOL/CDQOL on the impact on the patient's daily living and the PROMIS on anxiety and depression are deemed most relevant. There was no difference in the amount of low-potency TCS between placebo and baricitinib high dose, but the use of medium-potency TCS was somewhat lower in the high dose group (median of 66 gram) as compared to placebo (median of 72 gram). Rescue to high dose TCS was also used more in the placebo group (n=10) than

in the high dose group (n=4). In the study as well as in clinical practice, it can be expected that TCS is stopped not until skin is clear (IGA 0), thus, the results on TCS use basically follow the expectations.

Clinical relevance

The treatment effects of the high dose (adults 4 mg dose equivalent), as compared to placebo, are considered clinically relevant. The primary aims of treatment are to reach a clear or almost clear skin, and to reduce itch, and these outcomes were reached. At week 16, the proportion of patients with IGA 0 or 1 was 42% in the high dose group, as compared to 16% in the placebo group ($p<0.0001$) in the ITT population. The proportion of patients with a response (≥4 points improvement) in itch was 36% in the high dose group, as compared to 16% in the placebo group ($p<0.05$) in the ITT population. Already at week 4, the difference in ≥4 points improvement in Itch NRS was (multiplicity adjusted) statistically significant ($p=0.0026$), with 7.3% in the placebo group and 32% in the high dose group. There was a relatively small treatment effect in patient-assessed symptom severity (POEM) and no effect in patient-assessed impact on daily living (IDQOL/CDQOL) and anxiety and depression (PROMIS). Despite this, the effects on primary and key secondary outcomes on signs (IGA 0 or 1, EASI75) and the results on the main symptom itch (Itch response) are deemed sufficiently supportive for clinical relevance of the treatment effects.

Maintenance and discontinuation

Follow-up data on the maintenance of efficacy were only available from week 16 up to week 24. At week 16 of the placebo-controlled study, there had been 42% (50/120) patients in the high dose group with an IGA 0 or 1, while 68% (81/120) had an IGA 0, 1 or 2 and, according to the protocol, remained on their dose in the extended data set. It is clear that treatment effects between placebo and baricitinib high dose will diminish if only responders at week 16 are studied. However, in principle, these data inform about the maintenance of the effect of prolonged treatment with the proposed high dose, in patients with at least some response (IGA 0, 1 or 2) after 16 weeks of initial treatment. At week 16 of the placebo-controlled study, there were 42% (50/120) patients in the high dose group with an IGA 0 or 1, while 68% (81/120) had an IGA 0, 1 or 2 and remained on their dose in the extended data set. From the n=81 patients on high dose who were at least partial responders at week 16 (cohort 1), there were 22 patients who lost response and were therefore 'transitioned' to high dose in the open-label study. Half (11/22) of these patients regained response before or at week 52. As response is not per se static, this is considered supportive for the maintenance of response over 52 weeks. Among the patients on high dose without a response at week 16 (n=38), few became responders by week 24 and only 5 had a response by week 52. This is overall supportive for recommending discontinuation of treatment if response has not been reached within 8 weeks treatment time. After 8 weeks, the proportion of patients showing >4 points improvement in Itch NRS did not increase, although the proportions of patients meeting IGA 0/1 or EASI75 still increased up to week 16. The timing of 8 weeks is however similar to adults with AD. Also similar to adults with AD, it is recommended in the SmPC that the dose may be reduced by half in patients who attained a durable good response. In contrast to adults, for adolescents there are no clinical data on dose tapering. However, it is considered that this principle can be extrapolated from adults to adolescents, based on similar pathophysiology and the same mode of action of the product, supported by the efficacy results of the 'medium dose' group.

Subgroups

The relevance of the predefined subgroups (age, weight, BMI, region, TCNI use and response, TCS use and response, systemic treatment, disease severity, atopic conditions) is agreed. For the primary endpoint, no statistical interaction tests (subgroup*treatment) were statistically significant ($p<0.10$). It therefore appears that the results are robust over relevant subgroups. From the currently presented

data, it can also be derived that the dose-response relationship for IGA 0/1 and EASI75 is similar when stratified by age (cut-off 10 years) or weight (cut-off 30 kg). The treatment effects (high dose – placebo) are largest in the 10 - 18 years and ≥30 kg strata, and smaller but still numerically present in the <10 years and <30 kg strata.

2.4.4. Conclusions on the clinical efficacy

In the study JAIP, the primary endpoint and the key secondary endpoints (multiplicity adjusted) were met. The high dose of baricitinib appears to be effective for the treatment of moderate-severe AD in patients from 2 to <18 years of age, who are candidates for systemic treatment. This includes the subgroups of <30 kg receiving 2 mg and ≥30 kg receiving 4 mg, in line with the proposed posology. Recommendations to discontinue treatment in case of absence of response, and tapering the dose of sustained good response have been included in the SmPC.

In conclusion, the CHMP considers that the efficacy of baricitinib supports the claimed indication: "Olumiant is indicated for the treatment of moderate to severe atopic dermatitis in adult and paediatric patients 2 years and older who are candidates for systemic therapy"

2.5. Clinical safety

Introduction

Baricitinib is a selective JAK1/JAK2 inhibitor with lower potency towards inhibition of JAK3 and TYK2 [16]. The proposed **indication** of this Application is baricitinib for the treatment of *moderate to severe atopic dermatitis in adult and paediatric patients 2 years of age and older who are candidates for systemic therapy*. The proposed **posology** is 2 mg QD for patients weighing <30 kg and 4 mg QD if ≥30 kg; the dose should be reduced by half for patients with decreased renal function (creatinine clearance between 30 and 60 mL/min) and for patients using strong OAT3 inhibitors (such as probenecid). It is proposed that baricitinib may be used with or without topical corticosteroids or concomitant topical calcineurin inhibitors.

Clinical development

The baricitinib clinical development programme for AD includes one pivotal Phase 3 study (**IV-MC-JAIP**; referred to as **JAIP**). Safety data from the 16-week double-blind treatment period (see the section on efficacy) were completed (period 3, last patient, last visit 24 April 2022); safety data from patients in the long-term extension (LTE, period 4) were also provided (data cut-off date 20 June 2022, database lock date 22 July 2022). The AD safety database included a total of 466 participants; 273 patients (59%) were exposed for at least 52 weeks. From those 273 patients, 229 (84%) were in the older age group (10 to < 18 years), and 44 (16%) were in the younger age group (2 < 10 years).

Safety profile of baricitinib

According to the **warnings** in the SmPC, baricitinib is associated with an increased rate of infections (including upper respiratory tract infections and viral reactivation such as herpes zoster); the occurrence of haematological abnormalities (neutropenia, lymphopenia, anaemia); hyperlipidaemia; hepatic transaminase elevations; and diverticulitis. There are specific warnings on increased risks for malignancy, venous thromboembolism (VTE), MACE, and serious infections (*reference is made to the JAKi Art 20 referral*). A warning is included for AD, stating that combinations with ciclosporin or other potent immunosuppressive medicinal products has not been studied and is not recommended.

In line with the above-mentioned warnings, laboratory values should be **monitored** for lipid parameters, absolute neutrophil and lymphocyte counts, haemoglobin, and hepatic transaminases.

Very common **Adverse drug reactions (ADRs)** of baricitinib, irrespective of the indication, are upper respiratory tract infections and hypercholesterolaemia. Common ADR's include urinary tract infections, herpes infections, pneumoniae, gastroenteritis, and folliculitis), thrombocytosis, headache, nausea, abdominal pain, increased ALT (≥ 3 x ULN), rash, acne, CK increase (> 5 x ULN). Uncommon ADRs are neutropenia (< 1 x 10^9 cells/L), swelling of the face, urticaria, hypertriglyceridemia, deep vein thrombosis, pulmonary embolism, diverticulitis, AST increased (≥ 3x ULN), and weight increase.

In the Risk Management Plan, **important identified risks** of baricitinib are herpes zoster and VTE. **Important potential risks** are malignancies, serious infections, myelosuppression, myopathy, drug-induced liver injury, GI perforation, MACE, and foetal malformation following in utero exposure. Use in paediatric patients is included in the safety concerns as **missing information**.

Patient exposure

The safety data originate from a single pivotal, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of baricitinib in paediatric patients with moderate to severe AD (study **JAIP**).

The safety population comprised all randomised patients who had had at least 1 dose of baricitinib and who did not discontinue the study due to 'lost to follow up' at first postbaseline visit. Three safety analyses sets were defined:

- The PC BARI AD Peds analysis set (referred to as the **PC BARI set** throughout this document) includes data from the 16-week placebo-controlled period (period 3) of baricitinib for the low, medium, and high dose (and equivalents based on weight; 1 mg, 2 mg, and 4 mg) with placebo (*Table 16*).
- The Ext BARI AD Peds analysis set (**Ext BARI set**) included data from the PC BARI set and data of the LTE period up to 30 days after the last dose of study drug (periods 3 and 4). Data are censored after transition to open-label baricitinib 4 mg (or high dose equivalent). A total of 103 PYE was included for placebo versus 99, 104, and 122PYE in the low, medium, and high baricitinib dosing groups respectively (Table 17)
- The All BARI AD Peds analysis set (**All BARI set**) includes all paediatric patients with AD exposed to whichever dose of baricitinib during the JAIP study (periods 2 – 5). A total of 751 PYE from 467patients was included (Table 17); 385patients (82%) were exposed to baricitinib for at least 52 weeks. Of these, 286 (74%) 74were in the older age group (10 to < 18 years), and 99(26%) were in the younger age group. The majority of patients (75%) is still ongoing in the JAIP study.

Table 16. Exposure by Treatment Group (PC BARI set)

	PBO	BARI Low Dose	BARI Med Dose	BARI High Dose
All participants 2 to <18 years	**N=122**	**N=120**	**N=120**	**N=120**
Mean days of exposure (SD)	110.4 (16.00)	113.6 (11.49)	113.5 (10.84)	113.7 (6.52)
Total patient-years	36.87	37.33	37.30	37.37
Older Subgroup 10 to <18 years	**N=88**	**N=87**	**N=86**	**N=88**
Mean days of exposure (SD)	109.1 (18.34)	113.2 (11.65)	114.5 (7.84)	114.3 (3.25)
Total patient-years	26.29	26.97	26.96	27.54
Younger Subgroup 2 to <10 years	**N=34**	**N=33**	**N=34**	**N=32**
Mean days of exposure (SD)	113.7 (6.06)	114.7 (11.17)	111.1 (16.03)	112.2 (11.41)
Total patient-years	10.58	10.37	10.34	9.83

Abbreviation: AD = atopic dermatitis; BARI = baricitinib; Med = medium; N = number of participants in the analysis set; PBO = placebo; PC = placebo-controlled; Peds = paediatric; SD = standard deviation.
Source: JAIP CSR Table JAIP.4.9; Table 2.7.4.2 in ClinSum Safety Peds AD Submission EU (p 18).

Table 17. Exposure by Treatment Group (Ext BARI and All BARI set)

	Ext BARI AD Peds				All BARI
	PBO N=123	BARI Low Dose N=120	BARI Med Dose N=120	BARI High Dose N=120	N=467
All Study Participants (2 to <18 years)					
Mean weeks of exposure (SD)	43.6 (38.2)	43.2 (35.2)	45.1 (37.9)	52.9 (37.7)	83.9 (33.9)
Total patient-years	102.9	99.4	103.6	121.6	750.7
Older Subgroup 10 to <18 years	**N=89**	**N=87**	**N=86**	**N=88**	**N=333**
Mean weeks of exposure (SD)	44.9 (40.5)	43.3 (37.4)	47.2 (40.2)	57.1 (39.6)	90.5 (33.6)
Total patient-years	76.5	72.2	77.8	96.2	577.9
Younger Subgroup 2 to <10 years	**N=34**	**N=33**	**N=34**	**N=32**	**N=134**
Mean weeks of exposure (SD)	40.4 (31.7)	43.0 (29.4)	39.7 (31.3)	41.3 (29.7)	67.3 (28.6)
Total patient-years	26.3	27.2	25.9	25.3	172.8

Abbreviations: AD = atopic dermatitis; BARI = baricitinib; Ext = extended; Med = medium; N = number of participants in the analysis set; PBO = placebo; Peds = paediatric; SD = standard deviation.
Source: JAIP CSR Addendum 1 Table JAIP.4.6.1; adapted from Table 2.7.4.3 in ClinSum Safety Peds AD Submission EU (p 19).

Adverse events

Summary of adverse events

Summaries of adverse events are presented in Table 18 and Table 19 and Table 20 below. No deaths were observed during the JAIP study.

SAEs were infrequent in the **PC BARI set**: n = 5 (4.1%) in the placebo group and n = 4 (1.1%) for the pooled baricitinib groups, with 1 SAE each in the medium and high dose and 2 SAE's in the low dose baricitinib groups. Half of the patients in both the placebo group and the baricitinib groups had at least one TEAE; n = 61 in the placebo group (50%) versus n = 184 (51%) in the pooled baricitinib group (50%, 53%, and 51% for low, medium, and high dose resp.) Study treatment discontinuation due to AEs was observed in 2 patients using placebo and 2 patients using baricitinib (1 using low dose, 1 high dose).

In the **Ext BARI set** 9 SAEs were reported in the baricitinib groups (1.7% (IR 2.0), 2.5% (IR 2.9), and 3.3% (IR 3.4) for low, medium, and high dose baricitinib) versus 7 SAE's (5.7%; IR 7.1) in the

placebo group. Rates of patients experiencing at least 1 TEAE were also rather comparable between the dosing groups (63%, 58%, and 65% with corresponding IRs of 148, 135, and 134 resp.). Permanent study treatment discontinuation due to AE's was seen in two additional patients compared to the PC BARI set, which makes 4 in total (2 using low, 2 using high dose baricitinib).

In the **All BARI set,** the number of SAEs increased (n = 31) and the IR was slightly higher compared to the IR in the high dose baricitinib group observed in the Ext BARI set (IR 4.2 versus 3.4 resp.). When stratified by weight (Table 20), SAE's were more frequent in the <30 kg group (2 mg dose according to posology; IR 13.1) compared to the ≥ 30 kg group (4 mg dose according to posology; IR 6.4). Patients in the ≥ 30 kg group (4 mg dose according to posology) had a lower IR (122) for at least 1 TEAE versus the < 30 kg group (IR 185). Discontinuation rates were correspondingly higher in the < 30 kg group.

Table 18. Summary of Adverse Events PC BARI set

	PBO N=122 n (%) [IR]	**BARI Low Dose N=120 n (%) [IR]**	**BARI Med Dose N=120 n (%) [IR]**	**BARI High Dose N=120 n (%) [IR]**	**Pooled BARI N=360 n (%) [IR]**
All Study Participants					
Total patient-years	36.87	37.33	37.30	37.37	112.00
Deaths	0	0	0	0	0
SAE's	5 (4.1) [13.5]	2 (1.7) [5.3]	1 (0.8) [2.7]	1 (0.8) [2.7]	4 (1.1) [3.6]
Participants with at least 1 TEAE	61 (50.0) [235.3]	60 (50.0) [228.2]	63 (52.5) [250.0]	61 (50.8) [253.4]	184 (51.1) [243.5]
Mild	33 (27.0)	36 (30.0)]	40 (33.3)	36 (30.0)	112 (31.1)
Moderate	22 (18.0)	22 (18.3)	22 (18.3)	23 (19.2)	67 (18.6)
Severe	6 (4.9)	2 (1.7)	1 (0.8)	2 (1.7)	5 (1.4)
AEs leading to permanent DC from study treatment	2 (1.6) [5.4]	1 (0.8) [2.7]	0	1 (0.8) [2.7]	2 (0.6) [1.8]

Abbreviations: AE = adverse event; AD = atopic dermatitis; BARI = baricitinib; DC = discontinuation; IR = incidence rate; Med = medium; N = number of participants in the analysis set; n = number of participants in the specified category; PBO = placebo; PC = placebo-controlled; Peds = paediatric; SAE's = serious adverse events; TEAE = treatment-emergent adverse events.

Sources: Table APP.2.7.4.7.1and JAIP CSR Table JAIP.5.43. Adjusted from Table 2.7.4.4 ClinSum Safety Peds AD Submission EU (p 24). Source: Adjusted Tables APP.2.7.4.7.3, 2.7.4.8 (ClinSumSafety Peds AD)

Table 19. Summary of Adverse Events; Ext and All BARI sets

	Ext BARI				**All BARI**
	PBO N=123 n (%) [IR]	**BARI Low Dose N=120 n (%) [IR]**	**BARI Med Dose N=120 n (%) [IR]**	**BARI High Dose N=120 n (%) [IR]**	**N=467 n (%) [IR]**
All Study Participants (2 to <18 years old)					
Total Patient-Years	102.9	99.4	103.6	121.6	750.7
Deaths	0	0	0	0	0
SAE's	7 (5.7) [7.1]	2 (1.7) [2.0]	3(2.5) [2.9]	4 (3.3) [3.4]	31(6.6) [4.2]
Participants with at least 1 TEAE	76(61.8) [150.2]	76(63.3) [148.3]	69(57.5) [135.1]	78(65.0) [133.7]	362(77.5) [125.3]
Mild	35 (28.5) [46.1]	45 (37.5) [65.6]	39 (32.5) [51.3]	38 (31.7) [40.2]	168 (36.0) [30.5]
Moderate	34 (27.6) [40.2]	28 (23.3) [32.4]	26 (21.7) [30.5]	35 (29.2) [35.8]	166 (35.5) [28.9]
Severe	7 (5.7) [7.0]	3 (2.5) [3.0]	4 (3.3) [3.9]	5 (4.2) [4.3]	28 (6.0) [3.8]
AEs leading to permanent DC from study treatment	2 (1.6) [1.9]	2 (1.7) [2.0]	0	2 (1.7) [1.7]	13 (2.8) [1.7]
Older Subgroup 10 to <18 years	**N=89**	**N=87**	**N=86**	**N=88**	**N=333**
Total Patient-Years	76.5	72.2	77.8	96.2	577.9
Deaths	0	0	0	0	0
SAE's	6 (6.6) [8.3]	0	2 (2.3) [2.6]	3 (3.4) [3.2]	22 (6.6) [3.9]
Participants with at least 1 TEAE	51 (57.3) [138.4]	50 (57.5) [130.1]	50 (58.1) [129.6]	58 (65.9) [131.5]	254 (76.3) [114.6]
Mild	26 (29.2) [47.5]	31 (35.6) [64.8]	28 (32.6) [48.3]	27 (30.7) [36.6]	114 (34.2) [26.4]

	Ext BARI				All BARI
	PBO N=123 n (%) [IR]	BARI Low Dose N=120 n (%) [IR]	BARI Med Dose N=120 n (%) [IR]	BARI High Dose N=120 n (%) [IR]	N=467 n (%) [IR]
Moderate	21 (23.6) [32.8]	17 (19.5) [25.7]	19 (22.1) [29.7]	27 (30.7) [34.9]	119 (35.7) [27.3]
Severe	4 (4.5) [5.4]	2 (2.3) [2.8]	3 (3.5) [3.9]	4 (4.5) [4.4]	21 (6.3) [3.7]
AEs leading to permanent DC from study treatment	2 (2.2) [2.6]	0	0	1 (1.1) [1.0]	8 (2.4) [1.4]
Younger Subgroup 2 to <10 years	**N=34**	**N=33**	**N=34**	**N=32**	**N=134**
Total Patient-Years	26.3	27.2	25.9	25.3	172.8
Deaths	0	0	0	0	0
SAE's	1 (2.9) [3.8]	2 (6.1) [7.3]	1 (2.9) [3.9]	1 (3.1) [4.0]	9 (6.7) [5.3]
Participants with at least 1 TEAE	25 (73.5) [181.8]	26 (78.8) [203.0]	19 (55.9) [152.1]	20 (62.5) [140.5]	108 (80.6) [160.9]
Mild	9 (26.5) [42.4]	14 (42.4) [67.4]	11 (32.4) [61.0]	11 (34.4) [53.2]	54 (40.3) [45.6]
Moderate	13 (38.2) [63.2]	11 (33.3) [54.4]	7 (20.6) [32.9]	8 (25.0) [39.2]	47 (35.1) [33.7]
Severe	3 (8.8) [11.7]	1 (3.0) [3.6]	1 (2.9) [3.9]	1 (3.1) [4.0]	7 (5.2) [4.1]
AEs leading to permanent DC from study treatment	0	2 (6.1) [7.3]	0	1 (3.1) [3.9]	5 (3.7) [2.9]

Abbreviations: AD = atopic dermatitis; AE = adverse events; BARI = baricitinib; DC = discontinuation; Ext = extended; IR = incidence rate; N = number of participants in the analysis set; n = number of participants in the specified category; Peds = paediatric; SAE's = serious adverse events; TEAE = treatment-emergent adverse events.
Source: JAIP CSR Addendum 1 Table JAIP.5.2.1., adjusted from Table 2.7.4.5 ClinSum Safety Peds AD Submission EU (p 25/26).

Table 20. Summary of Adverse Events; All BARI set after transition to open-label baricitinib

	Weight: 30 kg or more at time of transition to open-label BARI		Weight: less than 30 kg at time of transition to open-label BARI	
Parameter, n (%) [IR]	**2 mg per protocol (age-based dosing) N=18 PYE=9.5**	**4 mg N=208 PYE=191.3**	**2 mg N=48 PYE=22.8**	**4 mg per protocol (age-based dosing) N=3 PYE=3.7**
Deaths	0	0	0	0
SAE's	0	12 (5.8) [6.4]	3 (6.3) [13.1]	0
Participants with ≥1 TEAE	12 (66.7) [211.7]	130 (62.5) [122.3]	24 (50.0) [184.8]	2 (66.7) [93.7]
Severe TEAE's	0	7 (3.4) [3.7]	2 (4.2) [8.6]	0
AEs leading to permanent discontinuation of treatment	1 (5.6) [10.2]	4 (1.9) [2.1]	1 (2.1) [4.3]	0

Source: Adjusted from Table 5, JY3009104 AD Peds Day 90 Safety Regulatory Response

Common Adverse Events

In the **PC BARI set**, most common treatment-emergent adverse events (TEAEs) (> 5%) in the high dose baricitinib group occurred in the SOCs Infections and infestations (n = 31, 26%), Gastro-intestinal disorders (n = 18, 15%), Skin and subcutaneous tissue disorders (n = 12, 10%), Nervous system disorders (n = 8, 6.7%), and Respiratory, thoracic, and mediastinal disorders (n = 6, 5.0%). Most common TEAEs in the high dose baricitinib group by PT were mainly within these SOCs, i.e.:

- Abdominal pain (n = 6, 5.0%),
- Acne (n = 6, 5.0%),
- Headache (n = 6, 5.0%),
- Diarrhoea (n = 5, 4.2%), and
- Nasopharyngitis and upper respiratory tract infection (both n = 5, 4.2%).

Numerical imbalances between high dose baricitinib and placebo were found for the SOCs Gastro-intestinal disorders (15% for high dose baricitinib versus 11% for placebo), Blood and lymphatic system disorders (3.3% versus 1.6%), and Investigations (3.3% versus 1.6%). Imbalances in TEAE's by PT were found for:

- Abdominal pain (5.0% in high dose baricitinib versus 2.5% in placebo),
- Upper respiratory tract infection (4.2% versus 0.8%),
- Diarrhoea (4.2% versus 1.6%),
- Abdominal pain upper (3.3% versus 0.8%),
- Bronchitis (2.5% versus 0.8%), and
- Gastroenteritis and Decreased appetite (each 2.5% versus 0%)

A possible dose response relationship was observed for the PT's Upper respiratory tract infections and Gastro-enteritis; other gastro-intestinal problems including Abdominal pain, Abdominal pain upper, Diarrhoea, and Decreased appetite were also more common in medium / high dose compared to low dose baricitinib (Table 21).

Table 21. Summary of TEAE's by PT for the Overall Population with a Frequency of2% or More in the BARI High Dose Group or Pooled BARI Group; PC BARI Set

Preferred Term (≥2% frequency)	**PBO**	**BARI Low Dose**	**BARI Med Dose**	**BARI High Dose**	**Pooled BARI**
All Patients (2 to <18 years)	**N=122 n (%) [IR]**	**N=120 n (%)[IR]**	**N=120 n (%)[IR]**	**N=120 n (%)[IR]**	**N=360 n (%)[IR]**
Total Patient-Years	36.87	37.33	37.30	37.37	112.00
Abdominal pain	3 (2.5) [8.2]	3 (2.5) [8.1]	5 (4.2) [13.7]	6 (5.0) [16.5]	14 (3.9) [12.8]
Acne	5 (4.1) [13.7]	3 (2.5) [8.1]	4 (3.3) [10.9]	6 (5.0) [16.7]	13 (3.6) [11.8]
Headache	10 (8.2) [28.4]	7 (5.8) [19.6]	11 (9.2) [32.0]	6 (5.0) [16.6]	24 (6.7) [22.6]
Diarrhoea	2 (1.6) [5.4]	1 (0.8) [2.7]	2 (1.7) [5.4]	5 (4.2) [13.8]	8 (2.2) [7.2]
Nasopharyngitis	6 (4.9) [16.4]	4 (3.3) [10.9]	5 (4.2) [13.7]	5 (4.2) [13.6]	14 (3.9) [12.7]
Upper respiratory tract infection	1 (0.8) [2.7]	3 (2.5) [8.1]	4 (3.3) [10.9]	5 (4.2) [13.7]	12 (3.3) [10.9]
Abdominal pain upper	1 (0.8) [2.7]	2 (1.7) [5.3]	2 (1.7) [5.4]	4 (3.3) [10.9]	8 (2.2) [7.2]
Bronchitis	1 (0.8) [2.7]	6 (5.0) [16.3]	1 (0.8) [2.7]	3 (2.5) [8.2]	10 (2.8) [9.0]
COVID-19	4 (3.3) [10.9]	5 (4.2) [13.4]	5 (4.2) [13.6]	3 (2.5) [8.1]	13 (3.6) [11.7]
Decreased appetite	0	0	0	3 (2.5) [8.1]	3 (0.8) [2.7]
Gastroenteritis	0	0	2 (1.7) [5.4]	3 (2.5) [8.2]	5 (1.4) [4.5]

Abbreviations: AD = atopic dermatitis; BARI = baricitinib; COVID-19 = coronavirus disease 2019; Med = medium; N = number of participants in the analysis set; n = number of participants in the specified category;
PBO = placebo; Peds = paediatric; PC = placebo-controlled; PT = Preferred Term; TEAE = treatment-emergent adverse event.
Source: Table APP.2.7.4.7.4

In the **Ext BARI set**, the most common TEAE's (IR ≥10) in the high dose baricitinib group by SOC were much alike those in the PC BARI set, i.e. Infections and infestations (37.5%, IR 62.2), Gastrointestinal disorders (15.8%, IR 23.5), Skin and subcutaneous tissue disorders (11.7%, IR 16.7), Nervous system disorders (10.8%, IR 15.3), and Respiratory, thoracic and mediastinal disorders (8.3%, IR 11.5) [NB data not updated after first round]. Most common TEAE's (IR ≥ 5) in the high dose baricitinib group versus placebo by PT were mainly within these SOCs, i.e.:

- COVID-19 (12%, IR 12.5 versus 4.9%, IR 6.1 in the placebo group),
- Headache (10%, IR 10.6 versus 8.1%, IR 9.9),

- Acne (10%, IR 10.4 versus 4.9%, IR 6.0),
- Abdominal pain (6.7%, IR 7.0 versus 3.3%, IR 3.9),
- Influenza (6.0%, IR 5.1 versus 3.3%, IR 4.0).
- Nasopharyngitis (5.8%, IR 7.9 9 versus 7.4%, IR 11.9),
- Upper respiratory tract infection (5.8%, IR 5.8 versus 3.3%, IR 3.9), and
- Diarrhoea (5.0%, IR 5.1 versus 1.6%, IR 1.9).

Of these, for COVID-19, Abdominal pain, Diarrhoea, and Acne the largest numerical imbalances were found between high dose baricitinib versus placebo, as were for Gastro-enteritis (3.4%, IR 3.4 versus 1.6%, IR 1.9), Abdominal pain upper (3.3%, IR 3.3 versus 0.8%, IR 1.0), and Rhinitis (3.3%, IR 3.3 versus 0.8%, IR 1.0). A dose trend was seen for the PT's Influenza, Cough, Diarrhoea and Gastroenteritis (Table 22).

In the **All BARI set**, most common TEAE's (IR ≥10) in the baricitinib high dose group by SOC were Infections and infestations (n=284, 61%, IR 64.4), Skin and subcutaneous tissue disorders (n=10, 23%, IR 16.5), Respiratory, thoracic, and mediastinal disorders (n=77, 17%, IR 11.2), and Gastrointestinal disorders (n=69, 15%, IR 10.2). Most common AE's (IR ≥ 5) by PT were:

- COVID-19 (19%, IR 12.8)
- Nasopharyngitis (14%, IR 9.6),
- Acne (11%, IR 7.4),
- Headache (9.9%, IR 6.5), and
- Upper respiratory tract infection (9.2%, IR 6.0).

Table 22. Summary of TEAE's with a Frequency of ≥ 2% by PT for the BARI High Dose Group in the Ext BARI and / or All BARI Set

	Ext BARI AD Peds				**All BARI AD Peds**
Preferred Term	**PBO**	**BARI Low Dose**	**BARI Med Dose**	**BARI High Dose**	**All BARI**
All Patients (2 to <18 years old)	**N=123 n (%) [IR]**	**N=120 n (%) [IR]**	**N=120 n (%) [IR]**	**N=120 n (%) [IR]**	**N=467 n (%) [IR]**
Patient-Years of Exposure	*102.9*	*99.4*	*103.6*	*121.6*	*750.7*
COVID-19	6 (4.9) [6.1]	8 (6.7) [8.4]	12 (10.0) [12.9]	14 (11.7) [12.5]	88 (18.8) [12.8]
Nasopharyngitis	9 (7.3) [9.3]	9 (7.5) [9.4]	7 (5.8) [7.2]	9 (7.5) [7.7]	66 (14.1) [9.6]
Acne	6 (4.9) [6.0]	6 (5.0) [6.6]	5 (4.2) [5.1]	12 (10.0) [10.4]	51 (10.9) [7.4]
Headache	10 (8.1) [9.9]	7 (5.8) [7.4]	12 (10.0) [12.7]	12 (10.0) [10.6]	46 (9.9) [6.5]
Upper respiratory tract infection	4 (3.3) [3.9]	5 (4.2) [5.2]	7 (5.8) [7.0]	7 (5.8) [5.8]	43 (9.2) [6.0]
Pyrexia	2 (1.6) [1.9]	5 (4.2) [5.1]	6 (5.0) [6.0]	4 (3.3) [3.3]	34 (7.3) [4.7]
Abdominal Pain	4 (3.3) [3.9]	3 (2.5) [3.1]	7 (5.8) [7.1]	8 (6.7) [7.0]	26 (5.6) [3.5]
Influenza	4 (3.3) [4.0]	0	2 (1.7) [2.0]	6 (5.0) [5.1]	23 (4.9) [3.1]
Pharyngitis	1 (0.8) [1.0]	5 (4.2) [5.2]	6 (5.0) [5.9]	3 (2.5) [2.5]	22 (4.7) [3.0]
Bronchitis	5 (4.1) [4.9]	8 (6.7) [8.3]	1 (0.8) [1.0]	4 (3.3) [3.4]	20 (4.3) [2.7]
Asthma	4 (3.3) [3.9]	1 (0.8) [1.0]	5 (4.2) [4.9]	4 (3.3) [3.4]	19 (4.1) [2.6]
Blood creatine phosphokinase increased	1 (0.8) [1.0]	1 (0.8) [1.0]	1 (0.8) [1.0]	2 (1.7) [1.7]	18 (3.9) [2.4]

	Ext BARI AD Peds				All BARI AD Peds
Preferred Term	**PBO**	**BARI Low Dose**	**BARI Med Dose**	**BARI High Dose**	**All BARI**
All Patients (2 to <18 years old)	**N=123 n (%) [IR]**	**N=120 n (%) [IR]**	**N=120 n (%) [IR]**	**N=120 n (%) [IR]**	**N=467 n (%) [IR]**
Cough	4 (3.3) [3.9]	2 (1.7) [2.0]	3 (2.5) [3.0]	5 (4.2) [4.2]	16 (3.4) [2.1]
Diarrhoea	2 (1.6) [1.9]	1 (0.8) [1.0]	2 (1.7) [1.9]	6 (5.0) [5.1]	16 (3.4) [2.2]
Vomiting	3 (2.4) [2.9]	2 (1.7) [2.0]	3 (2.5) [2.9]	1 (0.8) [0.8]	16 (3.4) [2.1]
Gastroenteritis	2 (1.6) [1.9]	0	3 (2.5) [2.9]	4 (3.3) [3.4]	15 (3.2) [2.0]
Herpes Simplex	2 (1.6) [1.9]	1 (0.8) [1.0]	1 (0.8) [1.0]	1 (0.8)	15 (3.2) [2.0]
Impetigo	5 (4.1) [5.0]	1 (0.8) [1.0]	3 (2.5) [2.9]	2 (1.7) [1.6]	15 (3.2) [2.0]
Rhinitis	1 (0.8) [1.0]	4 (3.3) [4.1]	1 (0.8) [1.0]	4 (3.3) [3.3]	14 (3.0) [1.9]
Abdominal pain upper	1 (0.8) [1.0]	3 (2.5) [3.0]	2 (1.7) [2.0]	4 (3.3) [3.3]	12 (2.6) [1.6]
Arthralgia	0	4 (3.3) [4.2]	2 (1.7) [1.9]	0	12 (2.6) [1.6]
Folliculitis	2 (1.6) [2.0]	1 (0.8)	0	3 (2.5) [2.5]	12 (2.6) [1.6]
Dysmenorrhoea	3 (4.6) [5.7]	1 (1.6) [1.8]	3 (4.8) [5.5]	0	6 (2.5) [1.6]
Oral herpes	2 (1.6) [1.9]	3 (2.5) [3.1]	1 (0.8) [1.0]	1 (0.8) [0.8]	11 (2.4) [1.5]
Skin Infection	1 (0.8) [1.0]	3 (2.5) [3.0]	1 (0.8) [1.0]	1 (0.8) [0.8]	11 (2.4) [1.5]
Tonsillitis	2 (1.6) [1.9]	2 (1.7) [2.0]	0	0	10 (2.1) [1.3]

Abbreviations: BARI = baricitinib; COVID-19 = coronavirus disease 2019; IR = incidence rate; Med = medium; n = number of patients in the specified category; N = number of patients in the safety population; PBO = placebo; PT = preferred term; TEAE = treatment-emergent adverse event.
a Denominator and patient-years adjusted because event is specific to females: N = 65 (PBO), N = 62 (BARI low), N = 63 (BARI medium), N = 53 (BARI high), N = 236 (All BARI).
Source: Table JAIP.8.3.26

Adverse events by maximum severity

Most adverse events during the JAIP study were mild to moderate in severity.

In the **PC BARI set** 27% (n = 33) of the patients in the placebo group versus 31% (n = 112) in the pooled baricitinib group had mild TEAE's. Moderate TEAE's were reported in 18% (n = 22) versus 19% (n = 67) of the patients respectively; severe TEAE's were reported in 6 patients allocated to placebo (4.9%) versus 5 patients allocated to baricitinib (1.4%) of whom 1 (0.8%) patient was from the high dose group (Table 18).

Severe TEAE's in the baricitinib groups were (by PT) corneal abscess, ligament sprain, ophthalmic herpes simplex (high dose baricitinib), vertigo CNS origin (medium dose), bronchospasm, and EBV infection (low dose). In the placebo group COVID-19, lice infestation, suicide attempt, and atopic dermatitis were reported. Except for Dermatitis atopic in the placebo group (n = 4) no severe TEAE occurred more than once.

The majority of the TEAE's in the **Ext BARI set** were mild to moderate in severity (Table 19). Severe TEAE's were most common in the high dose baricitinib group (n = 5, 4.2%, IR 4.3), versus n = 3 (2.5%, IR 3.0) in low dose and n = 4 (3.3%, IR 3.9) in medium dose. For placebo, these numbers were higher (n = 7, 5.7%, IR 7.0). Additionally reported severe TEAE's in the Ext BARI set compared to the PC BARI set, were single cases of Fibrous cortical defect, Gastro-intestinal bacterial infection, and Impetigo in the high dose baricitinib group, single cases of Dysmenorrhoea and Fungal skin infection as well as two cases of Asthma in the medium dose group, and a single event of Blood IgE

increased in the low dose group. Two severe events thus occurred more than once, i.e. Asthma in the medium dose baricitinib group, and Dermatitis atopic in the placebo group.

In the **All BARI set**, a total of 28 severe TEAE's were reported (6.0%, IR 3.8), with Food allergy (n = 3; IR 0.4), and Asthma, Dermatitis atopic, and Ophthalmic herpes simplex (n = 2 for each PT, IR 0.4). Compared to the Ext BARI set, additional severe TEAE's were Food allergy (n = 3), Dermatitis atopic (n = 2), and single cases of Ophthalmic herpes simplex, Eczema, Eczema impetiginous, Erythrodermic atopic dermatitis, Escherichia urinary tract infection, Forearm fracture, Herpes simplex, Interstitial lung disease, Meniscus injury, Neurectomy, Neuroma, Postprocedural haemorrhage, Pruritis, and Tonsillar hypertrophy.

Serious adverse event and deaths

Deaths

No **deaths** were reported during the JAIP study through the data cut-off date of 20 June 2022.

Serious adverse events

In the **PC BARI set**, 11 SAE's occurred in 9 patients; 5 patients (4.1%) in the placebo group versus 4 in baricitinib (2 in low dose baricitinib (1.7%), and 1 each in the moderate and the high dose baricitinib groups (0.8%)). The SAE's in the baricitinib groups were Corneal abscess and ophthalmic herpes simplex in 1 patient (high dose), Vertigo of central nervous system (medium dose), and Bronchospasm and Dermatitis atopic (both low dose). In the placebo group Dermatitis atopic (n = 3), and COVID-19, Impetigo, Suicide attempt (n = 1 each) occurred.

For a total of 38 patients, at least 1 SAE was reported during the JAIP study (**All BARI set**) 7 in placebo and 31 in baricitinib (6.6%, IR 4.2). IR's increased with increasing dose (IR 2.0, 2.89, and 3.4 for low, medium, and high dose baricitinib respectively) but these were lower than for placebo (IR 7.1) (**Ext BARI set**). SAE's were more incident in the younger age group (IR 5.3) compared to the older age group (IR 3.9); reported were Dermatitis atopic (n = 2), Adenoidal hypertrophy, Bronchospasm, Erythrodermic atopic dermatitis, E. urinary tract infection, Fungal skin infection, Gastro-intestinal bacterial infection, Interstitial lung disease, and Lymphadenitis.

SAE's reported in more than 1 patient in the All BARI set, were:

- Ophthalmic herpes simplex (n = 2; older age group; both high dose; temporary disruption of baricitinib),
- Herpes simplex (n = 2; both high dose, older age group; 1 case discontinued baricitinib),
- Asthma (n = 2; medium and high dose; older age group, baricitinib continued),
- Dermatitis atopic (n = 3; low dose (n = 1, younger age group, baricitinib continued) and high dose (n = 2, older age group), in both latter cases baricitinib was discontinued).

Eleven patients (2.4%) in the All BARI set experienced at least 1 severe infection (IR 1.5).

A 15 years old female experienced epilepsy for which hospitalization was required. There was no history of seizures. She participated in the double-blind treatment period followed by the LTE at a baricitinib medium dose (2 mg/day) and eventually transitioned to a high dose (4 mg/day). On day 452 she was hospitalized due to juvenile epilepsy (EEG confirmed). Baricitinib was not interrupted, nor was the dose changed. The patient recovered.

Finally, two SAE's of angioedema were reported in two patients, resp. 42 and 60 days after termination of baricitinib treatment.

Table 23. Summary of SAE's by SOC and PT Ext BARI AD Peds and ALL BARI AD Peds Analysis Sets

	Extended BARI Population				
SAE by SOC and PT	**PBO N=123 n (%) [IR]**	**BARI Low Dose N=120 n (%) [IR]**	**BARI Med Dose N=120 n (%) [IR]**	**BARI High Dose N=120 n (%) [IR]**	**All BARI N=467 n (%) [IR]**
Patient-years of exposure	*102.9*	*99.4*	*103.6*	*121.6*	*750.7*
Participants with ≥1 SAE	7 (5.7) [7.1]	2 (1.7) [2.0]	3 (2.5) [2.9]	4 (3.3) [3.4]	31 (6.6) [4.2]
Blood and lymphatic system disorders	**0**	**0**	**0**	**0**	**1 (0.2) [0.1]**
Lymphadenitis	0	0	0	0	1 (0.2) [0.1]
Infections and infestations	**2 (1.6) [2.0]**	**0**	**1 (0.8) [1.0]**	**2 (1.7) [1.7]**	**11 (2.4) [1.5]**
Ophthalmic herpes simplex[a,b]	0	0	0	1 (0.8) [0.8]	2 (0.4) [0.3]
Herpes simplex[b]	0	0	0	0	2 (0.4) [0.3]
Appendicitis	0	0	0	0	1 (0.2) [0.1]
Ascariasis[c]	0	0	0	0	1 (0.2) [0.1]
COVID-19	1 (0.8) [1.0]	0	0	0	1 (0.2) [0.1]
Corneal abscess[a]	0	0	0	1 (0.8) [0.8]	1 (0.2) [0.1]
Eczema herpeticum	0	0	0	0	1 (0.2) [0.1]
Eczema impetiginous	0	0	0	0	1 (0.2) [0.1]
Escherichia urinary tract infection	0	0	0	0	1 (0.2) [0.1]
Fungal skin infection	0	0	1 (0.8) [1.0]	0	1 (0.2) [0.1]
Gastrointestinal bacterial infection	0	0	0	1 (0.8) [0.8]	1 (0.2) [0.1]
Gastrointestinal bacterial overgrowth[c]	0	0	0	0	1 (0.2) [0.1]
Impetigo	1 (0.8) [1.0]	0	0	0	0
Skin and subcutaneous tissue disorders	**4 (3.3) [3.9]**	**1 (0.8) [1.0]**	**0**	**0**	**4 (0.9) [0.5]**
Dermatitis atopic[d,e]	3 (2.4) [2.9]	1 (0.8) [1.0]	0	0	3 (0.6) [0.4]
Erythrodermic atopic dermatitis	0	0	0	0	1 (0.2) [0.1]

	Extended BARI Population				
SAE by SOC and PT	**PBO N=123 n (%) [IR]**	**BARI Low Dose N=120 n (%) [IR]**	**BARI Med Dose N=120 n (%) [IR]**	**BARI High Dose N=120 n (%) [IR]**	**All BARI N=467 n (%) [IR]**
Urticaria	1 (0.8) [1.0]	0	0	0	0
Respiratory, thoracic, and mediastinal disorders	**0**	**1 (0.8) [1.0]**	**1 (0.8) [1.0]**	**1 (0.8) [0.8]**	**6 (1.3) [0.8]**
Adenoidal hypertrophy	0	0	0	0	1 (0.2) [0.1]
Asthma	0	0	1 (0.8) [1.0]	1 (0.8) [0.8]	2 (0.4) [0.3]
Bronchospasm	0	1 (0.8) [1.0]	0	0	1 (0.2) [0.1]
Interstitial lung disease	0	0	0	0	1 (0.2) [0.1]
Tonsillar hypertrophy[f]	0	0	0	0	1 (0.2) [0.1]
Injury, poisoning, and procedural complications	**0**	**0**	**0**	**0**	**3 (0.6) [0.4]**
Meniscus injury	0	0	0	0	1 (0.2) [0.1]
Postprocedural haemorrhage[f]	0	0	0	0	1 (0.2) [0.1]
Wrist fracture	0	0	0	0	1 (0.2) [0.1]
Musculoskeletal and connective tissue disorders	**0**	**0**	**0**	**0**	**2 (0.4) [0.3]**
Arthritis	0	0	0	0	1 (0.2) [0.1]
Pseudarthrosis	0	0	0	0	1 (0.2) [0.1]
Nervous system disorders	**0**	**0**	**1 (0.8) [1.0]**	**0**	**2 (0.4) [0.3]**
Epilepsy	0	0	0	0	1 (0.2) [0.1]
Vertigo of CNS origin	0	0	1 (0.8) [1.0]	0	1 (0.2) [0.1]
Immune system disorders	**0**	**0**	**0**	**0**	**2 (0.4) [0.3]**
Anaphylactic reaction	0	0	0	0	1 (0.2) [0.1]
Food allergy	0	0	0	0	1 (0.2) [0.1]
Metabolism and nutrition disorders	**0**	**0**	**0**	**0**	**1 (0.2) [0.1]**
Dehydration	0	0	0	0	1 (0.2)

SAE by SOC and PT	Extended BARI Population				
	PBO N=123 n (%) [IR]	BARI Low Dose N=120 n (%) [IR]	BARI Med Dose N=120 n (%) [IR]	BARI High Dose N=120 n (%) [IR]	All BARI N=467 n (%) [IR]
					[0.1]
Neoplasms benign, malignant, and unspecified (includes cysts and polyps)	0	0	0	1 (0.8) [0.8]	1 (0.2) [0.1]
Fibrous cortical defect	0	0	0	1 (0.8) [0.8]	1 (0.2) [0.1]
Psychiatric disorders	2 (1.6) [2.0]	0	0	0	0
Suicidal ideation	1 (0.8) [1.0]	0	0	0	0
Suicide attempt[e]	1 (0.8) [1.0]	0	0	0	0

Abbreviations: BARI = baricitinib; CNS = central nervous system; COVID-19 = coronavirus disease 2019; IR = incidence rate; Med = medium; n = number of patients in the specified category; N = number of patients in the safety population; PBO = placebo; PT = preferred term; SAE = serious adverse event; SOC = system organ class.

a Two SAEs (corneal abscess and ophthalmic herpes simplex) occurred in the same participant on BARI high dose at the same time.

b SAE of ophthalmic herpes simplex was reported by 1 participant in Study Period 3 and 1 participant in Study Period 4 who also reported the SAE of herpes simplex at the same time as SAE of ophthalmic herpes simplex in Study Period 4.

c Two SAEs (ascariasis and gastrointestinal bacterial overgrowth) occurred in the same participant at the same time.

d SAE of dermatitis atopic was reported by 4 participants in Study Period 3 and 2 participants in Study Period 4.

e Two SAEs (suicide attempt and atopic dermatitis) occurred in the same PBO-treated participant at the same time.

f Two SAEs (tonsillar hypertrophy and postprocedural haemorrhage) occurred in the same participant sequentially in the same timeframe.

Source: Table JAIP.8.3.31

Adverse events of special interest (AESI's)

AESI's discussed were infections, hematologic changes, lipid changes, MACE, VTE, ATE, CPK increases and muscle-related symptoms, NMSC and malignancy other than NMSC, abnormal hepatic tests, effects on renal function, GI perforation, depression and suicidality, allergic reactions and hypersensitivity, and photosensitivity reactions.

Infections

In the JAIP study, patients were not eligible for participation if they had a history of eczema herpeticum in the previous 12 months or 2 previous episodes in general, if they had actual skin infections, or if they had recurrent infections including o.a. herpes zoster, hepatitis B or C, TB, typhoid infections, or herpes simplex at randomization.

In the **PC BARI set**, infections occurred in 36 patients (30%) in the low dose baricitinib group, 32 (27%) in the medium dose group, and 31 patients (26%) in the high dose group versus 35 (n = 29%) in the placebo group. Most common in the high dose group versus placebo were Nasopharyngitis (n = 5, 4.2% versus n = 6, 4.9%), Upper respiratory tract infections (n = 5, 4.2% versus n = 1, o.8%), bronchitis (n = 3, 2.5% versus n = 1, 0.8%), and COVID-19 (n = 3, 2.5% versus n = 4, 3.3%). One patient permanently discontinued the study drug due to infections (low dose, herpes zoster). One patient had serious infections in the baricitinib high dose group (0.8%, IR 2.7; corneal abscess and ophthalmic herpes simplex; see narratives above, treatment interrupted but not resumed at time of data cut off).

In the **Ext BARI set**, infections occurred in 153 patients in both low (n = 50, 42%, IR 68.2) and medium (n = 47, 39%, IR 63.4) dose baricitinib groups, and 54 patients (45%, IR 60.7) in high dose baricitinib versus 45 (37%, IR 63.3) in the placebo group. Overall (**ALL BARI set**) 284 patients had infections (61%, IR 64.4), most common (> 5%) were COVID-19, nasopharyngitis, and upper respiratory tract infection. Eleven patients (2.4%, IR 1.47) reported at least one serious infection, which were Herpes simplex (n =2), Ophthalmic herpes simplex (n = 2), Appendicitis, Ascariasis, Corneal abscess, Eczema herpeticum, Eczema imetiginous, Escherichia urinary tract infection, Fungal skin infection, Gastrointestinal bacterial infection, Gastrointestinal bacterial overgrowth, and Impetigo (n = 1 each; see also section above). Three cases reported 2 or more serious infections, all treated with high dose baricitinib (herpes simplex (n=2) and ophthalmic herpes simplex (n=2)). In 52 (11%) cases, antibiotic treatment was required for the treatment of infections. Permanent discontinuation due to infection was seen in 5 patients due to herpes zoster (n=2), eczema impetiginous, herpes simplex, and respiratory tract infection (n=1 each); temporary discontinuation in 62 patients due to infections (IR 8.9).

Herpes zoster infections

In the **PC BARI set**, 1 case of herpes zoster was reported among patients treated with baricitinib (low dose; 0.3%) which was reason for discontinuation, and 1 in the placebo group (0.8%). These were not marked as SAE's and both cases recovered. In the **Ext BARI set**, 2 additional cases of herpes zoster were reported (2 on low dose (1.7%), 1 on high dose baricitinib (0.8%)). Altogether 7 patients in the All BARI set (1.5%) reported herpes zoster. None were with ocular, visceral or motor nerve involvement. One case concerned a 12-year-old male who was treated with baricitinib high dose who developed disseminated herpes zoster infection at day 331 (non-SAE); baricitinib was temporary interrupted and resumed without recurrence of infection. The patient fully recovered. No differences were observed in the across weight classes.

Herpes simplex infections

Herpes simplex occurred in 7 cases in the pooled baricitinib group (1.9%), among which 3 in the high dose group (2.5%) versus 4 in the placebo group (3.3%) (**PC BARI set**). Another 3 cases occurred in the **Ext BARI set**, with a total of 28 (6.0%; IR 3.85) in the **All BARI set** Table 24.

Table 24. Summary of Herpes simplex infections

	Extended BARI Population				
	PBO N=123 n (%) [IR]	BARI Low Dose N=120 n (%) [IR]	BARI Med Dose N=120 n (%) [IR]	BARI High Dose N=120 n (%) [IR]	All BARI N=467 n (%) [IR]
Patient-years of exposure	*102.9*	*99.4*	*103.6*	*121.6*	*750.7*
Participants with ≥1 TE event	4 (3.3) [3.88]	4 (3.3) [4.09]	2 (1.7) [1.94]	4 (3.3) [3.37]	28 (6.0) [3.85]
Herpes simplex	2 (1.6) [1.93]	1 (0.8) [1.0]	1 (0.8) [0.96]	1 (0.8) [0.83]	15 (3.2) [2.02]
Oral herpes	2 (1.6) [1.93]	3 (2.5) [3.07]	1 (0.8) [0.97]	1 (0.8) [0.82]	11 (2.4) [1.47]
Eczema herpeticum	0	0	0	1 (0.8) [0.82]	3 (0.6) [0.40]
Ophthalmic herpes simplex	1 (0.8) [0.96]	0	0	1 (0.8) [0.83]	2 (0.4) [0.26]
Maximum severity					
Mild	3 (2.4) [2.91]	3 (2.5) [3.06]	2 (1.7) [1.94]	1 (0.8) [0.83]	17 (3.6) [2.29]
Moderate	1 (0.8) [0.96]	1 (0.8) [1.00]	0	2 (1.7) [1.65]	9 (1.9) [1.21]
Severe	0	0	0	1 (0.8) [0.83]	2 (0.4) [0.26]
SAE	0	0	0	1 (0.8) [0.83]	4 (0.9) [0.53]
Led to study drug interruption	3 (2.4) [2.90]	1 (0.8) [1.00]	0	2 (1.7) [1.65]	9 (1.9) [1.20]
Led to study drug discontinuation	1 (0.8) [0.96]	0	0	0	1 (0.2) [0.13]
Treated with antiviral medicine	3 (2.4) [2.90]	4 (3.3) [4.09]	0	3 (2.5) [2.49]	19 (4.1) [2.57]
Recovered or resolved	4 (3.3) [3.88]	3 (2.5) [3.07]	2 (1.7) [1.94]	4 (3.3) [3.37]	25 (5.4) [3.43]

Abbreviations: BARI = baricitinib; IR = incidence rate; Med = medium; n = number of participants in the specified category; N = number of participants in the safety population; PBO = placebo; SAE = serious adverse event; TE = treatment-emergent.

Source: Table JAIP.8.3.41

Tuberculosis and opportunistic infections

No cases of tuberculosis were reported in the JAIP study. One participant (0.2%, IR 0.13; high dose) in the All BARI AD set had a confirmed opportunistic infection (disseminated herpes zoster, see case narrative at section on Herpes zoster).

Viral reactivation

Among those with a detectable Hepatitis B core antibody at baseline and a postbaseline test result (n = 4 in the **All BARI set**), no reactivation occurred post-baseline.

MACE and VTE

No cases of adjudicated MACE, other cardiac events, or VTE occurred.

Malignancy and NMSC

No cases of malignancy or NMSC occurred.

Physical growth, skeletal development, and fractures

Physical growth (height, weight, BMI) was assessed longitudinally throughout the JAIP study and was compared with age- and sex-matched peers (CDC 2000). The distribution of the observed percentile and Z-score remained consistent over time for the three growth parameters, and the change in

percentile or Z-score on average remained (close to) 0. In the **Ext Bari set**, mean (sd) weight changes were 3.47 kg (sd 4.6) in placebo (n = 41), 3.91 (sd 5.9) in low dose baricitinib (n = 44), 2.54 kg (sd 2.7) in medium dose baricitinib (n = 45), and 4.19 (sd 4.5) in the high dose baricitinib (n = 56). Generally, patients remained close to their growth percentile track and Z-score at which they entered the study. Overall (**All BARI set**), n = 61 (13%) of the patients had a treatment-emergent event of low weight (IR 8.9).

Skeletal development was quantified by taking wrist/hand/finger X rays at baseline, week 16, and every 6 months thereafter, using the *Greulich and Pyle* bone age method (*1959*). Knee X-rays were collected for assessment of growth plate closure at the distal femur and the proximal tibia; data sampling started after study enrolment due to a regulatory request and was performed every 6 months. Growth plates were classified as either open, narrowed, partially closed, or closed.

In the **Ext BARI set**, from those who had *X-rays of hand/wrist/fingers* at baseline, 34 patients in the placebo group had X-rays at 52 weeks, versus 36, 37, and 47 in the low, medium, and high dose baricitinib groups. Mean differences were -0.14 (sd 1.4) in the placebo group and -0.06 (sd 1.6), 0.19 (sd 1.3), and -0.08 (sd 1.5) for the baricitinib groups. The majority of patients remained in their baseline category or shifted towards normal, i.e. they remained within the boundaries of a mean difference between chronological and bone age <2 years (Table 25), although the number of patients at long-term follow-up rapidly decreased.

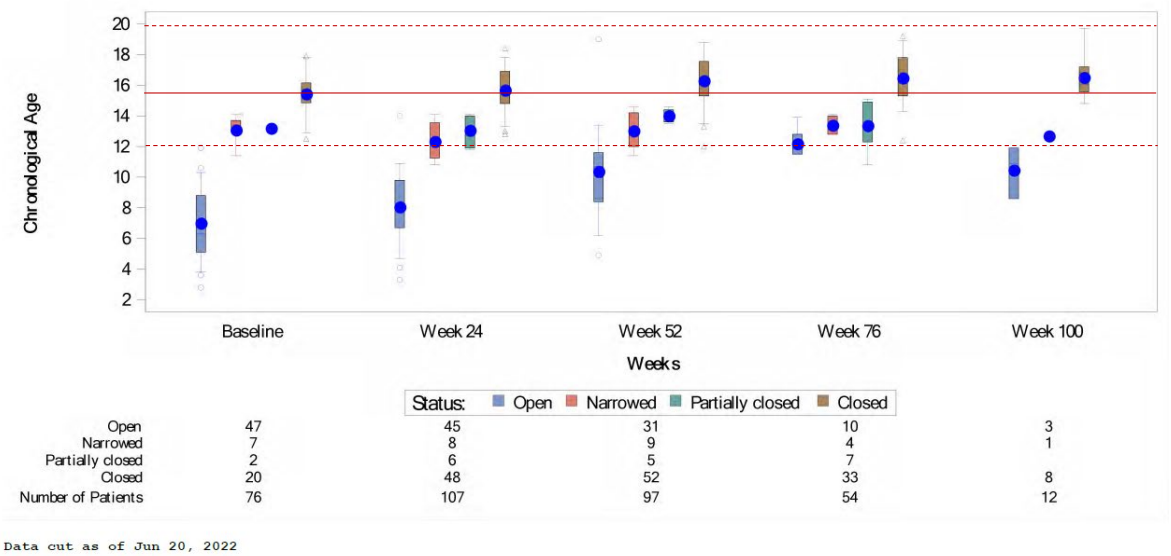
Table 25. All BARI Population: Percentage of Participants in the Normal Range (Absolute Difference between Bone Age and Chronological Age <2 Years) at Each Time Point (Hand/Wrist/Finger X-ray)

	Extended BARI Population				
Time Point	**PBO n/N (%)**	**BARI Low n/N (%)**	**BARI Medium n/N (%)**	**BARI High n/N (%)**	**All BARI n/N (%)**
Baseline for participants with a 52-week result	28/33 (84.8)	27/35 (77.1)	30/36 (83.3)	34/45 (75.6)	227/284 (79.9)
52 weeks	29/33 (87.9)	29/35 (82.9)	32/36 (88.9)	38/45 (84.4)	237/284 (83.5)
76 weeks	23/27 (85.2)	18/21 (85.7)	24/28 (85.7)	32/37 (86.5)	187/228 (82.0)
100 weeks	10/12 (83.3)	7/12 (58.3)	10/14 (71.4)	13/14 (92.9)	102/127 (80.3)
124 weeks	No data	No data	No data	No data	39/49 (79.6)

Abbreviations: BARI = baricitinib; Med = medium; n = number in normal category; N = number observed; PBO = placebo.
Sources: Table JAIP.8.3.70 and Table JAIP.8.3.71

Knee X-ray growth plate closure data were presented for both the distal femur and the proximal tibia at baseline and weeks 24, 52, 76, and 100; data for the distal femur are presented below (Table 26 for females and Table 27 for males). The red lines indicate the minimal, mean, and maximum age of growth plate closure observed. Please note that these graphs were not yet updated as from the data cut off in the initial application. Results show increasing growth plate closure with progressing age, which is to be expected. In females, growth plate closure was observed as early as 12 years of age, and in males this was slightly older than 13 years.

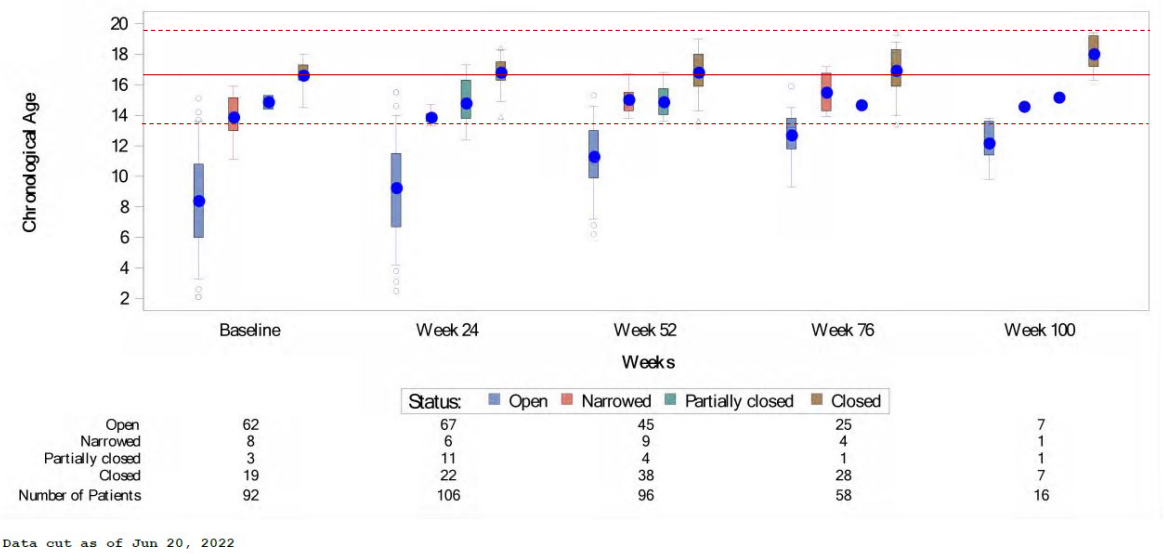
Table 26. Knee X-ray based growth plate closure of distal femur in females



Open	47	45	31	10	3
Narrowed	7	8	9	4	1
Partially closed	2	6	5	7	
Closed	20	48	52	33	8
Number of Patients	76	107	97	54	12

Data cut as of Jun 20, 2022

Table 27. Knee X-ray based growth plate closure of distal femur in males



Open	62	67	45	25	7
Narrowed	8	6	9	4	1
Partially closed	3	11	4	1	1
Closed	19	22	38	28	7
Number of Patients	92	106	96	58	16

Data cut as of Jun 20, 2022

Fractures were studied as part of the bone safety and growth monitoring program in the JAIP study.

In the **PC BARI set**, 4 fractures were seen in the pooled baricitinib group (1.1%) versus 1 (0.8%) in the placebo group. Among these, 1 knee trauma occurred in the low dose group, and 2 radius fractures and 1 hand fracture occurred in the high dose group. All fractures were associated with trauma, and they all recovered. In the **Ext BARI set**, 4 fractures were reported in the low dose baricitinib group (3.3%, IR 4.1; 1 radius fracture, epiphyseal fracture, foot fracture, and joint injury) and 3 in the high dose baricitinib group (2.5%, IR 2.5; one hand fracture and two radius fractures). All fractures recovered.

Considering all patients treated with baricitinib (**All BARI set**), 16 fractures were reported (3.4%, IR 2.1). An additional number of 3 hand fractures, 1 radius fracture, 1 wrist fracture, 1 ankle fracture, 1 foot fracture, and 2 forearm fractures) was seen (Table 28). All bone fractures were trauma-related and recovered; 15/18 fractures occurred in patients in the older age group.

Table 28. Summary of Fractures in Ext BARI AD Peds and All BARI AD Peds Analysis Sets

	Extended BARI Population				
Preferred Term	PBO	BARI Low Dose	BARI Med Dose	BARI High Dose	All BARI
All Patients (2 to <18 Years)	N=123 n (%) [IR]	N=120 n (%) [IR]	N=120 n (%) [IR]	N=120 n (%) [IR]	N=467 n (%) [IR]
Fracture (cluster)	2 (1.6) [1.9]	4 (3.3) [4.1]	0	3 (2.5) [2.5]	16 (3.4) [2.1]
Hand fracture	0	0	0	1 (0.8) [0.8]	4 (0.9) [0.5]
Radius fracture	0	1 (0.8) [1.0]	0	2 (1.7) [1.7]	4 (0.9) [0.5]
Wrist fracture	1 (0.8) [1.0]	0	0	0	2 (0.4) [0.3]
Ankle fracture	0	0	0	0	1 (0.2) [0.1]
Epiphyseal injury (actual term: injury of epiphyseal plate)	0	1 (0.8) [1.0]	0	0	1 (0.2) [0.1]
Foot fracture	0	1 (0.8) [1.0]	0	0	2 (0.4) [0.3]
Forearm fracture	0	0	0	0	2 (0.4) [0.3]
Joint injury (actual term: trauma to the knee)	0	1 (0.8) [1.0]	0	0	1 (0.2) [0.1]
Upper limb fracture	1 (0.8) [1.0]	0	0	0	0

Abbreviations: BARI = baricitinib; IR = incidence rate; Med = medium; n = number of participants in the specified category; N = number of participants in the safety population; PBO = placebo.
Source: Table JAIP.8.3.57.

Allergic reactions and hypersensitivity

A larger proportion of patients in the placebo group (n = 9, 7.4%) compared to the low, medium, and high dose baricitinib groups (n = 4, 3.3%; n = 6, 5.0%; and n = 4, 3.3% resp.) reported AE's related to allergic reactions and hypersensitivity (narrow) (n = 9, 7.4% versus n = 4, 3.3%) in the **PC BARI set**.

In the **Ext BARI set**, no dose response relation was observed.

Overall, 58 patients (12.4%, IR 8.27) in the **All BARI set** had at least 1 TEAE (narrow search). Angioedema (narrow) was found for 13 (2.8%, IR 1.75) patients, and PT's were Urticaria (n = 9), Angioedema (n = 2), Eyelid oedema, Face oedema, and Urticaria cholinergic (n = 1 for each).

Two anaphylactic reactions occurred in the JAIP study (All BARI set; 0.4%) which were both ascribed to known allergies. One case had an allergic reaction to food, at day 296 after starting baricitinib. The other patient had anaphylaxis that required treatment in the ER, due to underlying baseline allergies; study drug was not changed.

Laboratory findings

Lipids

Total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were investigated during the JAIP study.

A dose-dependent increased frequency in shifting towards '(borderline) high' was observed for both total cholesterol and LDL cholesterol in the **PC BARI set** (Table 29) and the **Ext BARI set**. A total of 8.8% (n = 37) of the patients in the **All BARI set** had total cholesterol that increased to high, and 20% (n = 75) of the patients had an LDL that increased to borderline or high. Increased triglycerides and decreased HDL were more common in placebo compared to the baricitinib groups in the **Ext BARI set**.

Similar proportions of hyperlipidemia-related TEAE's (PT: blood cholesterol increased and hypertriglyceridemia) were reported in the pooled baricitinib group (n = 3, 0.8%), baricitinib high dose group (n = 1, 0.8%), and the placebo group (n = 1, 0.8%) of the **PC BARI set**. A total of 7 patients (1.5%) reported 1 or more hyperlipidemia-related AE's (PT hypercholesterolemia, hypertriglyceridemia, blood cholesterol increased, and blood triglycerides increased).

Table 29. Clinically Relevant Changes in Laboratory Analytes PC BARI Set

Analyte	Category	PBO n/NAR (%)	BARI Low Dose n/NAR (%)	BARI Med Dose n/NAR (%)	BARI High Dose n/NAR (%)	All BARI n/NAR (%) [IR]
Cholesterol	Increase to "high"	2/102 (2.0)	2/98 (2.0)	9/97 (9.3)	10/98 (10.2)	21/293 (7.2)
LDL cholesterol	Increase to "borderline high" or "high"	5/94 (5.3) [4.86]	8/90 (8.9) [8.04]	10/94 (10.6) [9.65]	22/89 (24.7) [18.10]	75/370 (20.3) [9.99]
	Increase to "high"	6/108 (5.6) [5.83]	2/101 (2.0) [2.01]	6/106 (5.7) [5.79]	10/105 (9.5) [8.23]	37/419 (8.8) [4.93]
HDL cholesterol	Decrease to "low"	22/95 (23.2) [21.39]	7/77 (9.1) [7.04]	7/102 (6.9) [6.76]	5/89 (5.6) [4.11]	33/358 (9.2) [4.40]
	Increase to "acceptable"	11/35 (31.4) [10.69]	10/37 (27.0) [10.06]	11/22 (50.0) [10.62]	16/33 (48.5) [13.16]	74/113 (65.5) [9.86]
Triglycerides	Increase to "borderline high" or "high"	23/66 (34.8) [22.36]	20/60 (33.3) [20.11]	23/81 (28.4) [22.20]	24/68 (35.3) [19.74]	121/269 (45.0) [16.12]
	Increase to "high"	22/90 (24.4) [21.39]	17/89 (19.1) [17.09]	15/100 (15.0) [14.48]	11/87 (12.6) [9.05]	88/357 (24.6) [11.72]

Abbreviations: ALT = alanine aminotransferase; BARI = baricitinib; HDL = high-density lipoprotein; IR = incidence rate; LDL = low-density lipoprotein; Med = medium; n = number of participants in the specified category; NAR = number of participants at risk for the specified abnormality in each treatment group (missing excluded); PBO = placebo; ULN = upper limit of normal.
a One participant treated with BARI medium dose had elevated creatinine >1.5x ULN (at 1.1 mg/dL [1.6x ULN]), which returned to normal at next test.
Sources: Table JAIP.8.3.61, Table JAIP.8.3.62, and Table JAIP.8.3.63

Haematology

Neutrophils

Decreased neutrophil counts were more often observed in the baricitinib-treated patients compared to patients on placebo in the **PC BARI set** (201% in pooled baricitinib group versus 16% in placebo); of these, two were grade 3 (both in baricitinib high dose (1.7%) and placebo group (1.6%)) and three were grade 3 or higher in the low dose baricitinib group (0.8%). None were Grade 4. Among those with decreased neutrophil counts Grade 2 or higher, one patient had an infection (high dose baricitinib, 14%; bronchitis) versus 2 in the placebo group (33%; rhinitis, tonsillitis, upper respiratory tract infection).

In the **Ext BARI set**, Grade 3 decreased neutrophils were found in 8 patients using baricitinib (2 (1.7%) in the low, 2 (1.7%) in the medium, and 4 (3.3%) in the high dose group), pointing to a higher risk for decreased neutrophils in the highest baricitinib dose. No decreased neutrophil counts grade 4 were observed in any of the groups. Overall, (**All BARI set**) grade 3 decreased neutrophil counts were seen in 14 patients (3.0%). No grade 4 decreases were reported.

For both the Ext BARI set and the All BARI set, serious infections were tabulated versus neutropenia in Table 30 below.

Table 30. Summary of Infections and Neutropenia

	Extended BARI Population				
	PBO n (%) [IR]	**BARI Low Dose n (%) [IR]**	**BARI Med Dose n (%) [IR]**	**BARI High Dose n (%) [IR]**	**All BARI n (%) [IR]**
All study participants (2 to <18 years old)	**N=122**	**N=120**	**N=120**	**N=120**	**N=466**
Patient-years of exposure	*79.9*	*78.6*	*79.1*	*91.1*	*533.6*
Patients with ≥1 TE of Infection	46 (37.7) [78.37]	44 (36.7) [69.67]	44 (36.7) [72.64]	45 (37.5) [62.15]	242 (51.9) [69.57]
Serious Infection	2 (1.6) [2.52]	0	0	2 (1.7) [2.20]	7 (1.5) [1.31]
Patients with Neutrophils Grade 2 or Higher	**N=6**	**N=7**	**N=6**	**N=7**	**N=25**
TE Infections Among Patients with Neutrophils Grade 2 or Higher (within ± 14 days)	2 (33.3) [81.8]	0	0	1 (14.3) [19.1]	2 (8.0) [7.2]

Abbreviations: BARI = baricitinib; IR = incidence rate; Med = Medium; N = number of participants in the analysis population; n = number of participants in the specified category; PBO = placebo; PYE = patient-years of exposure; TE = treatment-emergent.
Sources: Table JAIP.8.2.32 in CSR addendum 1; Table JAIP.4.6.1 in CSR addendum 1;Table JAIP.8.2.45 in CSR addendum 1.

Lymphocytes

Decreased lymphocyte counts were less often observed in the baricitinib groups compared to the placebo group (5.0% in pooled baricitinib versus 7.4% in placebo), and most were Grade 1 or 2 in the **PC BARI set**. None were Grade 4. Grade 3 was seen in 1 patient on high dose baricitinib (0.8%) and 1 patient in the placebo group (0.8%). A relation between decreased lymphocytes (Grade 2 or higher) and infections could not been found due to small numbers (1 in high dose baricitinib, nasopharyngitis; and 1 in placebo, tonsillitis).

In the **Ext BARI set**, decreased lymphocyte counts grade 3 was found in 1 patient using baricitinib (0.8%, high dose group); the relation between baricitinib treatment and decreased lymphocyte counts could not be verified.

In the **All BARI set**, 2 patients (0.4%, IR 0.27) had Grade 3. Only 2 of the patients with decreased lymphocytes Grade 2 or higher had infections (influenza and nasopharyngitis).

Hemoglobin

In the **PC BARI set**, Hb decreases were seen in 11.5% (n=14) in the placebo group versus 12.5% (n=15), 13.4% (n=16), and 15.8% (n=19) in the baricitinib low, medium and high dose groups. In the baricitinib groups, all concerned Hb decreases were classified as Grade 1, and none as Grade 2 or higher.

In the **Ext BARI set**, no abnormal values ≥ Grade 2 were observed for haemoglobin.

In the **All BARI set**, 1 patient (0.2%) using baricitinib showed a decrease in Hb classified as CTCAE Grade 2. No abnormal values ≥ Grade 2 were observed.

Platelets

Increased platelet numbers were observed in 2 patients (1.7%) in the low dose baricitinib group (**PC BARI set**), 1 patient (0.8%) in the high dose baricitinib group (0.8%), and 1 (0.8%) in the placebo group. These all concerned Grade 1. Thrombocytes ≤ 600 billions/L to > 6000 billions/L in the Ext BARI group was found in 1 patient in the placebo group (0.8%), and 3 in each dose baricitinib group (2.5% each); 18 cases were observed altogether in the **All BARI set** (3.9%).

Liver enzymes

In the **PC BARI set**, no ALT or AST ≥ 3 ULN was found in any of the baricitinib-treated patients, compared to 2 (ALT) in the placebo group. TBL was increased ≥ 2 ULN in 1 patient on low dose baricitinib and 1 on placebo without other liver enzyme increases, and a direct bilirubin < 30%. Increased ALP values were more frequent in placebo than in (pooled) baricitinib (3.3% versus 2.2%), corresponding physiological growth.

No dose-response could be observed in the **Ext BARI set**. In the **All BARI set**, 6 patients (1.3%) had AST levels ≥ 3 ULN, 2 (0.4%) had AST ≥ 5 ULN, and 1 (0.2%) ≥ 10 ULN, each with normal total bilirubin. Two patients (0.4%) had ALT levels ≥ 3 ULN; no higher levels were observed and no patient had concomitant complaints. Serum bilirubin was increased ≥ 2 ULN in 7 patients (1.5%) which is likely due to Gilbert syndrome; no higher levels were observed. Increased ALP values ≥ 1.5 ULN were found in 28patients (6.0%), and ≥ 2 ULN in 8 patients (1.7%), which is most likely related to normal physiological bone growth.

Other laboratory findings

Creatine phosphokinase changes and muscle related symptoms

Increased CK values were more frequent for baricitinib-treated patients in the **PC BARI set** (n = 68, 18.9% for the pooled baricitinib group) compared to those in the placebo group (n = 19, 15.6%). Most had CTCAE Grade 1 or 2. Grade 3 was found for placebo (n = 1, 0.8%) and 2 in baricitinib (1 in low and 1 in medium dose; both 0.8%). TEAE's myalgia were reported by 2 patients (1 in placebo and 1 in baricitinib low dose; 0.8% each).

In the **Ext BARI set**, 3 patients in the placebo group (2.5%) versus 5 (4.2%), 2 (1.7%), and 2 (1.7%) patients in the low, medium and high dose baricitinib groups had increased CK values Grade 3. Grade 4 increases were seen in 2 (1.6%), 2 (1.7%), 0, and 1 (0.8%) of the patients respectively. In the **All BARI set** 179 patients (38.7%) had any Grade of increased CK, with 20 patients having Grade 3 (4.3%), and 9 (1.9%) Grade 4.

In the majority of cases, increased CK was ascribed to physical exercise or athletic activity by the investigator; a CTCAE Grade 2 or higher was not associated with AEs of muscle injury (myalgia).

Serum glucose

In the **PCBARI set**, the percentages of patients with the TEAE low fasting serum glucose was higher for the patients treated with baricitinib versus those in the placebo group. Mean changes during the placebo-controlled period were rather small (between -0.01 and + 0.19 for the placebo and the baricitinib groups), without a dose-response relation.

In the **Ext BARI set**, 2 (1.6%, IR 2.0) patients had low fasting serum glucose, versus 7 (5.8%, IT 7.2), 9 (7.5%, IR 9.6), and 5 (4.2%, IR 4.2) in the low, medium, and high dose baricitinib groups. In the **All BARI set** 35 patients reported low fasting serum glucose 7.5%, IR 4.9). The majority of cases had only one episode reported of low fasting serum glucose and there were no adverse events reported associated with hypoglycaemia. Seven episodes of serum fasting glucose < 3.0 were reported, with the lowest value of 1.11 mmol/L in two separate patients.

Safety in special populations

The impact of intrinsic and extrinsic factors on the occurrence of common TEAE's (defined as occurring ≥ 2% in the participants in the PC BARI set) was evaluated to identify possible subgroups of patients on baricitinib with different AE profiles compared to other subgroups.

The TEAE's assessed were acne, abdominal pain, abdominal pain upper, bronchitis, COVID-19, decreased appetite, diarrhoea, gastro-enteritis, headache, nasopharyngitis, and upper respiratory tract infection.

Intrinsic factors were defined as baseline renal function, age (young versus older age group), gender (female, male), baseline BMI (<18.5 kg/m2 [underweight], ≥18 - <25 kg/m2 [normal weight], ≥25 to <30 kg/m2 [overweight] and ≥30 [obese], and race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islanders, White, and multi-racial). Extrinsic factors were defined as region of the world (Europe, Japan and the rest of the world), and prior systemic therapy for AD (yes versus no).

Gender

Out of 466 participants in the **All BARI set** 50.4% were female, and 49.6% were male. TEAE's were more common in females (n=172, 73.2%, IR 154.3) versus males (n=154, 66.7%, IR 126.1). TEAE's reported at higher IR in females versus males, were (by SOC):

- Immune system disorders (n=12, 5.1%, IR 4.5 versus n=5, 2.2%, IR 1.9),
- Reproductive system and breast disorders (n=14, 6.0%, IR 5.3 versus n=2, 0.9%, IR 0.8), mostly driven by Dysmenorrhoea (IR 2.2 versus 0), and
- Surgical and medical procedures (n=7, 3.0%, IR 2.6 versus n=2, 0.9%, IR 0.8.

No clear differences in IR's for TEAE's by SOC were reported in males versus females.

Age

At baseline, 133 patients (28.5%) were aged 2 to <10 years, and 333 (71.5%) were 10 to < 18 years.

TEAE's with ≥ 2% of patients in the high dose baricitinib group in the **PC BARI set** were assessed for differences with regard to age categories. In the **PC BARI set**, the proportion of younger patients experiencing at least 1 TEAE in the pooled baricitinib group (15.3%, n = 55) was almost half the proportion of the older age group (35.8%, n = 129), and this was also true for the placebo group (17.2%, n = 21) in younger age group versus 32.8% (n=40) in older age group).

In the **All BARI set,** TEAE's were more common in the younger age group (n = 108, 81%, IR 161) than in the older age group (n = 254, 76%, IR 115), and this was also observed for SAE's (6.7%, IR 5.3 versus 6.6%, IR 3.9 resp.) and AE's leading to discontinuation of study drug (3.7%, IR 2.9 versus 2.4%, IR 1.4 resp.). Most TEAE's were mild/moderate in both groups (Table 18 and Table 19).

TEAE's more common in younger versus older age groups in the **All BARI set**, were (by SOC / SMQ):

- Respiratory, thoracic, and mediastinal disorders (n=24, 18%, IR 24.0 in younger age group versus n=33, 9.9%, IR 8.3 in older age group), mostly drive by Cough (IR 6.3 versus IR 0.9), Bronchospasm (IR 3.6 versus IR 0.2), and Oropharyngeal pain (IR 3.6 versus IR 0.5).

TEAE's more common in older versus younger age groups in the **All BARI set**, were (by SOC / SMQ):

- Skin and subcutaneous tissue disorders (n=73, 22%, IR 20.5 versus n=11, 8.3%, IR 10.3), mostly driven by Acne (IR 10.1 versus IR 1.8).

- Injury, poisoning and procedural complications (n=32, 9.6%, IR 8.0 versus n=4, 3.0%, IR 3.6),
- Eye disorders (n=19, 5.7%, IR 4.6 in older age group versus n=2, 1.5%, IR 1.8 in younger age group),
- Psychiatric disorders (n=11, 3.3%, IR 2.7 versus n=0), and

Weight

Out of 466 participants in the **All BARI set** 102 (22%) were < 30 kg, and 364 (78%) were ≥ 30 kg. TEAE's had a higher IR in the <30 kg subgroup (69%, IR 161.7) than in the ≥ 30 kg subgroup (70%, IR 134.5). TEAE's reported at higher IR in <30 kg versus ≥ 30 kg group, were (by SOC):

- Immune system disorders (n=5, 4.9%, IR 5.8 versus n=12, 3.3%, IR 2.7, respectively), mostly driven by Food allergy (IR 2.3 versus IR 0.9), and
- Respiratory, thoracic and mediastinal disorders (n=20, 19.6%, IR 26.4 versus n=37, 10.2%, IR 8.8), mostly driven by Cough (IR 7.0 versus IR 1.1), Bronchospasm (IR 3.4 versus IR 0.4), and Oropharyngeal pain (IR 3.5 versus IR 0.7).

TEAE's reported at higher IR in ≥ 30 kg versus <30 kg group, were (by SOC):

- Injury, poisoning and procedural complications (n=33, 9.1%, IR 7.8 versus n=3, 2.9%, IR 3.5)
- Nervous system disorders (n=52, 14.3%, IR 13.0 versus n=5, 4.9%, IR 5.8), mostly driven by Headache (IR 8.9 versus IR 4.6),
- Psychiatric disorders (n=11, 3.0%, IR 2.5 versus n=0), and
- Surgical and medical procedures (n=9, 2.4%, IR 2.0 versus n=0).

The safety data in the weight group below 30 kg was also presented by weight class with a cut-off of 20 kg (Table 31). The safety in these two subgroups will also be followed post-marketing. In the subgroup of 10 to <20 kg, there were less patients with at least 1 TEAE but these were more frequently of moderate severity. SAEs were infrequent in both groups and overall not considered related to treatment, except for one case of corneal abscess and ophthalmic herpes simplex in a patient weighing 20 to <30 kg (also presented in the SAE section and the infection section). There was no apparent difference in the occurrence of infections between the two groups, except for the number of patients with skin infections requiring antibiotic treatment. None of the skin infections requiring antibiotic treatment in patients weighing 10 to less than 20 kg was severe, serious, or led to discontinuation of study treatment.

Table 31. Overview of TEAES in patients weighing 10 to <20 kg or weighing 20 to <30 kg of the All Baricitinib population (N=102) of study JAIP

Parameter, n (%) [IR]	**20 to <30 kg PYE=59.5 N=59**	**10 to <20 kg PYE=27.8 N=43**
Patients with ≥1 TEAE	42 (71.2) [143.4]	28 (65.1) [199.9]
TEAEs by severity		
Mild	29 (49.2) [72.5]	9 (20.9) [36.7]
Moderate	10 (16.9) [18.9]	17 (39.5) [84.4]
Severe[a]	3 (5.1) [5.1]	2 (4.7) [7.1]
Death	0	0
SAEs	3 (5.1) [5.1]	4 (9.3) [14.4]
Discontinuation of the study drug due to AE[b]	2 (3.4) [3.3]	1 (2.3) [3.5]
Discontinuation from the study due to AE	2 (3.4) [3.3]	1 (2.3) [3.5]
Patients with ≥1 TE infection	32 (54.2) [82.1]	22 (51.2) [125.8]
Serious infections	2 (3.4) [3.4]	1 (2.3) [3.5]
Infections that led to permanent discontinuation of the study drug	1 (1.7) [1.7]	0
Infections that led to temporary interruption of the study drug	6 (10.2) [10.4]	5 (11.6) [19.6]
Confirmed TE opportunistic infection	0	0
TE herpes zoster	1 (1.7) [1.7]	0
TE herpes simplex	5 (8.5) [8.6]	2 (4.7) [7.1]
TE tuberculosis	0	0
Participants with ≥1 skin infection requiring antibiotic treatment	3 (5.1) [5.1]	6 (14.0) [22.6]

Abbreviations: AE = adverse event; IR = incidence rate; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the analysis population; n = number of subjects with an AE; PYE = patient-years of exposure; PYR = patient-years at risk; SAE = serious adverse event; TE = treatment emergent; TEAE = treatment-emergent adverse event.

[a] Severe TEAEs were also reported as SAEs (Table 2.2)

[b] AEs leading to discontinuation of the study drug were herpes zoster and myalgia in participants 20 to <30kg and urticaria in a participant 10 to <20kg.

Note: IR is the exposure-adjusted IR per 100 PYR.

Note: MedDRA Version 25.0

Note: Data cut-off as of 20 June 2022

BMI

Out of 466 participants in the **All BARI set**, 241 patients (51.7%) had a BMI <20 kg/m2, 206 patients (44.2%) had a BMI >20 to <30 kg/m2, and 18 patients (3.9%) had a BMI >30 kg/m2. The IR of TEAE's was 135.5, 141.9, and 156.1 respectively. No SOCs were clearly reported more often in one of the three groups.

Race

In the **All BARI set**, 346 patients (74.2%) were of White race, 85 (18.2%) Asian, 12 (2.6%) Black or African American, and 8 patients (1.7%) were of American Indian or Alaska Native race. One patient was reported multi-racial, and for 14 patients (3.0%) no race was reported. Excluding the latter two groups, the IR of TEAE's was highest for Black or African American (n=8, 66.7%, IR 169.5), White (n=243, 70.2%, IR: 138.2), and Asian patients (n=59, 69.4%, IR 136.0). Comparison of the two largest groups (White race and Asian race), TEAE's with a higher IR in the White versus the Asian subgroup (by SOC) were:

- Blood and lymphatic system disorders (n=19, 5.5%, IR 5.1 versus n=1, 1.2%, IR 0.9),

- Nervous system disorders (n=44, 12.7%, IR 12.6 versus n=4, 4.7%, IR 3.5), mostly driven by Headache (IR:8.6 versus IR 0.9),
- Psychiatric disorders (n=10, 2.9%, IR 2.6 versus n=1, 1.2%, IR 0.9),
- Reproductive system and breast disorders (n=13, 3.8%, IR 3.4 versus n=2, 2.4%, IR 1.7), and
- Respiratory, thoracic and mediastinal disorders (n=47, 13.6%, IR 13.0 versus n=7, 8.2%, IR 6.5), mostly driven by Asthma (IR 2.9 versus IR 0.9) and Cough (IR 2.3 versus IR0.9).

Region of the world

Out of 466 participants in the **All BARI set**, there were 166 (35.6%) in Europe, 35 (7.5%) in Japan, and 265 (56.9%) in the Rest of World. The IR of TEAE's was highest in Europe (n=132, 79.5%, IR 208.2) versus Japan (n=25, 71.4%, IR 148.3), and Rest of World (n=169, 63.8%, IR 110.2). TEAE's with a higher IR in Europe compared to Rest of World subgroup, were (by SOC):

- Nervous system disorders (IR 21.9 versus IR 7.8), mostly driven by Headache (IR 15.0 versus IR 5.6) and Dizziness (IR 3.9 versus IR 0.7),
- Gastrointestinal disorders (IR 21.8 versus IR 8.6), mostly driven by Diarrhoea (IR 7.3 versus IR 0.7), Vomiting (IR 4.9 versus IR 1.3), and Abdominal pain upper (IR 4.3 versus IR 1.0),
- Investigations (IR 12.3 versus IR 5.5, respectively), mostly driven by Blood creatine phosphokinase increased (IR 3.2 versus IR 1.4, respectively),
- Injury, poisoning and procedural complications (IR 11.5 versus IR 3.0) mostly driven by Ligament sprain (IR 3.2 versus IR 0.3),
- General disorders and administration site conditions (IR 10.3 versus IR 4.1), mostly driven by Pyrexia (IR 6.7 versus IR 2.7),
- Blood and lymphatic system disorders (IR 6.7 versus IR 3.1), mostly driven by Lymphadenopathy (IR 4.2 versus IR 0.3), and
- Eye disorders (IR 6.7 versus IR 2.7).

Prior systemic therapy

A total of 205 (44%) participants had used prior systemic therapy, versus 261 (56%) participants who had not used prior systemic therapy. The IR of TEAE's was higher in the group with prior systemic therapy (185.1) versus those without prior systemic therapy (IR 113.3). TEAE's reported more often in the Prior systemic therapy subgroup compared to the No prior systemic therapy subgroup, were (by SOC):

- Blood and lymphatic system disorders (IR 6.6 versus IR 2.0), mostly driven by Lymphadenopathy (IR 2.9 versus IR 0.7),
- Eye disorders (IR 6.2 versus IR 2.4), mostly driven by Conjunctivitis allergic (IR 1.3 versus IR 0.3),
- Immune system disorders (IR 5.2 versus IR 1.7), mostly driven by Food allergy (IR 2.1 versus IR 0.3), and
- Reproductive system and breast disorders (IR 4.3 versus IR 2.0), mostly driven by Dysmenorrhoea (IR 3.3 versus IR 1.4).

Discontinuation due to adverse events

In the placebo-controlled period (**PC BARI set**), 4 patients (2 in placebo, 1 in low dose and 1 in high dose baricitinib) permanently discontinued from study treatment. In the baricitinib group, these AE's were: Herpes zoster (baricitinib low dose, 9 years of age, resolved upon discontinuation), and Lichen planus (baricitinib high dose, 8 years of age, ongoing at discontinuation). Study treatment was temporarily discontinued more often in placebo compared to the baricitinib group. In the placebo group, 16 patients temporarily discontinued treatment (13%) versus 22 (6.1%) in the pooled baricitinib groups. In all but 5 patients, the interruption was due to an AE (mainly SOC Infections and infestations); other reasons were abnormal lab results and the investigator's decision.

In the **Ext BARI set**, one additional patient permanently discontinued the study drug (PT Myalgia) in the low dose baricitinib group. Study treatment was temporarily discontinued in 14 (11.7%) in the low dose group, 10 (8.3%) in the medium dose group, and 16 (13.3%) patients in the high dose group. Most common reasons were AE's in SOC Infections and infestations, with an IR of 11.8 in low dose, IR 6.5 in medium dose, and IR 11.5 in high dose baricitinib (Table 32).

In the **ALL BARI set,** an additional number of 7 patients treated with baricitinib (total number of 10; IR 1.9) permanently discontinued study drug due to AE's, which by PT were Dermatitis atopic (n = 2), Headache (n = 2), and Urticaria, Herpes Zoster, and Respiratory tract infection (n = 1 each). Study treatment was temporarily discontinued in 93 (20%, mean duration 10.3 days), 81% of the due to AE's in the SOC Infections and infestations (n = 49, IR 9.7).

Table 32. Summary of Temporary Interruptions of the Study Drug

	Extended BARI Population				
	PBO N=122 n (%)	BARI Low Dose N=120 n (%)	BARI Med Dose N=120 n (%)	BARI High Dose N=120 n (%)	All BARI N=466 n (%)
Participants with ≥1 dose interruption	21 (17.2)	14 (11.7)	10 (8.3)	16 (13.3)	93 (20.0)
Reasons for Dose Interruption					
Adverse Event	16 (13.1)	11 (9.2)	8 (6.7)	14 (11.7)	75 (16.1)
Abnormal Laboratory Result	4 (3.3)	3 (2.5)	0	2 (1.7)	11 (2.4)
Suspected Pregnancy	0	0	0	0	1 (0.2)
Investigator Decision[a]	3 (2.5)	2 (1.7)	0	0	8 (1.7)
Protocol (deviation)[b]	1 (0.8)	0	1 (0.8)	0	2 (0.4)
Other epidemic or pandemic reasons or mitigation[c]	0	0	0	0	2 (0.4)
Met pre-defined improvement criteria (voluntary study drug interruption)	2 (1.6)	0	1 (0.8)	0	1 (0.2)
Duration of dose interruption, mean days (SD)	17.1 (22.23)	6.2 (5.35)	15.6 (24.06)	17.2 (18.66)	10.3 (12.17)

Abbreviations: AD = atopic dermatitis; BARI = baricitinib; COVID = coronavirus disease; Med = medium; MMR = measles, mumps, and rubella; N = number of participants in the safety population; n = number of participants in the specified category; PBO = placebo; SD = standard deviation.

[a] Investigators' rationale for interrupting the study drug: participant's AD was worsening (3 cases) and due to risk of infection (2 cases), interrupted due to procedure (1 case), COVID vaccine (4 cases), and other live vaccine (1 case).

[b] Interruptions due to protocol (deviation) were due to use of systemic steroid, due to live vaccine, and due to delay of laboratory result availability to confirm eligibility.

[c] Interruptions due to live vaccination (MMR) or COVID vaccine.

Source: Table JAIP.8.2.31.

2.5.1. Discussion on clinical safety

The safety profile of baricitinib is quite well established, mainly based on data from adults with RA. Recently a comparable safety profile with RA was observed in adults with AA or AD.

The Art 20 **JAK referral** imposed stricter warning text (SmPC section 4.4) for serious infection, MACE, VTE, and malignancy including NMSC for baricitinib. The posology is being adjusted, in that for adult patients with risk factors for MACE, VTE, and malignancy the 2 mg dose is recommended over the 4 mg dose (irrespective of the indication). No such specific statements are included for the paediatric population. This can be agreed because MACE, VTE, and malignancy a priori are rare in children and no such events occurred in the JAIP study. Furthermore, this is in line with the SmPC for Rinvoq (paediatric population with AD) and the procedure for JIA (EMA/H/C/004085/X/0035/G). An additional warning to point to the class effects of oral JAK inhibitors covered by the Art. 20 referral is considered not required, because paediatric patients do not tend to accumulate risk factors for MACE, VTE, malignancies and NMSC, and existing warnings, e.g., for serious infections, NMSC, etc. already apply.

Clinical studies and exposure

Safety data of baricitinib in paediatric patients with AD originate from one pivotal phase III study (JAIP) including 467 patients. At time of data cut-off, 751 PYE were available, with 385 patients exposed for over 52 weeks. From these patients, 286 were older aged (10 to <18 years) and 99 were younger aged (2 to <10 years) children. After completion of the JAIP study, in December 2026, long-term safety data in the youngest age group will be available for a maximum of 133 patients, which is considered sufficient. However, rather than age-based, the population stratification based on body weight is considered more relevant, as this corresponds to the proposed posology using a cut-off body weight of 30 kg. Since the exposure in paediatric patients weighing 10 to <20 kg is higher compared to adults with the proposed posology, the probability of developing adverse events could increase. Therefore, the MAH committed to follow safety in these weight groups, especially also in the children weighing 10 to <20 kg (see PK section).

Three safety databases were defined from the JAIP study. The **PC BARI set** enables placebo-controlled comparison of the safety of baricitinib during 16 weeks of treatment, including the effect of dose. The **Ext BARI set** adds long-term dose related safety data from the LTE study, but interpretation is complicated because only patients with at least some response (IGA 0, 1, or 2) proceed with their allocated dose or placebo in the LTE and due to the selective drop-out it does not totally represent a placebo-controlled study period. The **All BARI set** includes significantly more PYE (total PYE 751) including exposure >1 year on baricitinib.

Permanent discontinuation and temporary discontinuation of baricitinib during the JAIP study were infrequent in the PC and Ext BARI sets, but up to 20% in the All BARI set. AE's were the most common reasons for discontinuation, mainly Infections and infestations. There was no difference with placebo. Overall, 10 patients (IR 1.9) using baricitinib permanently discontinued, and 93 patients (20%) temporarily discontinued. Mean duration of interruption was longest in the high dose baricitinib group, but still comparable to the placebo group.

Overview of adverse events

No **deaths** were reported during the JAIP study.

Overall, the **most common TEAE's** for baricitinib in paediatric patients with moderate to severe AD were generally in line with the known ADR's for baricitinib. In the placebo-controlled period, TEAE's by **SOC** that occurred more frequently in high dose baricitinib compared to placebo, were Gastro-intestinal disorders (15% for high dose baricitinib versus 11% for placebo), Blood and lymphatic system disorders (3.3% versus 1.6%), and Investigations (3.3% versus 1.6%). TEAE's by **PT** that

occurred more frequently in high dose baricitinib compared to placebo were Abdominal pain (5.0% versus 2.5%), Upper respiratory tract infections (4.2% versus 0.8%), Diarrhoea (4.2% versus 1.6%), Abdominal pain upper (3.3% versus 0.8%), Bronchitis (2.5% versus 0.8%), and Gastro-enteritis and Decreased appetite (each 2.5% versus 0%). Abdominal pain, upper respiratory tract infections, diarrhoea, and gastro-enteritis are acknowledged ADR's for baricitinib; no additional safety measures are considered required.

Considering all data from the JAIP study, **dose response relations** were observed for Upper respiratory tract infections (including Influenza and Cough), and Gastro-enteritis / gastro-intestinal symptoms (Abdominal pain, Abdominal pain upper, Diarrhoea, and Decreased appetite).

TEAE's generally were mild to moderate in severity; **severe TEAE's** were more frequent in placebo group than in the pooled baricitinib group during the double-blind period. Altogether, 28 severe TEAE's were reported during baricitinib use in the JAIP study so far. Food allergy was reported three times, Dermatitis atopic and Ophthalmic herpes simplex were reported twice; the other TEAE's were reported just once. Among the severe TEAE's there were 10 infections, i.e. Ophthalmic herpes simplex infection (n = 2), Corneal abscess, Fungal skin infection, Herpes simplex, Impetigo, Eczema impetiginous, EBV infection, urinary tract infection with E. coli, and Gastrointestinal bacterial infection (all n = 1). Tonsillar hypertrophy might also be the result of an infection. The remaining severe TEAE's were generally not considered associated with baricitinib, but with atopic dermatitis or atopic constitution more generally.

Serious adverse events

Rates of **SAE's** were low, but highest in the high dose baricitinib group and the placebo group. In the Ext BARI set, IR's increased with increased dosing (IR 2.0, 2.89, and 3.4 for low, medium, and high baricitinib dose). Considering all patients who received at least one dose baricitinib (All BARI set), 31 SAE's were reported, with Ophthalmic herpes simplex, Herpes simplex, Asthma, and Dermatitis atopic reported more than once. The Herpes cases were all in the high dose, older age group, except for one case of ophthalmic herpes (SAE) in a patient weighing 20 – 30 kg. Not all SAE's were associated with baricitinib use (see also above), including events of angio-edema which occurred > 30 days after treatment termination.

One SAE of juvenile epilepsy (EEG confirmed) was reported in a patient using high dose baricitinib (4 mg QD). Considering the entire baricitinib database as presented by the MAH, thus including also data from RA, AD, AA, and JIA, an association with baricitinib treatment was considered unlikely mainly because of: a) relevant comorbidity such as (fatal) sepsis which may evoke seizures, b) long-term use of baricitinib before first event, c) occurrence of a single event despite treatment continuation, d) occurrence of an epileptic event / seizure > 2 weeks after treatment termination, and / or e) the limited amount of BBB crossing (1-2%).

Adverse events of special interest

Infections are included in sections 4.4 and 4.8 of the SmPC; serious infections are an important potential risk for baricitinib (see also section on SAE's above). Current data align with findings in other indications, in that infections are mainly mild to moderate and predominantly comprise nasopharyngitis, upper respiratory tract infections, bronchitis, and COVID. Although increasing rates with increasing baricitinib doses were seen, still higher rates were seen in the placebo group than in the high dose baricitinib group. Herpes zoster and herpes simplex occurred in a few patients, and one had a disseminated herpes zoster infection classified as opportunistic (but not an SAE). This patient fully recovered. Eleven patients (2.4%) experienced at least 1 severe infection. Tuberculosis did not emerge. Thus, the current text in the SmPC on infections is considered adequate and does not require rephrasing.

No additional safety measures are considered necessary on (serious) infections in the SmPC, because: 1) infections (including herpes zoster) are already listed as ADR for baricitinib, 2) serious infections are listed as important potential risk in the RMP, 3) section 4.4 already includes warnings in case of infections prior to start of baricitinib as well as during use of baricitinib, and finally 4) stricter warning texts have already been included on serious infections in section 4.4 of the SmPC and also dose recommendations were included based for those at risk for e.g. serious infections based on the JAKi article 20 referral.

MACE, VTE (both important identified risks of baricitinib), and **Malignancies** and **NMSC** (important potential risks) were not observed in the paediatric AD population. Although these safety issues *might* hypothetically emerge in the paediatric population the risks are considered nil; the texts in the current SmPC are considered adequate.

Non-clinical data from baricitinib in juvenile rat studies have given rise to concerns on **physical growth, skeletal development,** and **fractures** (*EU Risk management plan version 17.1; VV-PVG-098605*); adverse effects were observed at doses 0.6- to 10-fold the exposure in humans at 4 mg/day. Upon request the MAH provided more detailed data on this issue. Physical growth parameters indicated that patients generally remained close to their growth percentile and Z-score, which is reassuring. Data on skeletal development was illustrated by X-rays; data were available for a subset of patients only. The MAH provided a comparison with medical literature for reference and generally the data from the JAIP study corresponded to this. The lowest reported age of growth plate closure in the JAIP study was younger than in the general population (12 years for the female population and slightly older than 13 years for the male population. However, the few instances of early growth plate disclosure usually were related to advanced bone age at baseline. A total of 16 fractures was reported in the All BARI set; all were trauma related and recovered. The majority was in the upper extremity, which corresponds to fracture patterns in general. There was no clear dose response. Fractures were more frequent in the older age group, which can be understood given the main cause of the fractures (i.e. trauma / sports). The reported IR for fractures in the JAIP study does not exceed the IR in the general population. Follow-up is however too short to draw firm conclusions, and due to the effects on bone metabolism detected in non-clinical data, 'impaired growth and skeletal development in children >2 years of age and adolescents' is added as important potential risk to the safety specification of the RMP.

Laboratory findings

Raised blood **lipids**, notably high LDL-cholesterol and hypertriglyceridemia are acknowledged ADR's for baricitinib, and it is recommended to monitor lipid values during treatment (SmPC section 4.4). Higher levels of total cholesterol and LDL cholesterol were indeed observed in the JAIP study for those treated with baricitinib versus placebo, with an evident dose dependency. Because hyperlipidemia is (much) less common in the general paediatric population, it is now explicitly mentioned in the SmPC that lipid levels should be monitored and treated according to international clinical guidelines in '*paediatric and adult patients treated with baricitinib*'.

Baricitinib is known to affect **haematologic parameters**; Thrombocytosis > 600 x 109 cells/L and neutropenia < 1 x 109 cells/L are ADR's included in section 4.8 and lymphopenia and decreased haemoglobin are included in section 4.4 of the SmPC of baricitinib. In the placebo-controlled period, decreased neutrophil counts grade 2 and 3 were more common in baricitinib treated patients (21%) compared to placebo (16%), and the highest rates were in the high dose baricitinib group. No events with Grade 4 occurred during the entire JAIP study. A relation between neutropenia and serious infections was not demonstrated. Thrombocytosis was seen in a small number of patients and were all (except 1 Grade 2) Grade 1. It is already currently stated in the SmPC (section 4.8) that thrombocytosis is uncommon in AD trials. Lymphopenia was also uncommon, with higher rates in

placebo compared to baricitinib, and were predominantly Grade 1-2, except for 2 cases Grade 3. Decreased haemoglobin was slightly more common in baricitinib compared to placebo, but were all (except 1 Grade 2) Grade 1 and thus considered not clinically relevant. For both lymphopaenia and decreased haemoglobin, no changes are considered required in the SmPC.

Abnormal liver enzymes are associated with baricitinib use in adults; ALT and AST ≥ 3 ULN are recognized ADR's (common and uncommon resp.) included in section 4.8 of the SmPC of baricitinib. In the JAIP study, abnormal liver enzymes were rare: 2 patients had an ALT elevation ≥ 3 ULN without clinical symptoms and with a spontaneous decrease after 2 weeks, two patients had increased AST ≥ 5 ULN with normalization within 2 weeks after interruption of baricitinib, and 1 patient had AST ≥ 10 ULN. In the current SmPC (section 4.8) it is reported that increased ALT ≥ 3 ULN is uncommon in AD, but for AST such a statement is not included.

Increased **CK** (≥ 5 ULN) is a recognized ADR included in section 4.8 of the SmPC of baricitinib. In the All BARI set, 38% of the patients had Grade 1 or 2 CK elevations and 1.9% (n = 9) and 1.3% (n = 6) of the patients had Grade 3 and 4 resp. (indicating CK values ≥ 5 ULN), without a dose relation. Increased CK values were mainly ascribed to physical exercise. No changes to the SmPC are considered required.

Overall, 35 patients reported low fasting **serum glucose** (7.5%, IR 4.9; All BARI set). Absolute values presented by the MAH upon request, revealed 2 cases with incidental serum glucose of 1.11 mmol/L.

Subgroups

Subgroup comparisons were performed for TEAE's that were most common (≥ 2%) in the high dose baricitinib group (PC BARI set); strata were defined by in- and extrinsic factors that might affect safety profiles. The MAH additionally provided stratification analyses based on the All ARI set.

Younger patients (2 to < 10 years) were more susceptible to TEAE's (IR 175) than the older age group (10 to < 18 years; IR 129), especially for the SOC SOCs Respiratory, thoracic, and mediastinal disorders (IR 24 versus IR 8.3, mainly driven by Cough, Bronchospasm, and Oropharyngeal pain). Considering that the increased risk in the low weight patient population is valid, the findings may be ascribed to immaturity of the immune system in younger patients compared to adults, and atopic reactions triggered by viral infections which are more common in younger children. Older patients reported psychiatric disorders (e.g., suicidal ideation and suicide attempt) while this was not observed in the youngest age group. Also Skin and subcutaneous disorders and nervous system disorders (headache in particular) were more prevalent. These findings are not surprising; AD itself is associated with psychiatric disorders, and the impact emerges especially during (early) puberty when self-awareness increases. With regard to headache, it is known that younger children are less capable than older children to ascribe physical symptoms to a specific body region.

Stratification by **weight** was additionally provided by the MAH. This was essential because the proposed posology is based on weight. IR's were higher in the lower weight group (< 30 kg) compared to the higher weight group (⩾ 30 kg) (IR 162 versus 134), which corresponds to the increased IR's in younger age compared to older age (see section above). The safety in the subgroups of 10 to <20 kg and 20 to <30 kg will be followed post-marketing, as study JAIP was added as a Category 3 Study of the RMP.

The observed differences in IR's for the strata **race**, **region of world**, and **prior systemic treatment** status were not discussed by the applicant. With regard to prior systemic treatment status, most differences in IR were due to events that are common in patients with an atopic constitution (such as allergy, allergic conjunctivitis) and/or the paediatric population in general (lymphadenopathy).

Furthermore, the differences in IR's are mainly driven by small numbers. This issue is not further pursued.

2.5.2. Conclusions on clinical safety

Based on the available data, baricitinib in the proposed doses is considered acceptable in the paediatric population of patients with AD, and the safety profile appears to be in line with what is already known from other indications and in adults. The possibility of increased adverse events due to the exposure in paediatric patients weighing 10 to <20 kg being higher when compared to exposure in adults, will be monitored post-authorisation in a Category 3 study and through routine monitoring by the MAH. From non-clinical data a risk regarding bone safety, skeletal development, and growth was identified and added to the RMP as missing information. The available data from Study JAIP do not suggest an overall effect of baricitinib treatment on skeletal maturation in paediatric patients. More clinical data in paediatric patients will be collected over a longer follow-up time as the study JAIP was been included as a Category 3 study of the RMP.

2.5.3. PSUR cycle

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.

2.6. Risk management plan

The MAH submitted an updated RMP version 21.2 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 21.2 is acceptable.

The CHMP endorsed this advice.

The CHMP endorsed the Risk Management Plan version 21.2 with the following content:

Safety concerns

Table 33. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Herpes zoster VTE
Important potential risks	Malignancies (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers) Serious and opportunistic infections (including tuberculosis, *Candida* infections, PML) Myelosuppression (agranulocytosis) Myopathy including rhabdomyolysis Potential for drug-induced liver injury Gastrointestinal perforation MACE as an outcome of hyperlipidaemia Foetal malformation following exposure in utero
Missing information	Long-term safety Use in very elderly (≥75 years) Use in patients with evidence of hepatitis B or hepatitis C infection Use in patients with a history of or current lymphoproliferative disease Use in patients with active or recent primary or recurrent malignant disease Long-term safety in paediatric patients including growth and bone development, maturation and pubertal development, and adverse response to vaccination

Abbreviations: MACE = major adverse cardiovascular event; PML = progressive multi-focal leukoencephalopathy; PRAC = Pharmacovigilance Risk Assessment Committee; VTE = venous thromboembolic events.

Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
I4V-MC-B011: Retrospective Cohort Study to Assess Safety of Baricitinib in Nordic countries (Ongoing)	Primary Objectives: 1. To compare the incidence rates and profiles of the following aggregate outcomes of serious infections overall (including herpes zoster) and opportunistic infections (including tuberculosis, Candida infections, and PML), MACE, malignancies overall (including lymphoma and typically virus-induced malignancies such as	Important identified risks: • Herpes zoster • VTE Important potential risks: • Serious and opportunistic infections (including tuberculosis, *Candida* infections, PML) • Potential for DILI • MACE as an outcome of hyperlipidaemia • Malignancy (including lymphoma and typically virus-	**For RA study**: Study progress reports Final study report (Objectives 1-3)	**For RA study:** Annually in PBRER/PSUR submitted in April of each year 31 December 2027

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	cervical and many oropharyngeal cancers), and VTE, among RA and AD patients treated with baricitinib versus similar patients treated with other medications indicated for respective condition. 2. To describe the incidence rates of the following individual outcomes: lymphoma; herpes zoster; opportunistic infections such as tuberculosis, *Candida*, and PML; rhabdomyolysis; agranulocytosis; hyperlipidaemia (hypercholesterolaemia, hypertriglyceridaemia); GI perforations; liver injury; and all-cause mortality. Secondary Objectives: 3. To monitor the incidence rates of the aggregate outcomes of serious infections overall, MACE, malignancies overall, and VTE in very elderly patients, that is, ≥75 years of age. 4. To assess the effectiveness of risk minimisation activities by describing the pattern of use of baricitinib among patients with AD and the occurrence of pregnancy, active tuberculosis or active viral hepatitis, and the monitoring of lipid levels in relation to baricitinib use in routine clinical care.	induced malignancies such as cervical and many oropharyngeal cancers) • Foetal malformation following exposure in utero • Myelosuppression (agranulocytosis) • Myopathy including rhabdomyolysis • GI perforation Missing information: • Long-term safety • Use in very elderly (≥75 years)	**For AD Study:** Study progress reports Final report for Objective 4, AD cohort Final Report	**For AD Study**: Annually in PBRER/ PSUR submitted in April of each year To be determined based on at least 24 months of data in at least 50% of the discrete healthcare databases 31 December 2028

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
I4V-MC-B012 Observational post marketing Surveillance in 3 European Registries (Ongoing)	Primary Objectives: 1. To monitor the incidence rate and profile of the following aggregate outcomes of serious infections (including herpes zoster) and opportunistic infections (including tuberculosis, *Candida* infections, and PML), MACE, malignancies (including lymphoma and typically virus-induced malignancies, such as cervical and many oropharyngeal cancers), and VTE among patients with long-term exposure to baricitinib compared to patients with long-term exposure to other medications used for moderate-to-severe RA, as possible given the data available in the BSRBR, RABBIT, and ARTIS registries. 2. To describe the occurrence of the following individual outcomes: lymphoma, herpes zoster, opportunistic infections, rhabdomyolysis, agranulocytosis, PML, GI perforations, and evidence of DILI.	Important identified Risks: • Herpes zoster • VTE Important potential risks: • Malignancies (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers) • Serious and opportunistic infections (including Tuberculosis, *Candida* infections, PML), • Myelosuppression (agranulocytosis) • Myopathy including rhabdomyolysis • Potential for DILI • GI perforation • MACE as an outcome of hyperlipidaemia	Study progress reports Final study report	Annually in PBRER/ PSUR submitted in April of each year 31 March 2024
I4V-MC-B025: Survey to assess the effectiveness of the baricitinib additional risk minimisation measures (Planned)	1. To assess the understanding of and adherence to the key risk minimisation messages and required mitigating actions in the updated HCP Educational Material and PAC among a sample of dermatologists and rheumatologists 2. To assess the effectiveness of a DHPC distributed to communicate changes in SmPC	Important identified risks • Herpes zoster • VTE Important potential risks: • Serious and opportunistic infections (including tuberculosis, *Candida* infections, PML) • MACE as an outcome of hyperlipidaemia • Foetal malformation following exposure in utero • Malignancy	Protocol submission Final study report	25 April 2023 Six months after the end of data collection; estimated 30 April 2025

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
I4V-MC-JAJA and I4V-MC-JAJD These studies are reported jointly for reasons described in Section III.2. (Ongoing)	**Study JAJA**: Primary objective: 1. To compare baricitinib (combined dose groups) to TNF inhibitors with respect to VTE Secondary objectives: 1. To compare baricitinib (combined dose groups) to TNF inhibitors with respect to key safety outcomes 2. To compare each baricitinib dose to TNF inhibitors with respect to key safety outcomes **Study JAJD:** Primary objective: 1. To compare the risk of VTE among patients with RA treated with baricitinib (combined 2- and 4-mg dose groups) to similar patients treated with TNF inhibitors Secondary objectives: 1. To compare the risk of key safety outcomes among patients with RA treated with baricitinib (combined 2- and 4-mg dose groups) to similar patients treated with TNF inhibitors 2. To compare the risk of key safety outcomes among patients with RA treated with each baricitinib dose to similar patients treated with TNF inhibitors	Important identified risks • VTE Important potential risks: • MACE • Opportunistic infection • Serious infection • Malignancy	Study progress reports Start of data collection End of data collection Final study report	Included annually in Baricitinib PBRER/ PSUR 25 April 2019 (JAJA), 13 February 2020 (JAJD). 30 September 2027 31 March 2028
Drug utilisation study to assess prescribing patterns of baricitinib (Planned)	This study aims to measure the effectiveness of newly updated prescribing recommendations by evaluating prescribing behaviours	Important identified risks: • VTE Important potential risks: • MACE • Opportunistic infection • Serious infection • Malignancy	Protocol submission Final study report	25 April 2023 Within 12 months of end of data collection, estimated 30

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
				December 2027
I4V-MC-JAHX (Ongoing)	Primary objective: To evaluate the long-term safety and tolerability of baricitinib in patients with JIA or systemic JIA. Secondary objective: To evaluate the long-term efficacy of baricitinib in children with JIA or sJIA, ERA or JPsA, and the potential effects of baricitinib on the cellular and humoral immune system	Missing information • Long-term safety in paediatric patients including growth and bone development, maturation and pubertal development, and adverse response to vaccination	Study report (JAHV cohort) Final study report (including both JAHV and JAHU)	04 April 2028 31 March 2031
I4V-MC- JAIP (Ongoing)	Primary objective: To demonstrate the superiority of each dose of baricitinib versus placebo in the treatment of patients with moderate-to-severe AD Select econdary objectives: To evaluate potential effect of baricitinib on cellular and humoral immune system To assess growth and bone safety during longer-term treatment	Missing information • Long-term safety in paediatric patients including growth and bone development, maturation and pubertal development, and adverse response to vaccination	Final study report	31 December 2026

Abbreviations: ARTIS = Antirheumatic Therapies in Sweden; BSRBR = the British Society for Rheumatology Biologics Register; DHPC = Direct Healthcare Professional Communication; DILI = drug-induced liver injury; ERA = enthesitis-related arthritis; GI = gastrointestinal; HCP = health care professional; JIA = juvenile idiopathic arthritis; JPsA = juvenile psoriatic arthritis; MACE = major adverse cardiovascular event; PAC = patient alert card; PBRER = periodic benefit-risk evaluation report; PML = progressive multi-focal leukoencephalopathy; PSUR = periodic safety update report; RA = rheumatoid arthritis; RABBIT = Rheumatoid Arthritis Observation of Biologic Therapy; sJIA = systemic juvenile idiopathic arthritis; SmPC = Summary of Product Characteristics; TNF = tumour necrosis factor; US = United States; VTE = venous thromboembolic event.

Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Herpes zoster	[Routine risk minimisation measures:] SmPC Section 4.8 • SmPC section 4.4 recommends that if an infection develops, the patient should be monitored carefully, and Olumiant should be temporarily interrupted and not be resumed until the infection resolves. There is a further recommendation that, prior to starting treatment, all patients including patients with JIA, be brought up to date with all immunisations. PIL sections 2 and 4 PL Section 2 advises that the patient should tell their doctor if they develop signs of shingles. [Additional risk minimisation measures:] • Health care Professional Educational Material • Patient Alert Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection • Herpes zoster follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to monitor the incidence of herpes zoster in patients exposed to baricitinib RA: • EU registries • Nordic health care study AD: • Nordic health care study
VTE	[Routine risk minimisation measures:] SmPC Sections 4.2, 4.4 and 4.8 (DVT and PE) PIL Section 2 SmPC Section 4.2 states that a dose of 2 mg once daily is recommended for patients at higher risk of VTE, MACE, and malignancy, for patients aged ≥65 years and for patients with a history of chronic or recurrent infections.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Thromboembolic follow-up form • Clotting and/or coagulation disorders follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to compare the incidence of VTE, including VTE validated based on clinical information, among patients

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	SmPC Section 4.4 advises that in patients with cardiovascular or malignancy risk factors, baricitinib should only be used if no suitable treatment alternatives are available. In patients with known VTE risk factors other than cardiovascular or malignancy risk factors, baricitinib should be used with caution. VTE risk factors other than cardiovascular or malignancy risk factors include previous VTE, patients undergoing major surgery, immobilisation, use of combined hormonal contraceptives or hormone replacement therapy, and inherited coagulation disorder. If clinical features of VTE occur, treatment should be discontinued and patients should be evaluated promptly and appropriately treated. PL Section 2 advises patients: • To talk to their doctor or pharmacist before and during treatment if they have previously had a VTE or if they develop symptoms of VTE • Olumiant should be used with caution in patients with risk factors for VTE That treatment should be discontinued if clinical symptoms of VTE occur. [Additional risk minimisation measures:] • Health care Professional Educational Material • Patient Alert Card • DHPC	exposed to baricitinib being treated for moderate-to-severe: RA: • EU registries • Nordic health care study • Randomised, controlled post-authorisation safety studies in US (JAJA/JAJD) AD: • Nordic health care study
Malignancies (including lymphoma and typically virus-induced malignancies, such as cervical and many oropharyngeal cancers)	[Routine risk minimisation measures:] SmPC Sections 4.2 and 4.4 PIL section 2 SmPC Section 4.2 states that a dose of 2 mg once daily is recommended for patients at higher risk of VTE, MACE, and malignancy, for patients aged ≥65 years and for patients with a	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Cancer/neoplasm follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to compare the incidence of malignancy in patients exposed to baricitinib with patients exposed to other medications used for:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	history of chronic or recurrent infections. SmPC Section 4.4 advises that in patients over 65 years of age, patients who are current or past long-time smokers, or with other malignancy risk factors (e.g., current malignancy or history of malignancy), baricitinib should only be used if no suitable treatment alternatives are available. PL Section 2 advises patients to tell their doctor or pharmacist before and during treatment if they have cancer. [Additional risk minimisation measures:] • Healthcare Professional Educational Material • DHPC	Moderate-to-severe RA: • EU registries • Nordic health care study • Randomised, controlled post-authorisation safety studies in US (JAJA/JAJD) Moderate-to-severe AD: • Nordic health care study
Serious and opportunistic infections (including TB *Candida* infections, PML)	[Routine risk minimisation measures:] SmPC Sections 4.4 and 4.8 PL Section 2 SmPC Section 4.4 advises that the risks and benefits of treatment should be considered prior to initiating therapy in patients with active, chronic, or recurrent infections. In patients over 65 years of age, baricitinib should only be used if no suitable treatment alternatives are available. It also recommends that if an infection develops, the patient should be monitored carefully and Olumiant should be temporarily interrupted for any infection that is not responding to standard therapy. Treatment should not be resumed until the infection resolves. •SmPC Section 4.4 advises that patients should be screened to rule out active TB and active viral hepatitis before starting Olumiant. •SmPC Section 4.4 advises that live, attenuated vaccines should not be used during or immediately prior to treatment. It also	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *Candida* infection follow-up form • Pneumonia follow-up form • Viral reactivation follow-up form • Unspecified infection follow-up form • Extrapulmonary TB follow-up form • Pulmonary TB follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to compare the incidence of serious and opportunistic infections (including TB, *Candida*, and PML) in patients exposed to baricitinib with patients exposed to other medications used for moderate-to-severe: RA: • EU registries • Nordic health care study • Randomised, controlled post-authorisation safety studies in US (JAJA/JAJD) AD: • Nordic health care study

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	recommends that, prior to starting treatment, all patients particularly patients with JIA, be brought up to date with all immunisations. •Section 2 of the PL advises patient that they need to talk to their doctor or pharmacist before and during treatment with Olumiant if they have an infection or if they often get infections. It also advises patents that they should tell their doctor if they get signs of TB, herpes zoster or have, or have previously had, hepatitis B or C. [Additional risk minimisation measures:] • Health care Professional Educational Material • Patient Alert Card • DHPC	
Myelosuppression (agranulocytosis)	[Routine risk minimisation measures:] SmPC Sections 4.2, 4.4, 4.8, and 5.3 PL sections 2 and 4 SmPC Sections 4.2 and 4.4 recommend that treatment should not be initiated or should be temporarily interrupted in patients with white cell counts or a haemoglobin that is below a certain level. PL Section 2 advises patients that they may need blood tests prior to or during treatment to check if they have a low red or white blood cell counts. [Additional risk minimisation measures:] None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Blood and Bone Marrow Disorders follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to monitor the incidence of myelosuppression in patients exposed to baricitinib: RA: • EU registries • Nordic health care study AD • Nordic health care study
Myopathy including rhabdomyolysis	[Routine risk minimisation measures:] SmPC Section 4.8 (increases in CPK PL Section 4 (increases in CPK)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Rhabdomyolysis follow-up form Additional pharmacovigilance activities:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	[Additional risk minimisation measures:] None.	Observational post-marketing safety studies to monitor the incidence of myopathy including rhabdomyolysis in patients exposed to baricitinib RA: • EU registries • Nordic health care study AD: • Nordic health care study
Potential for drug-induced liver injury	[Routine risk minimisation measures:] SmPC Sections 4.2, 4.4, and 4.8 PIL Sections 2 and 4 SmPC Section 4.2 recommends that Olumiant should not be used in patients with severe hepatic impairment. Section 4.4 recommends that if increases in ALT or AST are observed and drug-induced liver injury is suspected, Olumiant should be interrupted. •Section 2 of the PL advises patients to speak to their doctor if they have, or have previously had, hepatitis B or C or if they have poor liver function. [Additional risk minimisation measures:] None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Hepatic disorders follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to monitor the incidence of potential drug-induced liver injury among patients exposed to baricitinib: RA: • EU registries • Nordic health care study AD: • Nordic health care study
GI Perforations	[Routine risk minimisation measures:] None [Additional risk minimisation measures:] None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Fistula and/or GI perforation follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to monitor the incidence of GI perforations in patients exposed to baricitinib RA: • EU registries • Nordic health care study AD: • Nordic health care study
MACE	[Routine risk minimisation measures:]	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
(as an outcome of hyperlipidaemia)	SmPC Sections 4.2, 4.4 and 4.8 (hypercholesterolaemia and hypertriglyceridaemia) PIL Section 2 and 4 SmPC Section 4.2 states that a dose of 2 mg once daily is recommended for patients at higher risk of VTE, MACE, and malignancy, for patients aged ≥65 years and for patients with a history of chronic or recurrent infections. SmPC Section 4.4 advises that lipid parameters should be assessed at 12 weeks following treatment initiation and thereafter according to international guidelines for hyperlipidaemia. Moreover, SmPC Section 4.4 advises that in patients over 65 years of age, patients who are current or past long-time smokers, and patients with a history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, baricitinib should only be used if no suitable treatment alternatives are available. PL Section 2 advises patients that they may need blood tests while taking Olumiant to check if they have a high cholesterol level. [Additional risk minimisation measures:] • Health care Professional Educational Material (lipid monitoring) • Patient Alert Card • DHPC	• Cardiac disorders follow-up form • Cerebrovascular accident follow-up form • Mortality follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to compare the incidence of hyperlipidaemia and MACE among patients exposed to baricitinib: RA: • EU registries • Nordic health care study • Randomised, controlled post-authorisation safety studies in US (JAJA/JAJD) AD • Nordic health care study
Foetal malformation following exposure in utero	[Routine risk minimisation measures:] SmPC Sections 4.3, 4.6, and 5.3 PIL Section 2 SmPC Sections 4.3 and 4.6 state that pregnancy is a contraindication. SmPC Section 4.6 advises that patients of childbearing potential should use effective method of contraception to avoid becoming	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Pregnancy data collection – maternal follow-up form • Pregnancy data collection – paternal follow-up form • Pregnancy outcome – maternal follow-up form • Pregnancy outcome – paternal follow-up form

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	pregnant during treatment and for at least 1 week after the last treatment. Section 4.6 of the SmPC also advises that a decision must be made whether to discontinue breastfeeding or to discontinue Olumiant therapy. PL Section 2 • States that patients should not take Olumiant if they are pregnant or think that they may be pregnant • Advises patients that if they are pregnant, think they may be pregnant, or are planning to have a baby, they should ask their doctor or pharmacist for advice before taking the medicine • States that patients should use an effective method of contraception to avoid becoming pregnant during treatment and for at least 1 week after the last Olumiant treatment • States that patients must tell their doctor if they become pregnant as Olumiant should not be used during pregnancy [Additional risk minimisation measures:] • Health care Professional Educational Material • Patient Alert Card	Additional pharmacovigilance activities: Observational post-marketing safety studies to monitor the incidence of foetal malformation following exposure in utero among patients exposed to baricitinib for both RA and AD: • Nordic health care study
Long-term safety	[Routine risk minimisation measures:] SmPC Sections 4.4 and 4.8 (hypercholesterolaemia and hypertriglyceridaemia) PL Sections 2 and 4 No additional recommendations are included in the SmPC or PL other than those already stated for malignancy and MACE. [Additional risk minimisation measures:] None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Cardiac disorders follow-up form • Cerebrovascular accident follow-up form • Mortality follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to monitor long-term safety in patients exposed to baricitinib RA: • EU registries • Nordic health care study

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		AD: • Nordic health care study
Use in very elderly (≥75 years)	[Routine risk minimisation measures:] SmPC Sections 4.2, 4.4 (lymphocytosis) and 5.2 PIL section 3 SmPC Section 4.2 states that • clinical experience in patients, ≥75 years is very limited. • a dose of 2 mg once daily is recommended for patients at higher risk of VTE, MACE, and malignancy, for patients aged ≥65 years and for patients with a history of chronic or recurrent infections. [Additional risk minimisation measures:] None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Observational post-marketing safety studies to monitor the incidence of use in very elderly (≥75 years) in patients exposed to baricitinib: RA: • Nordic health care study AD: • Nordic health care study
Use in patients with evidence of hepatitis B or hepatitis C infection	[Routine risk minimisation measures:] SmPC Section 4.4 PL Section 2 SmPC Section 4.4 recommends that screening for viral hepatitis should be performed before starting treatment and that if the test is positive, a liver specialist should be consulted Section 2 of the PL advises patients to speak to their doctor if they have, or have previously had, hepatitis B or C. [Additional risk minimisation measures:] None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: hepatic disorders follow-up Additional pharmacovigilance activities: None
Use in patients with a history of or current lymphoproliferative disease	[Routine risk minimisation measures:] SmPC Section 4.4 PL Section 2 PL Section 2 advises patients to tell their doctor or pharmacist before and during treatment if they have cancer.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	[Additional risk minimisation measures:] None	
Use in patients with active or recent primary or recurrent malignant disease	[Routine risk minimisation measures:] PIL Section 2 PL Section 2 advises patients to tell their doctor or pharmacist before and during treatment if they have cancer. [Additional risk minimisation measures:] None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Long-term safety in paediatric patients including growth and bone development, maturation and pubertal development, and adverse response to vaccination	[Routine risk minimisation measures:] SmPC Section 4.2 PIL Section 2 SmPC Section 4.2 states • the safety and efficacy of baricitinib in children aged 0 to 2 years have not yet been established. No data are available. • the safety and efficacy of baricitinib in children less than 18 years of age with AD or AA have not yet been established. No data are available. PL Section 2 advises that Olumiant is not for use in children and adolescents younger than 2 years of age. It also advises that Olumiant is not for use in children and adolescents younger than 18 years old for AD and AA, because there is no information on use in these diseases. [Additional risk minimisation measures:] None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • Long-term extension in children with JIA (Study JAHX) • Long-term extension in children with AD (Study JAIP)

Abbreviations: AA = alopecia areata; AD = atopic dermatitis; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; DVT = deep vein thrombosis; GI = gastrointestinal; JIA = juvenile idiopathic arthritis; MACE = major adverse cardiovascular event; PE = pulmonary embolism; PL = Patient Information Leaflet; PML = progressive multi-focal leukoencephalopathy; RA = rheumatoid arthritis; SmPC = Summary of Product Characteristics; TB = tuberculosis; VTE = venous thromboembolic event.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation on the package leaflet with target patient groups has been submitted by the MAH and has been found acceptable for the following reason:

- The proposed text modifications do not significantly alter the structure and design of the PL.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

This application concerns an extension of the adult indication to include paediatric patients 2 years of age and older with atopic dermatitis (AD). The proposed indication is: *Baricitinib is indicated for the treatment of moderate to severe atopic dermatitis in adult and paediatric patients 2 years of age and older who are candidates for systemic therapy.*

In children, adolescents, and adults, AD is a common, chronic relapsing, symptomatic, inflammatory skin disease characterised by itch, dry skin, and eczematous lesions. The clinical manifestations of AD are overall similar in adults and paediatric patients, although the location and type of skin lesions may differ[1,2,3]. The fundamental pathophysiology of AD, with excessive T cell activation, is similar among adults, adolescents, and children[18,19].

The primary aims of therapy are the reduction of skin lesions and of itch, which is the main symptom of AD; the ultimate treatment goal is to reach clear or almost clear skin and no or manageable itch.

Baricitinib is an orally available, selective JAK inhibitor with potency and selectivity for JAK1 and JAK2, and less potency for JAK3 or tyrosine kinase 2[16].

3.1.2. Available therapies and unmet medical need

AD is standardly treated with emollients and topical corticosteroids (TCS): low-potency TCS for mild AD and medium and high-potency TCS for moderate-to-severe AD. Topical calcineurin inhibitors (TCNI) are approved for the treatment of AD in paediatric patients from the age of 2 years with inadequate response or intolerance to TCS (tacrolimus) or where treatment with TCS is either inadvisable or not possible (pimecrolimus). The use of TCNI's is commonly restricted to sensitive areas of skin, such as eyelids. Several systemic treatments have been authorised in the EU to treat the paediatric population with AD: Adtralza, Dupixent, and Rinvoq. No systemic treatments are approved for children with moderate-severe AD from 2-6 years of age.

Despite the recent approval of newer systemic treatments, there remains an unmet medical need for AD paediatric patients who do not respond to currently approved systemic therapies and for paediatric patients with AD of 2 – 6 years of age.

3.1.3. Main clinical studies

The baricitinib clinical development programme for paediatric AD includes one global clinical study (**JAIP**) to evaluate the PK, efficacy, and safety of baricitinib in paediatric patients with moderate-to-severe AD.

In JAIP, the results of the PK lead-in period (period 2) were used to confirm the appropriate dose selection for the age groups. Then, new patients were enrolled in the randomised, double-blind study part (period 3). In the double-blind part of the study, 483 participants with moderate-severe AD were enrolled, with n=350 aged 10 to <18 years and n=133 participants aged 2 to <10 years old. Participants were randomised (1:1:1:1) to placebo, baricitinib low-dose QD, medium-dose QD, or high-dose QD. Accordingly, the daily doses for participants 10 to <18 years old were 1 mg, 2 mg, and 4 mg; the doses for participants 2 to <10 years old were 0.5 mg, 1 mg, and 2 mg. Oral suspension was used for patients <10 years of age, and patients ≥10 years of age were supplied with tablets. Randomisation was stratified according to disease severity (IGA 3 versus 4). Background therapy with emollients and with medium-potency and/or low-potency TCS and topical TCNI for use on active lesions, until lesions were under control, was included for all patients. The primary outcome was IGA 0 or 1 at week 16. EASI75 at week 16 and improvement ≥4 points in Itch NRS (patients ≥10 years only) at weeks 4 and 16, were among the secondary outcomes that were adjusted for multiplicity. Instead of the Itch NRS, the PRISM was used to assess itch in children <10 years of age, not adjusted for multiplicity.

Patients who had participated in study periods 2 or 3 were eligible to continue in the long-term extension period for up to 4 additional years of treatment (period 4).

3.2. Favourable effects

Multiplicity was handled using the graphical testing procedure. Accordingly, the treatment effects of baricitinib high dose were statistically significantly different as compared with placebo, on all 16-week key efficacy endpoints and the Itch NRS 4-point improvement at 4 weeks. Conversely, treatment effects of the baricitinib medium and low doses versus placebo, were not statistically significant for any of the study endpoints.

Primary endpoint

At week 16, the proportion of patients with **IGA 0 or 1** was 42% in the high dose group, as compared to 16% in the placebo group ($p<0.0001$) in the ITT population. In the 4 planned sensitivity analyses, the treatment effect in IGA 0 or 1 of the high dose compared to placebo remained statistically significant. From week 4 to week 16, the treatment effects in the high dose group were larger than those in the medium dose group and the low dose and placebo groups.

Key secondary endpoints

At week 16, there was a (multiplicity adjusted) statistically significant treatment effect of baricitinib high dose (4 mg equivalent), as compared to placebo, in **EASI75** and **Itch NRS** ≥4 points improvement, supported by treatment effects in EASI90 and SCORAD75. At week 16, the proportion of patients with EASI75 was 53% in the high dose group, as compared to 32% in the placebo group ($p<0.01$) in the ITT population; the proportion of patients (>10 years) with Itch response ≥4 points was 36% in the high dose group, as compared to 16% in the placebo group ($p<0.05$) in the ITT population. At week 4, the difference in ≥4 points improvement in Itch NRS was (multiplicity adjusted) statistically significant ($p=0.0026$), with 32% in the high dose group and 7.3% in the placebo group.

At week 16, the LS mean (SE) change from baseline in PRISM score was -0.28 (0.16) in the high dose group and 0.02 (0.15) in the placebo group (p=0.12).

Subgroups

The predefined subgroup analyses using the IGA 0 or 1 at week 16 (primary endpoint) and EASI75 as endpoints showed that none of the interaction terms (subgroup*treatment) were statistically significant (p<0.10).

The treatment effect in IGA 0 or 1 in the high dose group, as compared to placebo, was numerically smaller in children weighing <30 kg who were on 2 mg, as compared to children and adolescents weighing ≥30kg who were on 4 mg (Figure 13). In both weight groups there was a visible dose-response relationship.

Maintenance

More patients from the high dose group had at least some response (IGA 0, 1 or 2) at week 16 of the placebo-controlled randomised period and continued on their original dose (n=81) as compared to the lower dose groups and placebo (n=57). In the high dose group, the proportion of patients with an EASI75 was 77% at week 16, and declined over time with 69% at week 20 and 47% at week 52, which was <10% higher than the EASI75 response in the responders in the placebo group.

3.3. Uncertainties and limitations about favourable effects

Itch NRS was only applied in patients >10 years of age; for younger patients, the PRISM was used and completed by caregivers. The PRISM is not finally validated, and the treatment effect between baricitinib high dose and placebo was not statistically significant but was numerically more favourable for the high dose than for placebo.

There was a relatively small treatment effect in patient-assessed symptom severity (POEM) and no effect in patient-assessed impact on daily living (IDQOL/CDQOL) and anxiety and depression (PROMIS). Despite these small treatment effect and no effect in POEM, IDQOL/CDQOL and PROMIS, the effects on primary and key secondary outcomes on signs (IGA 0 or 1, EASI75) and the results on the main symptom itch (Itch response) are deemed sufficiently supportive for clinical relevance of the treatment effects.

As the 4-year study JAIP is still ongoing, long-term maintenance effects in paediatric patients aged 2-18 years is not yet fully established. Despite uncertainties on the long-term maintained, the open-label period 4 of JAIP with data up to week 52 supports the efficacy maintenance.

3.4. Unfavourable effects

Safety data for baricitinib in paediatric patients with AD stems from one pivotal 'phase 3' study (**JAIP**), including 467 patients. At the time of data cut-off, 385 patients were exposed to baricitinib for over 52 weeks, 286 in the older age group ≥10 years. After the upcoming completion of the study, long-term safety data in the youngest age group 2-10 years will be available for a maximum of 133 patients.

No deaths were reported during the JAIP study. Rates of SAEs were low but highest in the high dose baricitinib group and the placebo group. No differences in the rates of TEAEs or AEs between placebo and baricitinib led to discontinuation of treatment.

Common adverse events

In the placebo-controlled period, TEAEs by SOC that occurred more frequently in high dose baricitinib compared to placebo, were gastro-intestinal disorders (15% for high dose baricitinib versus 11% for placebo), blood and lymphatic system disorders (3.3% versus 1.6%), and investigations (3.3% versus 1.6%). TEAEs by PT that occurred more frequently in high dose baricitinib compared to placebo were abdominal pain (5.0% versus 2.5%), upper respiratory tract infections (4.2% versus 0.8%), diarrhoea (4.2% versus 1.6%), abdominal pain upper (3.3% versus 0.8%), bronchitis (2.5% versus 0.8%), and gastro-enteritis and decreased appetite (each 2.5% versus 0%). In line with previous studies in adults, a dose-response relationship was observed for respiratory tract infections and gastro-intestinal symptoms.

Infections occurred in 153 patients in both low (n = 50, 42%, IR 68.2) and medium (n = 47, 39%, IR 63.4) dose baricitinib groups, and 54 patients (45%, IR 60.7) in high dose baricitinib versus 45 (37%, IR 63.3) in the placebo group in the Ext BARI set. Most common in the high dose group versus placebo were COVID-19, nasopharyngitis, and upper respiratory tract infections. Eleven patients (2.4%, IR 1.47) reported at least one serious infection. Treatment discontinuation due to infections was infrequent. Herpes zoster and herpes simplex occurred in a few patients, and one patient had a disseminated herpes zoster infection classified as opportunistic (but not a SAE). In the placebo-controlled period, however, herpes simplex was less common in baricitinib compared to placebo. Tuberculosis was not seen.

Adverse events of special interest and laboratory values

No cases of adjudicated MACE, other cardiac events, or VTE occurred, nor any malignancy or NMSC. Higher levels of total cholesterol and LDL cholesterol were observed in those treated with baricitinib compared to the placebo group, and there was an evident dose dependency. Decreased neutrophil counts were more common in baricitinib-treated patients (21%) compared to placebo (16%) and were mainly mild. Generally, blood cell dyscrasias were infrequent and relatively mild. Abnormal liver enzymes were rare.

3.5. Uncertainties and limitations about unfavourable effects

Long-term safety in paediatric patients aged 2-18 years is not yet fully established. Long-term safety data is currently included as missing information in the RMP.

In the pivotal study, the dosing was age-based, but the proposed posology is weight-based. The weight-based safety data analysis showed higher risks for TEAE's and SAE's in patients < 30 kg body weight. The higher (PK) exposure to baricitinib in those patients may explain the higher rate of adverse events, implying the highest safety risks in those at the lowest range of the < 30 kg group. Therefore, safety in paediatric patients weighing <20 kg will be followed-up post authorisation in a category 3 Study of the RMP and through routine monitoring by the MAH.

Non-clinical data have given rise to concerns about growth and bone development associated with treatment with baricitinib. The current data generally seem reassuring, except for a few cases with suggested very early growth plate closure; most of these patients however already had advanced bone age at baseline. The follow-up on growth and bone development is too short for drawing firm conclusions, and these safety aspects will be monitored in two Category 3 studies of the RMP.

3.6. Effects Table

Table 34. Effects Table for baricitinib for the treatment of atopic dermatitis (data cut-off:01 June 2022)

Effect	Short Description	Unit	Placebo	Baricitinib 'high dose'	Uncertainties/ Strength of evidence	References
Favourable Effects						
IGA 0/1	Clear or almost clear skin	%	16	42	SoE: p<0.0001.	JAIP
EASI75	≥75% improvement in skin signs	%	32	53	SoE: p<0.001; taps from same underlying construct as IGA 0/1	
Itch ≥4 response	Improvement ≥4 points in Itch NRS	%	16	36	SoE: p<0.05; treatment effect already present (multiplicity adjusted) at week 4. Unc: only in children>10 years; PRISM supportive if <10 years.	
Unfavourable Effects*						
SAE's	Serious Adverse Events	%	5.7	3.3	SoE: including serious infections	JAIP
Infections		%	38	38		

Abbreviations: IGA=Investigator's Global Assessment; EASI=Eczema Area and Severity Index; Itch NRS=Numerical Rating Scale for severity of pruritis.*Ext BARI set

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Despite the recent approval of newer systemic treatments, there remains an unmet medical need for paediatric AD patients who do not respond to currently approved systemic therapies, especially those between 2-6 years of age. Up to now, no systemic treatments are approved for children with moderate-severe AD from 2-6 years of age.

The size of the treatment effect (high dose – placebo) at week 16 was 26% for IGA 0/1, 21% for EASI75 and 20% in Itch response, which are considered clinically relevant between-group differences. Clinical relevance of the effects in main outcomes is supported by the onset of treatment effect in itch and in IGA 0/1 at week 4. As itch is the main symptom of AD, this is a patient-relevant result. The caregivers assessed the reduction of Itch in the youngest children, and only a numerical treatment effect was present. Still, the results in the older children and other outcomes can be relied on to infer that the high dose will also reduce itch in children <10 years of age. The patient-reported outcomes concerning patient-assessed symptom severity (POEM) and patient-assessed impact on daily living (IDQOL/CDQOL) and anxiety and depression (PROMIS), were not clearly supportive due to lack of treatment effect. However, the effects on skin manifestations and itch are large enough to consider the treatment with baricitinib as patient-relevant. Supportive patient-relevant effects were also found in reducing medium-potency TCS (high potency was generally not used). Although it seems that the response slowly declines over time, many patients with at least some response after 16 weeks of treatment could maintain a good response over 52 weeks.

The most common TEAEs observed for baricitinib in the treatment of moderate to severe AD in paediatric patients were in line with the known ADRs for baricitinib as included in the SmPC, which is mainly based on data from adults with RA but also adults with AD and AA. Upper respiratory tract infections, gastroenteritis, urinary tract infections, headache, abdominal pain, and acne are among the

(very) common ADRs for baricitinib in the current SmPC, and these were also identified in the JAIP study. These are all considered manageable. The data on growth did not give rise to immediate concerns. Longer follow-up for growth and maturation is needed in any case, which is already included in the RMP. Also, patients with lower body weights will be followed up post-marketing, as their exposure (C_{max}) appeared to be higher than older children and adults. The uncertainty is to some extent mitigated, as paediatric patients will continue to increase in weight till above 30 kg, limiting the period of calendar time in relative over-exposure.

The Art 20 JAK referral imposed stricter warning text (SmPC section 4.4) for serious infection, MACE, VTE, and malignancy, including NMSC for baricitinib. It is not considered necessary to add a special warning for the paediatric population to point to the class effects of oral JAK inhibitors covered by the Art. 20 referral. The reason is that paediatric patients do not tend to accumulate risk factors for MACE, VTE, malignancies and NMSC, and the existing warnings, e.g., for serious infections, NMSC, etc., already apply.

3.7.2. Balance of benefits and risks

Baricitinib is an oral treatment which can be a valuable treatment to address the unmet medical need for paediatric AD patients who do not respond to currently approved systemic therapies, especially those between 2-6 years of age. The global JAIP study demonstrate that the treatment effects of baricitinib high dose were statistically significantly different as compared with placebo. The overall safety profile observed in paediatric patients with AD is generally consistent with that observed in adult patients. Overall, baricitinib has a positive effect in the treatment of AD in patients 2 years and older with benefits that outweigh the risks.

3.8. Conclusions

The overall B/R of Olumiant in the treatment of atopic dermatitis in paediatric patients aged 2 years and older is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the treatment of paediatric patients (from 2 years of age and older) with moderate to severe atopic dermatitis for OLUMIANT, based on the final results from study I4V-MC-JAIP; this is a Phase III, multicentre, randomised, double blind, placebo controlled, parallel-group, outpatient study evaluating the pharmacokinetics, efficacy, and safety of baricitinib in paediatric patients with moderate-to-severe atopic dermatitis. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1,

5.2 of the SmPC are updated. The Package Leaflet has been updated accordingly. The RMP Version 21.2 is acceptable.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and III and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0311/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Olumiant-H-C-004085-II-0037'