26 February 2026
EMADOC-1700519818-3023275
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Olumiant

International non-proprietary name: baricitinib

Procedure No. EMA/VR/0000288098

Note

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

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List of abbreviations

Term	Definition
AA	alopecia areata
AD	atopic dermatitis
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
All BARI AA Adolescents	Safety analysis set that includes all participants with AA exposed to any dose of baricitinib at any time during the study
AT	alopecia totalis
ATE	arterial thromboembolism
AU	alopecia universalis
BMI	body mass index
CI	confidence interval
CL/F	apparent total clearance of the drug from plasma after oral administration
ClinRO	clinician-reported outcome
CPK	creatine phosphokinase
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
E-R	exposure-response
EB	eyebrow(s)
EL	eyelash(es)
Ext BARI AA Adolescents	Safety analysis set that includes all participants with AA exposed to baricitinib 2 mg or 4 mg from dose randomisation to dose or treatment change
FDLQI	Family Dermatology Life Quality Index
GBD	Global Burden of Disease Study
HADS	Hospital Anxiety and Depression Scale
IP	investigational product
IR	incidence rate
ITT	intent-to-treat
JAHO	I4V-MC-JAHO
JAIO	I4V-MC-JAIO
JAIP	I4V-MC-JAIP

Term	Definition
JAIR	I4V-MC-JAIR
JAK	Janus kinase
JIA	juvenile idiopathic arthritis
LTE	long-term extension
MACE	major adverse cardiovascular events
NMSC	nonmelanoma skin cancer
OAT3	organic anion transporter 3
OR	odds ratio
PC BARI AA adolescents	Safety analysis set that includes all adolescent participants with AA exposed to baricitinib in the placebo-controlled period
PD	Pharmacodynamic
PDCO	Paediatric Committee
PIP	paediatric investigation plan
PK	pharmacokinetic(s)
PRO	patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PYE	patient-years of exposure
QD	once daily
QoL	quality of life
RA	rheumatoid arthritis
RMP	risk management plan
SAE	serious adverse event
SALT	Severity of Alopecia Tool
SALT90	at least 90% improvement from Baseline in SALT score
SCS	Summary of Clinical Safety
SmPC	Summary of Product Characteristics
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
V/F	apparent volume of distribution
VTE	venous thromboembolism

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 July 2025 an application for a variation.

The following changes were proposed:

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

Extension of indication to include treatment of adolescent patients (12 to less than 18 years) with severe alopecia areata for OLUMIANT, based on results from study I4V-MC-JAIO; this is a Phase 3, double-blind, randomised, placebo-controlled trial to evaluate the efficacy, safety, and pharmacokinetics of baricitinib in children from 6 years to less than 18 years of age with alopecia areata. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 26.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the PI and to update the list of local representatives in the Package Leaflet.

The requested variation(s) proposed 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/0339/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0339/2021 not yet completed as some measures were deferred.

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 appointed by the CHMP was:

Rapporteur: Peter Mol

Timetable	Actual dates
Submission date	25 July 2025
Start of procedure:	16 August 2025
CHMP Rapporteur's preliminary assessment report circulated on:	10 October 2025
PRAC Rapporteur's preliminary assessment report circulated on:	17 October 2025
PRAC Rapporteur's updated assessment report circulated on:	24 October 2025
PRAC Outcome	30 October 2025
CHMP Rapporteur's updated assessment report circulated on:	07 November 2025
Request for supplementary information adopted by the CHMP on:	13 November 2025
MAH's responses submitted to the CHMP on:	19 December 2025
CHMP and PRAC Rapporteurs' preliminary assessment report on the MAH's responses circulated on:	03 February 2026
PRAC Outcome	12 February 2026
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on:	19 February 2026
CHMP opinion:	26 February 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Alopecia Areata (AA) is a chronic immune-mediated inflammatory disease characterised by patches of hair loss that can affect any hair-bearing site of the body. The disease targets anagen hair follicles and causes nonscarring hair loss. It most commonly presents with discrete and smooth patches of alopecia on the scalp but may also affect other hair-bearing areas including eyebrows, eyelashes, beard, torso, and extremities. The extent of hair loss can vary from isolated patches to complete hair loss.

State the claimed the therapeutic indication

The claimed extension of the indication is '… *for the treatment of severe alopecia areata in adult and adolescent patients 12 years of age and older (see section 5.1)'*.

Epidemiology

The incidence and prevalence of AA vary across the world. The overall incidence in the UK and the USA has been estimated at 0.21 – 0.26 per 1000 patient-years; the cumulative lifetime incidence is appr. 2 percent (i.e. 1 in 50 persons will develop alopecia areata at some time during life). The disease can manifest at any age; most patients are relatively young, with 40% of AA patients experiencing their first onset by the age of 20 years and 83% to 88% of AA patients experiencing their first onset by 40 years of age. Median onset in children is between 5 and 10 years of age. Early onset of AA during childhood has been reported to correlate with more extensive disease in multiple different studies. In a review of 392 children with AA, extensive disease (>50% hair loss) was reported in 12% of children aged 11 to 15 years, 5% of children aged 6 to 10 years, and 0% of children aged 1 to 5 years.

There is no evident gender difference for AA. Incidence rates among non-white populations are found to be higher compared to white populations, maybe due to social and environmental factors.

Aetiology and pathogenesis

Insights into the immunopathogenesis of alopecia areata (AA) began with the recognition of the hair follicle as being an immune-privileged site like the eye and testes (Paus et al. 2005). Disruption of this immune privilege occurs upon follicular influx by auto-reactive CD8+ T cells, leading to increases in major histocompatibility complex (MHC) Class I and II antigens and inflammation disrupting hair follicle biology (Islam et al. 2015; Strazzulla et al. 2018). Activation of the pathogenic T cells leads to IFNg production which contributes both to enhanced MHC class I and II antigens and interleukin-15 (IL 15) (Islam et al. 2015; Strazzulla et al. 2018) accompanied by additional cytokines including IL 2, IL-13, IL-23, and thymic stromal lymphopoietin (Suárez-Fariñas et al. 2015). All these inflammatory-related cytokines are dependent on JAK/STAT signalling, and of note IFNg utilises JAK1 and JAK2.

Clinical presentation, diagnosis

The diagnosis of AA is based upon the appearance of hair loss. A health

care provider will look for the characteristic patterns of hair loss, such as smooth patches with short, broken-off hairs around the borders. A skin biopsy is generally not required except for in young children (< 3 years of age). Up to 50% of patients who present with patchy alopecia areata experience spontaneous hair regrowth within one year, most will relapse months or years after remission.

Severe AA is recognised as a condition with emotional and psychosocial distress, including high prevalence of depression and anxiety. A 66% to 74% lifetime prevalence of psychiatric disorders has been reported in patients with AA, with a 38% to 39% lifetime prevalence of depression and a 39% to 62% prevalence of generalised anxiety disorder. Health related QoL is also consistently diminished in participants with AA. The Global Burden of Disease (GBD) Study calculated the burden of AA as 18.6 years of healthy life lost.

Management

There are two centrally approved treatment options for AA; both JAK inhibitors. Ritlecitinib was recently approved by the EMA for the treatment of severe AA in adults and adolescents 12 years of age and older. Baricitinib has been approved for severe AA in adults only.

Thus, except for ritlecitinib, there are no centrally approved therapeutic options for AA in adolescents. Off-label treatments for AA in adults are used empirically for paediatric patients. Current treatments for children <10 years of age include topical corticosteroid (Class I–III) monotherapy or in combination with topical retinoids, topical anthralin, and rarely systemic steroids (pulse therapy). Treatment in children >10 years of age may also include topical sensitisers and intralesional corticosteroids if tolerated (the latter treatment is locally approved in several European countries. According to European expert consensus statement on the systemic treatment of AA, methotrexate, hydroxychloroquine, azathioprine and other immunomodulators are used, despite limited efficacy data in this population. Use of minoxidil is controversial due to lack of efficacy and because of lightheadedness in children.

The limited authorised treatment options for (paediatric and) adolescent patients with AA, and the large psychosocial burden, present a significant unmet need in this population.

2.1.2. About the product

Baricitinib is an orally available, reversible, adenosine triphosphate (ATP) competitive Janus kinase (JAK) inhibitor. Janus kinases are intracellular enzymes that transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence immune cell functions and haematopoiesis. In cell-free isolated enzyme assays, baricitinib demonstrates potency and selectivity for JAK1 and JAK2 and less potency for tyrosine kinase 2 (Tyk2) and JAK3. Dual inhibition of JAK1 and JAK2, which may interrupt IFN-γ signalling and other inflammatory pathways that contribute to the immunopathogenesis of AA, and clinical evidence with other JAK inhibitors support the investigation of baricitinib in the treatment of AA.

As cytokines involved in the development of AA are dependent on JAK/STAT signalling, JAK inhibitors including baricitinib show the potential effect by reinitiating the production of mature terminally differentiated follicles at sites of prior inflammation. Animal models support the theory of AA in which autoreactive T cells (NKG2D+) drive hair loss by increasing IFNg and inflammatory gene expression signatures, as noted above, which could be reversed using JAK inhibition in mice.

Baricitinib is currently approved in the EU for

- moderate to severe active *rheumatoid arthritis* in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (DMARDs). Baricitinib may be used as monotherapy or in combination with methotrexate (first approval, EMEA/H/C/4085; 2017),
- moderate to severe *atopic dermatitis* in adult and paediatric **patients 2 years of age and older** who are candidates for systemic therapy,
- active *juvenile idiopathic arthritis* in **patients 2 years of age and older** who have had an inadequate response or intolerance to one or more prior conventional synthetic or biologic DMARDs (including polyarticular, extended oligoarticular, enthesitis-related, and juvenile psoriasis arthritis). Baricitinib may be used as monotherapy or in combination with methotrexate, and
- severe ***alopecia areata*** in **adult patients**.

For all approved indications, the recommended dose is 4 mg once daily for patients weighing 30 kg or more. 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. If disease control is reached, patients may be tapered from 4 mg to 2 mg.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The clinical development program for paediatric AA includes a single study, study JAIO, to evaluate the efficacy, safety, and PK of baricitinib in paediatric patients aged 6 to <18 years with AA affecting ≥50% of the scalp. Study JAIO is a phase 3, placebo-controlled, randomised, double-blind study. The study was ongoing at the time of submission and aimed to enrol 595 patients: 415 patients aged 12 to <18, and 180 patients between 6 and 12 years of age. Data from the latter group are not included in this Application, as patient enrolment was staggered and planned to start after data of the adolescent group had been collected, analysed, and the B/R for the adolescent age group has been determined.

A total of 257 adolescents were planned to be randomised 1:1:1 to double-blind treatment with placebo, baricitinib low dose, or baricitinib high dose and contribute to the efficacy analyses (placebo-controlled adolescent cohort); approximately 160 adolescents were randomised 1:1 to double-blind treatment with baricitinib low dose or high dose to further accumulate safety exposures and are not included in the placebo-controlled efficacy analyses (adolescent safety cohort).

The design of this phase 3 registration study was agreed with the PDCO (EMEA-001220-PIP08-20). In particular, the staggered patient inclusion, sample size (n planned 240), treatment duration (36 weeks followed by one-year open label LTE), main efficacy endpoints (including the primary endpoint SALT score ≤ 20 at week 36), and dose definition based on JIA development program.

2.1.4. General comments on compliance with GCP

The Applicant states that "study JAIO is conducted in accordance with Good Clinical Practices (ICH 2016) and applicable local laws and regulations".

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which is considered acceptable.

2.2.1. Ecotoxicity/environmental risk assessment

No increase in environmental exposure is anticipated for this extension of indication, hence updated ERA dossier has not been provided. The conclusions of the most recent submitted ERA (Submission number EMEA/H/C/004085/II/0037, 25 November 2022) remain valid.

2.2.2. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of baricitinib in adolescent AA.

2.3. Clinical aspects

2.3.1. Introduction

The clinical development program of baricitinib for paediatric AA includes a single pivotal study, study JAIO, to evaluate the efficacy, safety, and PK of baricitinib in paediatric patients aged 6 to <18 years with AA affecting ≥50% of the scalp. Study JAIO is a phase 3, placebo-controlled, randomised, double-blind study.

A total of 257 adolescents were included and randomised 1:1:1 to double-blind treatment with placebo, baricitinib low dose, or baricitinib high dose and contribute to the efficacy analyses (placebo-controlled adolescent cohort); approximately 160 adolescents were randomised 1:1 to double-blind treatment with baricitinib low dose or high dose to further accumulate safety exposures and are not included in the placebo-controlled efficacy analyses (adolescent safety cohort).

Table 1: Description of Phase 3 Study JAIO – Adolescent Placebo-Controlled Cohort

Number of participants	257 (total enrolled)
Population	Adolescents aged 12 to <18 years with AA affecting ≥50% of the scalp
Intent-to-treat population (double-blind)	12 to <18 years (N = 257)
Phase	Phase 3
Status	*Ongoing*
Primary endpoint	Primary endpoint for double-blind treatment period • Proportion of participants achieving an absolute SALT score of ≤20 at Week 36
Key secondary endpoints	• Proportion of participants achieving an absolute SALT score ≤20 at Weeks 16 and 24 • Proportion of participants achieving a $SALT_{50}$ at Week 12 • Proportion of participants achieving a $SALT_{90}$ at Week 36 • Proportion of participants achieving an absolute SALT score ≤10 at Weeks 24 and 36
Study periods	• a 5-week screening period • a 36-week double-blind treatment period • an approximately 2-year long-term extension period, and • a 4-week posttreatment follow-up period.

Abbreviations: AA = alopecia areata; SALT = Severity of Alopecia Tool; $SALT_{50}$ = at least 50% improvement from baseline in SALT score; $SALT_{90}$ = at least 90% improvement from baseline in SALT score.

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.

2.3.2. Pharmacokinetics

At the original MAA for the treatment of moderate to severe rheumatoid arthritis, the pharmacokinetics of baricitinib were investigated in 27 clinical *in vivo* PK studies after single (1-40 mg) or repeated dosing (up to 20 mg once daily for 10 days, up to 15 mg once daily for 28 days, and up to 10 mg daily for 28 days). In addition, several *in vitro* studies with human biomaterials were provided investigating the protein binding, metabolism, and the potential for baricitinib to cause DDIs. Three additional clinical PK studies were performed in patients with atopic dermatitis for the extension of indication for the treatment of patients with atopic dermatitis in which dosages of 1 mg, 2 mg and 4 mg once daily were investigated. Two additional clinical PK studies were performed in adult patients with alopecia areata in which dosages of 1 mg, 2 mg and 4 mg once daily were investigated. One clinical study was conducted for an extension of indication for the treatment of paediatric patients aged 2 to <18 years with juvenile idiopathic arthritis. Also, a clinical study was provided in an extension of indication for the treatment of paediatric patients aged 2 to <18 years with atopic dermatitis. Furthermore, a developed oral solution and the commercial film-coated tablets were shown to be switchable in line extension procedure EMEA/H/C/004085/X/0035/G.

Furthermore, PopPK and exposure-response analysis were performed to support the submission.

Analytical methods

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 (report 8520673). Labcorp Bioanalytical Services LLC (previously called Covance Bioanalytical Services LLC) located in Indianapolis, Indiana, USA, performed the bioanalytical methods. Samples above the limit of quantification were diluted to yield results within the calibrated range. Validation results are shown in Table 2.

Table 2: 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

In the phase 3 study JAIO, a micro-sampling assay using whole blood samples collected with a Mitra device was developed. A total of 1002 samples were analysed within 234 days of collection. During the bioanalysis of study samples, inter-assay accuracy (%relative error) and inter-assay precision (%relative standard deviation) ranged from 100.9 to 101.6% and -3.9% to 3.3%, respectively. No samples were reanalysed.

To be able to compare the pharmacokinetics of baricitinib in blood and plasma, plasma concordance samples with time-matched whole blood samples were collected in study JAIO from a subset of

participants in the older age (adolescent) group. A total of 29 plasma concordance samples were available from 31 participants. The blood-to-plasma ratio was determined as the slope of the regression line using time-matched blood and plasma samples. The slope (1.10) was used to convert the blood data to plasma equivalents.

Population PK model

The objective of the population pharmacokinetic analysis for baricitinib in patients with AA aged 12 to <18 years and weighing >30 kg is to support the posology. Specifically, the analyses aimed to:

- characterise the population PK of baricitinib and identify patient factors that may influence baricitinib disposition in this patient population.
- confirm the recommended clinical application of 2 mg or 4 mg adult equivalent exposure for adolescent and paediatric patients with alopecia areata.

A total of 799 baricitinib concentrations from 168 patients were used to characterise the PK in paediatric patients with AA. A total of 131 samples were excluded due to mis-sampling or shipment and storage without desiccant for a duration that exceeded stability testing at the time of analysis.

The PK data were analysed using population pharmacokinetic (PopPK) methodology. The final PopPK model used the same model structure as the previously developed PK model in paediatric and 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 inter-compartmental 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 alopecia areata 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 2 and 4 mg doses are shown in Figure 1.

Table 3: Pharmacokinetic and covariate parameters in final PopPK model for baricitinib in patients with alopecia areata aged 12 to <18 years and weighing >30 kg

Model Parameter (Unit)	Population Mean (%SEE)	BSV[a] (%SEE)	Mean (95% CI) from Bootstrap Analysis
D_1 (hr)	0.206 (24.8)	142 (9.84)	0.211 (0.182-0.238)
Box-Cox transformation parameter for D_1	0.683 (0.665)	---	0.620 (0.535-0.747)
CL_{nr}/F(L/hr)[b]	1.58 (36.4)	71.1 (19.0)	1.61 (1.45-1.78)
CL_r/F (L/hr)[b]	9.07 (11.8)	72.3 (12.2)	9.02 (8.54-9.45)
V_1/F (L)[c]	99.5 (10.2)	37.6 (84.5)	99.2 (96.1-102)
Q (L/hr)[d]	2.35 (8.52)	---	2.39 (2.22-2.54)
V_2/F (L)[e]	28.7 (164)	123 (28.6)	31.0 (17.3-49.9)
LAG (hr)	0.150 (3.16)	---	0.150 (0.149-0.152)
Allometric Scaling CL[b]	0.75 (FIX)	---	---
Allometric Scaling V[c,e]	1 (FIX)	---	---
Covariate for change in eGFR on CLr/F[f]	0.00469 (165)	---	0.00552 (-0.000680-0.0126)
Covariance for CLnr/F and CLr/F[g]	0.809 (37.3)	---	---
Covariance for CLr and V_1/F[g]	-0.283 (153)	---	---
Proportional error[h]	35.8 (29.4)	---	0.355 (0.337-0.378)

Abbreviations: AA = alopecia areata; BSV = between-subject variability; CI = confidence interval; CL = total body clearance; CL/F = apparent total clearance; CL_{nr}/F = apparent non-renal clearance; CL_r/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 = total 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] V_1/F=99.5*((WTE/74)^1.00).

[d] Q=2.35*((WTE/74)^0.75).

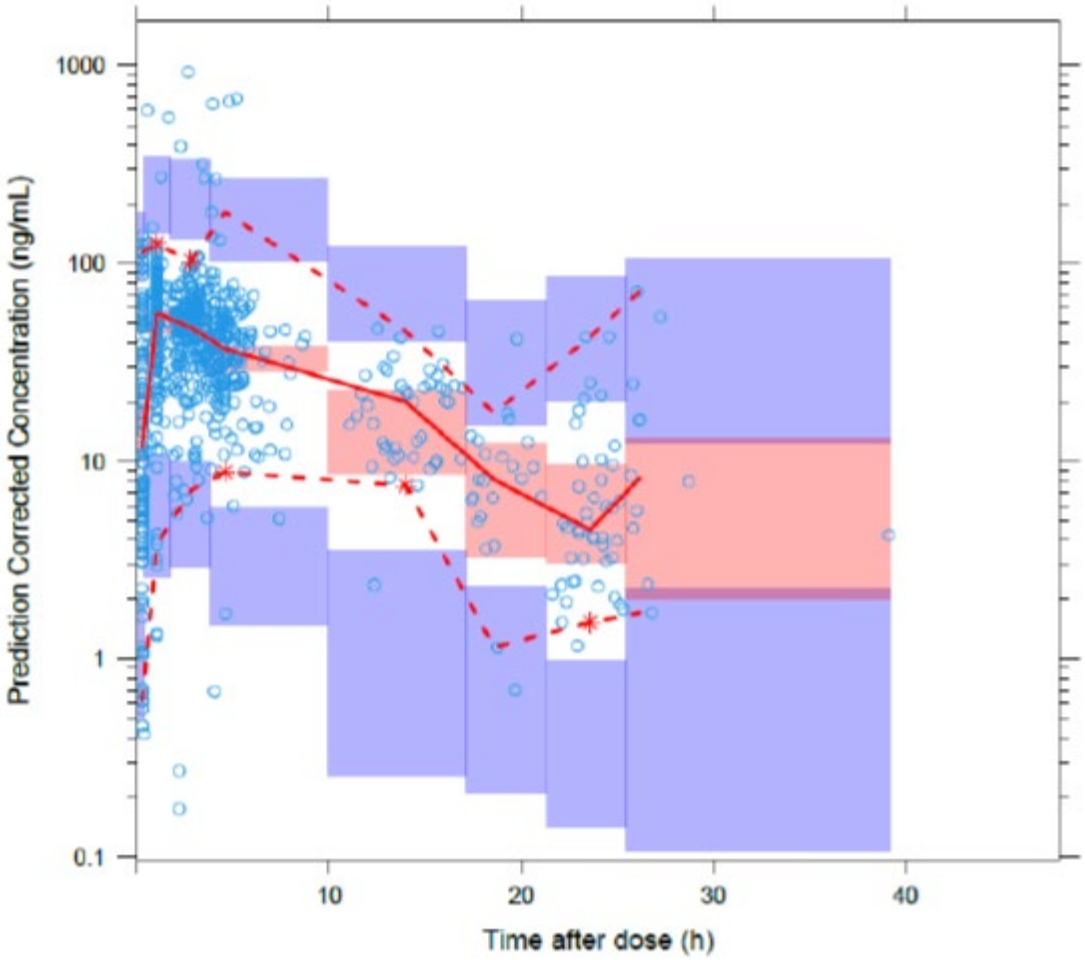
[e] V_2/F=28.7*((WTE/74)^1.00).

[f] eGFR was estimated using the Bedside Schwartz equation. CL_r/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 2 and 4 mg doses for the final pharmacokinetic model in paediatric patients with alopecia areata aged 12 to <18 years and weighing >30 kg



Absorption

In adult patients 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. Accumulation after repeated dose administration of baricitinib is minimal; the accumulation ratio ranged from 0.89-1.25-fold and 1.02-1.24-fold based on C_{max} and AUC, respectively.

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 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 paediatric patients aged 2 years and older with juvenile idiopathic arthritis weighing <30 kg, the C_{max} and AUC at steady state are 85.7 ng/mL and 464 ng × h/mL, respectively, at the clinically relevant dose of 2 mg. In paediatric patients aged 2 years and older with juvenile idiopathic arthritis weighing ≥30 kg, the C_{max} and AUC at steady state are 58.1 ng/mL and 388 ng × h/mL, respectively, at a clinically relevant dose of 4 mg. The C_{max} is higher in paediatric patients with juvenile idiopathic arthritis weighing <30 kg compared to adult patients with rheumatoid arthritis, atopic dermatitis and alopecia areata. The C_{max} in paediatric patients with juvenile idiopathic arthritis weighing ≥30 kg and the AUC in paediatric patients with juvenile idiopathic arthritis weighing <30 kg and ≥30 kg is comparable compared to adult patients with rheumatoid arthritis, atopic dermatitis and alopecia areata.

In paediatric patients aged 2 years and older with atopic dermatitis weighing <30 kg, the C_{max} and AUC at steady state are 57.1 ng/mL 298 ng × h/mL, respectively, at the clinically relevant dose of 2 mg. In paediatric patients with atopic dermatitis weighing ≥30 kg, the C_{max} and AUC at steady state are 50.3 ng/mL and 383 ng × h/mL, respectively, at the clinically relevant dose of 4 mg. 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 adult 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 is higher compared to healthy subjects (41% versus ~22%). The inter-individual variability was 50% for the AUC and 21% for the C_{max} in patients with atopic dermatitis.

Distribution

Based on data in adults 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 is also not warranted.

Transporters

In vitro studies indicate that baricitinib is a substrate for P-glycoprotein, BCRP, OAT3 and MATE2-K. Baricitnib 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. A higher

clearance of baricitinib due to the rs12943590 variant in MATE2-K 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-proportional 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

The PK in paediatric patients with alopecia areata was investigated in one clinical study study **JAIO.** In the double-blind treatment period patients were randomised (1:1:1) in a blinded manner to placebo, baricitinib low dose, or baricitinib high dose. Dosing was based on body weight with patients weighing ≥30 kg receiving a dose of 2 mg (low dose) or 4 mg (high dose) and patients weighing <30 kg receiving a dose of 1 mg (low dose) or 2 mg (high dose). A total of 84 patients were treated with the low dose and 85 patients with the high dose. Furthermore, 88 subjects were included in the placebo group. Subjects had a mean age of 14.7 ± 1.7 years (11.9-18 years), a mean body weight of 59.2 ± 16.3 kg (29.9-141.2 kg), and a mean BMI of 21.8 ± 4.7 kg/m^2 (14.3-43.8 kg/m^2).

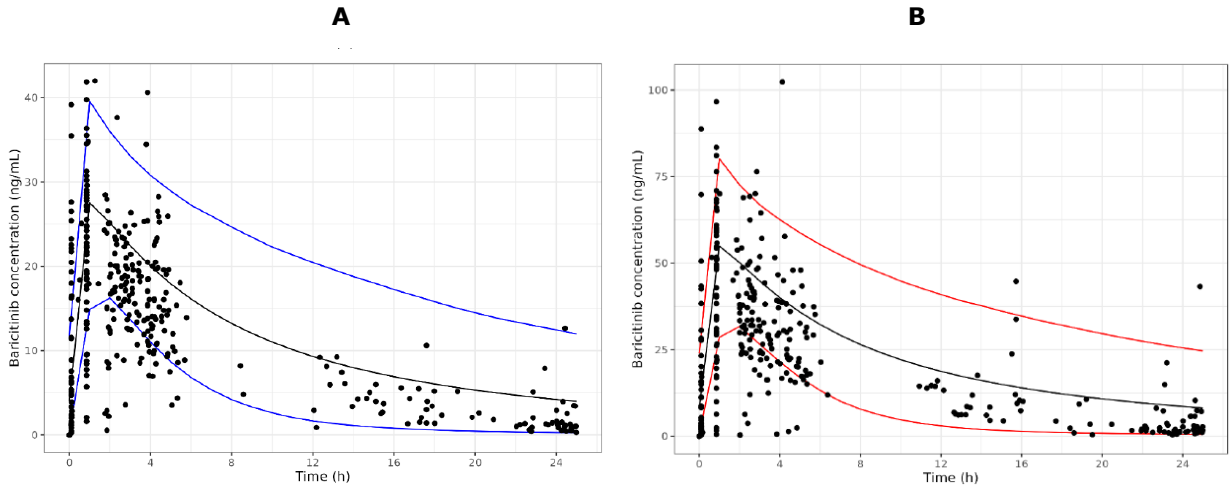
At Week 0, PK samples will be drawn 15 min and 1 h post-dose. At Week 4, PK samples are collected 2 to 4 hours post-dose. At Week 8 and Week 12, blood samples will be collected at any time pre-dose. At Week 16, blood sample are collected 4 to 6 h post-dose. PopPK modelling was used to obtain PK parameters from the measured concentrations. The PK parameters are summarised in Table 4.

Table 4: PopPK parameter estimates in paediatric patients aged 12 to <18 years with alopecia area based on study JAIO

dose	$C_{max,ss}$ (ng/ml)	$AUC_{\tau,ss}$ (ng × h/mL)	V/F (L)	$t_{½}$ (h)	CL/F (L/h)
2 mg	25.4 (CV%=19)	161 (CV%=35)	103 (CV%=24)	10.1 (5.2-29)	12.4 (CV%=35)
4 mg	52.5 (CV%=25)	301 (CV%=38)	93.6 (CV%=30)	9.4 (3.6-37)	13.3 (CV%=38)

The observed concentration data from adolescent participants aged 12 to <18 years old and weighing ≥30 kg receiving baricitinib 2 mg or 4 mg once daily were comparable with the baricitinib exposure data in adult participants with alopecia areata receiving 2 mg or 4 mg once daily (Figure 2).

Figure 2: Comparison of observed plasma concentrations in adolescent participants with alopecia areata (study JAIO) and plasma concentrations in adult participants with alopecia areata (study JAHO) receiving 2 mg (A) or 4 mg (B) once daily



Solid lines represent adult alopecia areata model (study JAHO) estimated median and 90% prediction interval of concentrations for 2 mg once daily (lower panel, blue lines, solid black line) and 4 mg once daily (upper panel, red lines, solid black line). Black symbols represent individual observed concentrations either from plasma or plasma-corrected micro-samples from adolescent participants in study JAIO.

Special populations

The effect on the pharmacokinetics of baricitinib on renal function, hepatic function, age, weight, race, gender, and erythrocyte sedimentation rate were investigated previously.

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 2.1 and 1.6 for moderate and mild renal impairment, respectively.

Moderate hepatic impairment, age (age range of 19 to 83 years) and Erythrocyte Sedimentation Rate (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.

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 ethnic origin (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.

Exposure relevant for safety evaluation

In paediatric patients aged 12 to <18 years with alopecia areata and weighing ≥30 kg, the C_{max} is 52.5 ng/mL, and the AUC_T is 301 ng × h/mL.

2.3.3. Pharmacodynamics

Mechanism of action

Baricitinib is an orally available, selective inhibitor of JAKs. Janus kinases are a family of tyrosine kinases that mediate cytokine receptor signalling through phosphorylation and activation of signal transducers and activators of transcription (STAT) proteins. There are 4 known JAK family members: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). The relative affinity of JAK inhibitors for different members of the JAK kinase family allows for differentiation of JAK inhibitors in relation to their enzymatic inhibitory profile.

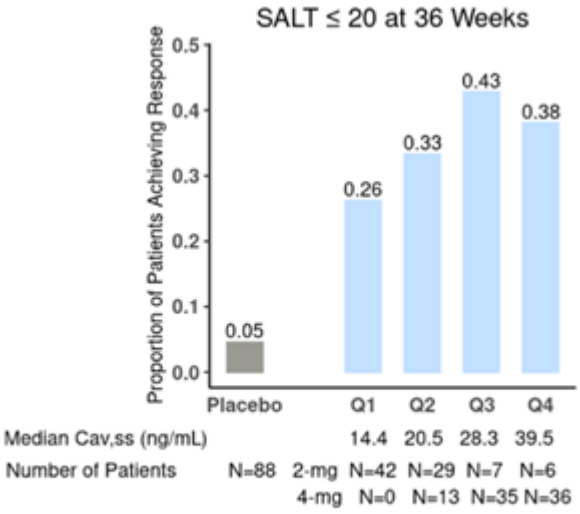
Primary and secondary pharmacology

In vitro assays indicate that baricitinib is a selective inhibitor of JAKs with potency and selectivity for JAK1 and JAK2 and less potency for JAK3 or TYK2. Dual inhibition of JAK1 and JAK2, which may interrupt interferon gamma (IFNγ) signaling and other inflammatory pathways that contribute to the immunopathogenesis of AA, and clinical evidence with other JAK inhibitors support the investigation of baricitinib in the treatment of AA.

2.3.4. PK/PD modelling

The E-R relation was studied for the primary endpoint of the JAIO study (SALT score of ≤20) at week 36), including data from 256 adolescents with AA (88 placebo). Clinically relevant higher rates of SALT ≤20 responses were observed at week 36 in the two upper quartiles of exposure compared to the two lower quartiles suggesting an E-R relationship. A similar pattern was found for the SALT 50% improvement.

Figure 3: Exposure-response analysis: Observed SALT values ≤20 at Week 36 by baricitinib average plasma concentration at steady-state ($C_{ay,ss}$) quartiles for patients receiving placebo, 2-, or 4-mg baricitinib once-daily doses in Study JAIO.



Abbreviations: Cav,ss = average concentration during a dosing interval at steady-state; N = number of patients analysed; Q = quartile; SALT = Severity of Alopecia Tool.
Note: Light blue bars indicate response rate.

2.3.5. Discussion on clinical pharmacology

Pharmacokinetics

A clinical study was conducted to evaluate the PK of baricitinib in paediatric patients with alopecia areata (study JAIO). The PK was investigated in patients aged 12 to <18 years receiving a dose of 2 mg once daily as a tablet or a dose of 4 mg once daily as a tablet. A total of 84 patients were treated with 2 mg baricitinib and also 85 patients were treated with 4 mg baricitinib. The PK aim of the study was to find a paediatric dose leading to similar exposure in paediatric patients with alopecia areata aged 12 to <18 years and weighing ≥30 kg compared to adult patients with alopecia areata.

A different bioanalytical method was used in study JAIO compared to the analytical methods at MAA. The analytical methods were sufficiently validated, and samples were analysed within the shown long term stability period. The matrix for the micro-sampling assay is whole blood whereas plasma was used as matrix for the bioanalytical assay in adults. Given the differences in matrix i.e. whole blood vs plasma a standard cross-validation could not be conducted. Instead, in a subset of patients time-matched plasma samples and whole blood samples were collected and the slope of the regression line using these samples was used to convert the blood data to plasma equivalents. This approach is considered acceptable.

Baricitinib is mainly excreted via urine and predominately as the parent compound. Furthermore, C_{max} and AUC increase dose-proportional over the clinical dose range of 1 to 4 mg following single and multiple dosing. No effect of age is expected in children aged 12 years and older; therefore, the approach of the Applicant to use the already developed PopPK model to determine the PK in paediatric patients with alopecia areata aged 12 to <18 years is acceptable. The model appears to be able to predict the PK in alopecia areata patients aged 12 to <18 years.

The Applicant did not prespecify acceptance criteria taking the therapeutic window into account to conclude similar exposure in paediatric patients and adult patients and thus similar efficacy and safety. The Applicant assumes that the disease is similar in adults and paediatric patients with alopecia areata and a similar exposure-response relationship. Based on PopPK modelling, the C_{max} is comparable in paediatric patients with alopecia areata weighing ≥30 kg and adult patients with alopecia areata with the current posology of 4 mg once daily (52.5 ng/mL and 47.5 ng/mL, respectively). The AUC is slightly lower in paediatric patients with alopecia areata weighing ≥30 kg (301 ng × h/mL) compared to adult patients with alopecia areata (435 ng × h/mL) with the current posology of 4 mg once daily. However, due to the observed inter-individual variability the lower AUC is not significantly different. Therefore, similar exposure can be concluded in paediatric patients with alopecia areata aged 12 to <18 years and weighing ≥30 kg compared to adults when treated with 4 mg once daily.

Pharmacodynamics

An exposure-response relationship was demonstrated in the adolescent AA population for the primary endpoint (SALT≤20) and a key secondary endpoint (SALT50) both at week 36.

2.3.6. Conclusions on clinical pharmacology

A clinical studied was conducted to evaluate the PK of baricitinib in paediatric patients with alopecia areata (study JAIO). Similar exposure can be concluded in paediatric patients with alopecia areata aged 12 to <18 years and weighing ≥30 kg compared to adults with alopecia areata when treated with 4 mg once daily. Exposure-response relationship was demonstrated. The clinical pharmacology data submitted are sufficient and supportive of the proposed extension of indication and section 5.2 of the SmPC has been updated to reflect the PK profile of baricitinib in adolescents.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

The doses of baricitinib 2 mg and 4 mg utilised in the adolescent cohort of Study JAIO were selected based on

- the Phase 3 AA studies (I4V-MC-JAIR and I4V-MC-JAHO) in adults where doses of 2 mg and 4 mg QD were found to be effective, and
- the pharmacokinetic, safety, and efficacy data from the paediatric studies in atopic dermatitis (I4V-MC-JAIP) and juvenile idiopathic arthritis (I4V-MC-JAHV).

In the paediatric atopic dermatitis and juvenile idiopathic arthritis studies I4V-MC-JAIP and I4V-MC-JAHV, respectively

- doses of 2 mg and 4 mg QD in a paediatric participant weighing at least 30 kg produced a similar exposure to 2 mg and 4 mg QD in an adult, and
- doses of 1 mg and 2 mg QD in a paediatric participant weighing less than 30 kg produced a similar exposure to 2 mg and 4 mg QD in an adult.

2.4.2. Main study

Title of Study

A Phase 3, Double-Blind, Randomised, Placebo-Controlled Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of Baricitinib in Children from 6 Years to Less than 18 Years of Age with Alopecia Areata. Brief title: BRAVE-AA-PEDS.

Methods

Objectives

The primary objective was to demonstrate the superiority of baricitinib *versus* placebo in the treatment of adolescent participants with severe AA, as assessed by the proportion of participants achieving SALT score ≤20 at Week 36.

The key secondary objective was to compare the efficacy of baricitinib high or low dose to placebo in adolescent participants with AA during the initial treatment period as measured by physician-assessed signs and symptoms of AA.

Other secondary objectives were

- To compare the efficacy of baricitinib high or low dose to placebo in adolescent participants with AA during the initial treatment period as assessed by PRO measures and QoL tools,
- To characterise the PK profile of baricitinib in adolescent participants with AA,
- To assess bone and growth safety of baricitinib in adolescent participants with AA,
- Evaluation of response to vaccines as appropriate in those participants who are eligible for protocol-specified, non-live vaccines,
- To assess the maintenance of efficacy during the long-term extension period, as measured by physician-assessed signs of AA,

- To assess growth during long-term treatment, and
- To describe the safety of baricitinib in adolescent participants with AA.

Exploratory Objectives included

- evaluating the response to baricitinib treatment regimens on clinical measures and patient-reported outcomes,
- the time to achieve absolute SALT score ≤20, and
- baricitinib PK through Week 16 will be characterised in the AA population and relationship between exposure and study endpoints at Week 36.

Design

Study JAIO consists of 4 periods (Figure 4):

1. The up to 5 weeks screening period (0 to 35 days before start of the study); in- and exclusion criteria are checked, including the vaccination status, the medical history and previous treatment, psychological impact of refractory AA, and history of psychological counselling related to AA.
2. The 36-weeks double-blind placebo-controlled period (36 weeks); patients were randomised (1:1:1) in a blinded manner to placebo QD, low dose baricitinib QD, or high dose baricitinib QD, starting at visit 2 (week 0, baseline). Dosing was based on body weight. Patients weighing 30 kg or more received the following baricitinib doses:

   • baricitinib 4 mg QD (high dose), or
   • baricitinib 2 mg QD (low dose).
   Patients weighing less than 30 kg received the following baricitinib doses:
   • baricitinib 2 mg QD (high dose), or
   • baricitinib 1 mg QD (low dose).

   After the required number of patients in this placebo-controlled period has been reached, all subsequent patients were assigned to the baricitinib high or low dose group for additional safety evaluation.
3. The Long-Term Extension (LTE) period (up to 2 years); during which patients were transitioned at several timepoints.

   At week 36,

   • responders (absolute SALT score of 20 or less) remained on the dose to which they were initially randomised (double-blind), and
   • non-responders (absolute SALT score of greater than 20) who were initially randomised to baricitinib high or low dose remained on the same dose to which they were initially randomised (double-blind), and those who were initially randomised to placebo were re-randomised in a double-blind manner to baricitinib high dose or baricitinib low dose.

   At week 52,

   • responders (SALT score of ≤10, ClinRO Measure for EB Hair Loss (0,1), and ClinRO Measure for EL Hair Loss (0,1)) remained on the same dose,
   • those receiving placebo or baricitinib low dose were transitioned to baricitinib high dose in a blinded manner according to their weight category at the current visit if they meet the

uptitration criteria: SALT score >10, and/or ClinRO Measure for EB Hair Loss ≥2, and/or ClinRO Measure for EL Hair Loss ≥2, and

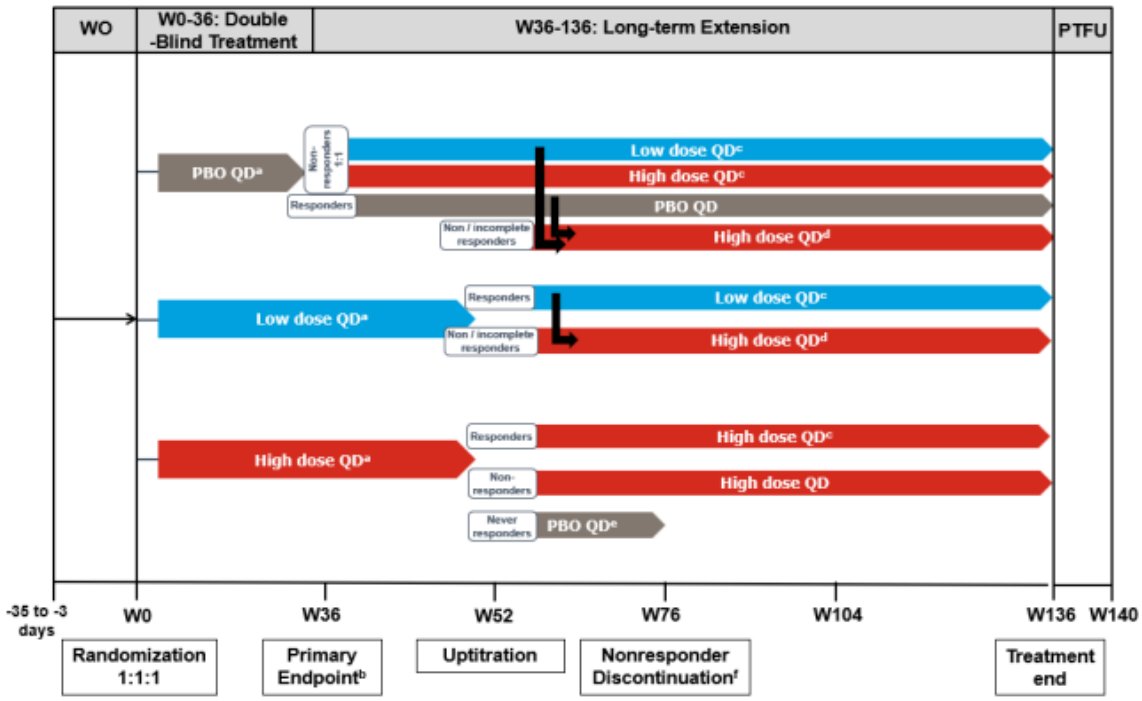
• those initially randomised to baricitinib high dose and never achieved a SALT score ≤20 at any visit up to and including Week 52, had not achieved a 2-point improvement in ClinRO Measure for EB Hair Loss at Week 52, and had not achieved a 2-point improvement in ClinRO Measure for EL Hair Loss at Week 52, were transitioned to placebo.

At week 76,

• non-responders at week 52 and week 76 (never achieved a SALT score ≤20 at any visit including Week 52 and Week 76, had not achieved a 2-point improvement in ClinRO Measure for EB Hair Loss at Week 52 and Week 76, and had not achieved a 2-point improvement in ClinRO Measure for EL Hair Loss at Week 52 and Week 76), were discontinued from the study.

Post-treatment follow-up period (28 days); for those who did not enter the LTE study (period 3).

Figure 4: JAIO study design



Abbreviations: ClinRO = clinician-reported outcome; EB = eyebrow; EL = eyelash; IP = Investigational Product; QD = once daily; SALT = Severity of Alopecia Tool; PTFU = posttreatment follow-up period; W = week; WO = washout.
a For participants weighing 30 kg or more: high dose is 4 mg QD and low dose is 2 mg QD. For participants weighing less than 30 kg: high dose is 2 mg QD and low dose is 1 mg QD.
b At Week 36, nonresponders with a SALT score >20 receiving placebo will be re-randomised in a blinded manner to either baricitinib high dose or baricitinib low dose, and nonresponders receiving baricitinib high dose or low dose will remain on the same dose to which they were initially randomised. At Week 36, responders with a SALT score ≤20 will continue to receive the same dose of IP to which they were initially randomised.
c At Week 52, participants meeting the following criteria will remain on the same dose to which they have been responding: • SALT score ≤10, and • ClinRO Measure for EB Hair Loss (0, 1), and • ClinRO Measure for EL Hair Loss (0, 1).
d At Week 52 and thereafter, participants receiving placebo or baricitinib low dose (according to their weight category at the current visit) will be transitioned to baricitinib high dose in a blinded manner if they meet the uptitration criteria listed below: • SALT score >10, and/or • ClinRO Measure for EB Hair Loss ≥2, and/or • ClinRO Measure for EL Hair Loss ≥2.
e At Week 52, if participants initially randomised to baricitinib high dose meet the criteria below, they will be transitioned to placebo in a blinded manner: • have never achieved a SALT score ≤20 at any visit up to and including Week 52 • have not achieved a 2-point improvement in ClinRO Measure for EB Hair Loss at Week 52, and • have not achieved a 2-point improvement in ClinRO Measure for EL Hair Loss at Week 52.
f At Week 76, participants who have met nonresponse criteria at Week 52 and Week 76, as defined below, will be permanently discontinued from the study: • have not achieved a SALT score ≤20 at any visit up to and including Week 52 and at Week 76 • have

not achieved a 2-point improvement in ClinRO Measure for EB Hair Loss at Week 76, and have not achieved a 2-point improvement in ClinRO Measure for EL Hair Loss at Week 76.

Study participants

In- and exclusion criteria

To be eligible to participate in the study, patients:

- had to be 6 to < 18 years of age, and at or above the 5th percentile of weight for age, at the time of informed consent. Patients 12 to 18 years had to weigh at least 30 kg and those who reached the age of 18 years during the study were allowed to continue participation,
- were male or non-pregnant, non-breastfeeding females,
- had severe AA, defined by all the following:
    - diagnosis of AA for at least 1 year,
    - current AA episode of at least 6 months' duration with hair loss encompassing ≥50% of the scalp,
    - SALT score ≥50 at Visit 1 AND Visit 2,
    - no spontaneous improvement of AA in the investigator's opinion (no more than a 10-point spontaneous reduction in SALT) over the past 6 months,
    - history of trial and failure with at least 1 available treatment (topical or other) for AA,
    - history of psychological counselling related to AA,
    - history of psychological impact from refractory AA as reported by the investigator, parent, or participant, and
    - current episode of severe AA of less than 8 years (those with severe AA for ≥8 years could be enrolled if episodes of regrowth, spontaneous or under treatment, were observed on the affected areas over the past 8 years).

Patients were excluded from participation, if they:

- had primarily "diffuse" type of AA (characterised by diffuse hair shedding).
- were, at the time, experiencing other forms of alopecia including, but not limited to: trichotillomania, telogen effluvium, chemotherapy-induced hair loss, or any other concomitant conditions (for example, tinea capitis, psoriasis, lupus erythematosus, or secondary syphilis) that would interfere with evaluations of the effect of study medication on AA,
- were, at the time, experiencing or having a history of unstable concomitant disease that required frequent hospitalisations and/or frequent use of systemic immunosuppressants that could interfere with participation in the study,
- had inadequate washout for other therapies including, but not limited to: corticosteroids, JAK inhibitors, monoclonal antibodies, phototherapy,
- had a history of VTE or were considered at high risk of VTE as deemed by the investigator or who met the following: BMI >35 kg/m2 , and oral contraceptive use,
- had a positive test for HBV infection, or
- had HCV infection (positive for anti-hepatitis C antibody with confirmed presence of HCV RNA).

Discontinuation

The investigator discontinued or temporarily interrupted study intervention in the following circumstances: laboratory abnormalities, pregnancy, malignancy, VTE, hepatitis B, use of prohibited medications, herpes zoster, suicidal ideation, in line with GCP, investigator's decision, enrollment in other studies and subject's decision.

Treatment

Investigational product

In study I4V-MC-JAIO, considering only the adolescents 12 to 18 years of age with a minimum weight of 30 kg, patients were randomised 1:1:1 to either placebo QD, baricitinib 2 mg QD, or baricitinib 4 mg QD. Baricitinib was provided in tablets; placebo tablets were matched to either the 2 or the 4 mg dose. For blinding purposes, placebo treatment consisted of one tablet resembling the 2 mg dose and one tablet resembling the 4 mg dose; patients assigned to the low dose group took 2 mg baricitinib and 4 mg placebo, and patients in the high dose group 2 mg placebo and 4 mg baricitinib.

The dosing regimen was chosen primarily based on results from the Phase 3 AA studies in adults (Studies JAIR and JAHO) and additionally supported by PK, safety, and efficacy data for baricitinib in paediatric studies of baricitinib in AD and JIA. A dose of 4 mg QD in a child or adolescent weighing at least 30 kg produce a similar exposure to 4 mg QD in an adult.

Concomitant treatments

The following medications were permitted during the study:

- topical corticosteroids or topical calcineurin inhibitors except on the scalp, eyebrows, and eyelids,
- topical corticosteroid or topical calcineurin inhibitors use for the treatment of adverse events on the scalp, eyebrows, and eyelids was limited to approximately 2 weeks,
- oral or topical minoxidil was allowed if the participant had been on a stable dose for 12 months and was anticipated to continue on a stable dose through Week 36,
- intranasal, ophthalmic, or inhaled steroid use,
- a maximum of 2 intra-articular or soft tissue (bursa, tendon, and/or ligament) corticosteroid injections were allowed up until the 36-week primary endpoint. After 36 weeks, such injections were permitted,
- non-live vaccinations, such as influenza vaccination, COVID-19 vaccination, and/or emergency vaccinations, such as rabies or tetanus vaccinations,
- bimatoprost ophthalmic solution (if on stable dose for 8 weeks prior to Visit 2), and
- HMG CoA reductase inhibitors or "statins" (for example, simvastatin and simvastatin + ezetimibe) for treatment of hypercholesterolaemia and the prevention of cardiovascular disease.

Rescue treatment

As explained in the design of trials, non-responders in the placebo group could receive baricitinib as a rescue treatment after week 36. Non-responders in low dose treatment groups could be rescued with 4-mg dose baricitinib. No other rescue treatment was considered in the design of the pivotal trials.

Outcomes/endpoints

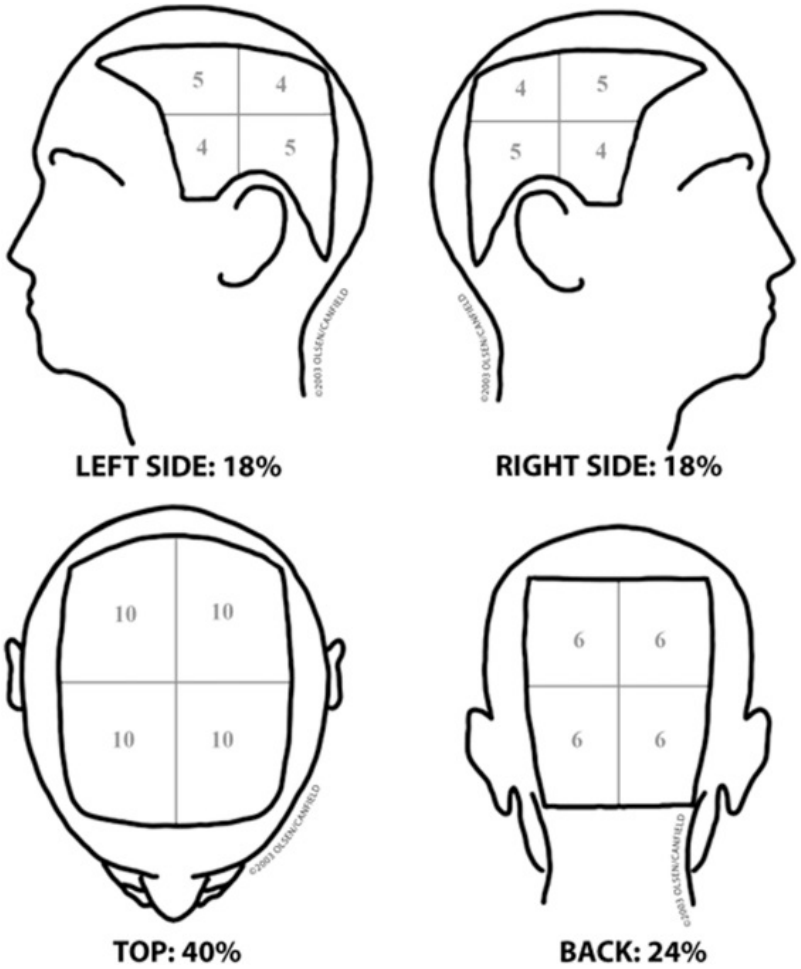
Primary Efficacy endpoint – The proportion of patients reaching an absolute SALT (Severity of Alopecia Tool) ≤ 20 at week 36.

The SALT score is a tool developed by the National Alopecia Areata Foundation Working Committee to assess the extent of scalp hair loss in patients with AA.

The SALT uses a visual aid showing the division of the scalp hair into 4 areas, each constituting the following percentage of total scalp surface area:

- Top - 40%.
- Posterior/back - 24%.
- Right side - 18%.
- Left side - 18%.

Figure 5: SALT aid for determining scalp surface area



The percentage of hair loss in each area is determined and is multiplied by the percentage of scalp covered by that area. The total sum of the 4 products of each area will give the SALT score. Only

terminal hair is included in the SALT when determining scalp coverage; areas with only vellus hair or any fine, downy hair are considered as missing hair.

The primary endpoint for the JAIO study is the proportion of patients reaching a SALT score of ≤20 at Week 36. This corresponds to scalp hair loss of ≤20% or at least 80% scalp hair coverage. According to the study in which SALT was developed, this endpoint was considered by both patients with AA and clinicians as a clinically meaningful improvement for patients with ≥50% scalp hair loss.

Key Secondary Efficacy Endpoints

Key secondary efficacy endpoints, controlled for multiplicity, included more stringent SALT assessments as well as SALT assessments at earlier timepoints:

- Proportion of participants achieving an absolute SALT score ≤20 at Weeks 16 and 24
- Proportion of participants achieving a SALT50 at Week 12
- Proportion of participants achieving a SALT90 at Week 36
- Proportion of participants achieving an absolute SALT score ≤10 at Weeks 24 and 36

Additional secondary efficacy endpoints

Additional secondary endpoints were not controlled for multiplicity. Secondary endpoints were:

1. Other derivates of SALT scores

   Other derivate SALT sores included changes from baseline at 12, 16, 24, and 36 weeks, proportions of patients achieving SALT50/75/90/100 at weeks 24 and / or 36.

Clinician and Patient Reported Outcomes (ClinRO's and PRO's)

2. Physician-Reported Outcomes (ClinRO's)

   ClinROs measure 3 manifestations of AA, and were developed by the Applicant. Psychometric properties (except for Nail Appearance) were assessed in a population with 40 adults and 5 adolescents; no formal validation was performed in adolescents.

- ClinRO Measure for Eyebrow (EB) Hair Loss,
- ClinRO Measure for Eyelash (EL) Hair Loss, and
- ClinRO Measure for Nail Appearance.

  See tables below for scoring. For each ClinRO, proportions of patients reaching score 0 or 1 with at least 2 points improvement at week 16, 24, and 36 compared to baseline were calculated (in those with baseline score 2 or higher).

3. Patient Reported Outcomes (PRO's)

   The Applicant also developed 4 PRO's evaluating signs and symptoms of AA. The PROs have not formally been validated in adolescents with AA.

- PRO for Scalp Hair Assessment is a 5-point, single-item patient assessment of the extent of scalp hair loss: 0 = No missing hair (0% of my scalp is missing hair; I have a full head of hair), 1 = A limited area (1% to 20% of my scalp is missing hair), 2 = A moderate area (21% to

49% of my scalp is missing hair), 3 = A large area (50% to 94% of my scalp is missing hair), and 4 = Nearly all or all (95% to 100% of my scalp is missing hair),

- PRO Measure for Eyebrow (EB) hair loss,
- PRO Measure for Eyelash (EL) hair loss, and
- PRO Measure for Nail Appearance.

See tables below for scoring. For each PRO, proportions of patients reaching score 0 or 1 with at least 2 points improvement at week 16, 24, and 36 compared to baseline were calculated (in those with baseline score 2 or higher).

Table 5: Final versions of ClinRO measures for eyebrow and eyelash hair loss, and PRO measures for eyebrows and eyelashes.

ClinRO Measure for Eyebrow Hair Loss™ Examine **both eyebrows** from **two feet** away and select the best response below. ❑$_0$ The eyebrows have full coverage and no areas of hair loss ❑$_1$ There are minimal gaps in eyebrow hair **and** distribution is even ❑$_2$ There are significant gaps in eyebrow hair **or** distribution is not even ❑$_3$ No notable eyebrow hair	**PRO Measure for Eyebrows™** Look at **the hair in both of your eyebrows**. Please rate your eyebrows, as they look **today**. This question asks about **gap(s)** in your eyebrows or **thinning** in your eyebrows. If you have gap(s) in your eyebrows **and** thinning in your eyebrows, please choose your answer based on the type of hair loss that bothers you the most. Please select **one** answer. ❑$_0$ I have full eyebrows on each eye ❑$_1$ I have a minimal gap(s) **or** a minimal amount of thinning in at least one of my eyebrows ❑$_2$ I have a large gap(s) **or** a large amount of thinning in at least one of my eyebrows ❑$_3$ I have no or barely any eyebrow hairs
ClinRO Measure for Eyelash Hair Loss™ Examine the **upper and lower eyelashes** of **both eyes** and select the best response option below. ❑$_0$ The eyelashes form a continuous line along the eyelids on both eyes ❑$_1$ There are minimal gaps **and** the eyelashes are evenly spaced along the eyelids on both eyes ❑$_2$ There are significant gaps along the eyelids **or** the eyelashes are not evenly spaced along the eyelids ❑$_3$ No notable eyelashes	**PRO Measure for Eyelashes™** Look at **your upper and lower eyelashes on both your eyes**. Please rate your eyelashes, as they look **today**. Please select **one** answer. ❑$_0$ I have full eyelashes on each eyelid ❑$_1$ I have a minimal gap **or** minimal gaps along the eyelids ❑$_2$ I have a large gap **or** large gaps along the eyelids ❑$_3$ I have no or barely any eyelash hair

ClinRO clinician-reported outcome, *PRO* patient-reported outcome

Table 6: Final versions of the ClinRO and PRO Measures for Nail Appearance

ClinRO Measure for Nail Appearance™	PRO Measure for Nail Appearance™
Examine the **fingernails** and **toenails** and select the best response below.	Examine your **fingernails** and **toenails**. Please rate your fingernails and toenails, as they look **today**.
❑$_0$ Nails are not at all damaged (e.g. pitted, rough, brittle, split)	Please select **one** answer.
❑$_1$ At least one nail is a little damaged (e.g. pitted, rough, brittle, split)	❑$_0$ Nails are not at all damaged (e.g. pitted, rough, brittle, split)
❑$_2$ At least one nail is moderately damaged (e.g. pitted, rough, brittle, split)	❑$_1$ At least one nail is a little damaged (e.g. pitted, rough, brittle, split)
❑$_3$ At least one nail is very damaged (e.g. pitted, rough, brittle, split) **or** subject has lost at least one nail	❑$_2$ At least one nail is moderately damaged (e.g. pitted, rough, brittle, split)
	❑$_3$ At least one nail is very damaged (e.g. pitted, rough, brittle, split) **or** you have lost at least one nail

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ClinRO clinician-reported outcome, *PRO* patient-reported outcome

Health outcomes and Quality of life measures

4. Hospital Anxiety and Depression Scale

   The HADS is a widely used 14-item self-assessment scale that determines the levels of Anxiety (7 items) and Depression (7 items) that a patient experienced over the past week. The HADS utilises a 4-point Likert response scale (i.e. 0-3) for each item and is intended for ages 12 years to 65 years. Scores for the domains Anxiety and Depression can range from 0 to 21, with higher scores indicating greater anxiety / depression. Although validation data are available in adolescents, there are no formal validation data in adolescents with AA nor clinical thresholds for the HADS in patients < 18 years of age. The thresholds used were based on Terluin et al. (2009) and Chan et al. (2010):

   a. HADS depression subscale ≥7 indicates possible depression and scores of ≥12 is indicative of moderate to severe depression, and

   b. HADS anxiety subscale scores of ≥9 indicate possible anxiety and scores of ≥16 indicate any anxiety disorder as well as panic disorder, agoraphobia, and social phobia.

5. Patient-Reported Outcomes Measurement Information System (PROMIS)

   The PROMIS is a set of person-centred measures that evaluates and monitors physical, mental, and social health in adults and children, for use in the general population and with individuals living with chronic conditions. It has been developed for universal rather than disease specific assessment. It has been validated across several chronic diseases including in adolescents but not specifically in adolescents with AA. The PROMIS Depression item bank assesses self-reported negative mood (sadness, guilt), views on self (self-criticism, worthlessness), and social cognition (loneliness, interpersonal alienation), as well as decreased positive affect and engagement (loss of interest, meaning, and purpose).

   a. PROMIS Anxiety short form: is available in a paediatric self-report (ages 8 to < 18 years), assessing anxiety "in the past 7 days". Response options range from 1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Often; to 5 = Almost always. Total raw scores are converted to T-Scores with higher scores representing greater anxiety.

   b. PROMIS Depression short form: is available in a paediatric self-report (ages 8 to < 18 years), assessing depression "in the past 7 days." Response options range from 1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Often; to 5 = Almost always. Total raw scores are converted to T-Scores with higher scores representing greater depression.

c. PROMIS Peer Relationships short form: Measures social functioning, friendship quality, and peer acceptance and is available in a paediatric self-report (ages 8 to < 18 years), assessing peer relationships "in the past 7 days." Response options range from 1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Often; to 5 = Almost always. Total raw scores are converted to T-Scores with higher scores representing greater quality of relationships.

6. Family Dermatology Life Quality Index

   A 10-item measure designed for adult (>16 years old) family members of participants. The questionnaire is completed by family members of the AA participant (for example, parents or caregivers) and measures the secondary impact of the participant's skin disease on family QoL. Response categories include "not at all/not relevant", "only a little", "quite a lot", and "very much", with corresponding scores of 0, 1, 2, and 3, respectively, with unanswered ("not relevant") responses scored as 0.

7. EQ-5D-Y

   A generic measure that assesses health status 'today' (EuroQol Reseacrh Foundation, 2020), to be completed by the adolescent. The questionnaire consists of 2 parts. Part 1 generate a *health state index score,* by assessing 5 dimensions (mobility, self-care, usual activities, pain or discomfort, anxiety or depression) with 3 possible levels of response (no problems, some problems, a lot of problems). Higher scores indicating better health utility. Part 2 consists of a VAS on which the patient rates their *perceived health state* from 0 ("the worst health you can imagine") to 100 ("the best health you can imagine"). Published studies by European Quality of Life Group members showed preliminary evidence of the instrument's feasibility, reliability, and validity.

8. EQ-5D 5L (European Quality of Life–5 Dimensions–5 Levels)

   A self-completed measure for paediatric participants 16 to 17 years. It provides a single index value for health status that can be used in the clinical and economic evaluation of health care as well as population health surveys. The EQ-5D 5L assesses 5 dimensions of health:

   • mobility

   • self-care

   • usual activities

   • pain or discomfort

   • anxiety or depression

   The items are scores on 5 levels, i.e. no problems, slight problems, moderate problems, severe problems, and unable to perform or extreme problems. A total of 3125 health states is possible. In addition to the health profile, a single health state index value can be derived based on a formula that attaches weights to each of the levels in each dimension. This index value ranges between less than 0 (where 0 is a health state equivalent to death; negative values are valued as worse than dead) to 1 (perfect health). In addition, the EQ VAS records the self-rated health status on a vertical graduated (0 to 100) scale; perceived health is rated from 0 (the worst imaginable health) to 100 (the best imaginable health). In conjunction with the health state data, it provides a composite picture of the respondent's health status.

9. Skindex-16 AA-Y

The Skindex-16 measures health-related quality of life in patients with skin diseases. The items' wordings have been adapted and validated for use among patients with scalp AA into the AA-Y version. The Skindex-16 is composed of 16 items grouped under 3 domains: Symptoms (4 items), Emotions (7 items), and Functioning (5 items). Patients answer each question with a number ranging from 0 (never bothered) to 6 (always bothered). Scores are transformed to a linear scale ranging from 0 (no effect) to 100 (effect experienced all of the time), with higher scores indicating greater impact on quality of life. Wording for 1 item was adapted for use among adolescents with AA (work --> study), and hereto after called the "Skindex-16 AA-Y" for this trial.

10. Neuro-Qol Paediatric Stigma short form

    Assesses self-reported quality of emotional health (perceptions of self and publicly enacted negativity, prejudice and discrimination as a result disease-related manifestations), by self-report of adolescents aged 10 to < 18 years. The short form includes 8 questions assessing emotional health "lately", with response options ranging from 1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Often; to 5 = Always. Total raw scores are converted to T-Scores with higher scores representing greater impact on emotional health.

Other secondary endpoints comprised the safety assessments (see safety section), also including growth monitoring (based on hight, weight, imaging of hand and knee (X-rays or MRI), and hormone levels), suicidal ideation and behaviour risk monitoring, and pharmacokinetic assessments (see pharmacology section).

Sample size

For the adolescent population, approximately 415 patients were planned to be enrolled, of whom 255 were to be randomised 1:1:1 to baricitinib low dose, high dose, or placebo. Based on the graphical testing schema, the high dose has approximately 98% power and the low dose has approximately 80% power based on the initial alpha allocation of 0.5% and 4.5%, respectively (provided in SAP from version 2.0 onwards). The assumptions used for the power calculation were:

- 34% response rate for baricitinib high dose
- 20% response rate for baricitinib low dose, and
- 5% response rate for placebo.

The remaining 160 adolescents will be randomised (blinded) to baricitinib low dose or high dose.

Randomisation

In the JAIR study in adults, patients were randomised to placebo, baricitinib low dose, or baricitinib high dose in a 1:1:1 ratio using a computer-generated random sequence using an interactive web-based response system (IWRS). The IWRS was programmed with blind-breaking instructions. Randomisation was stratified based on disease severity (SALT 50-94 versus SALT 95-100), duration of current AA episode (less than 4 years versus more than 4 years), and geographic region (US/Canada, Europe, Japan, and Rest of World).

Approximately 415 adolescent participants aged 12 to < 18 years old were planned for enrolment into the JAIO study. Of these, a minimum of 255 adolescents were to be randomised 1:1:1 to double-blind treatment with placebo, baricitinib low dose, or baricitinib high dose and contribute to efficacy analyses. After completion of enrolment, the following approximately 160 adolescents were to be

randomised 1:1 to double-blind treatment with baricitinib low dose or high dose to further accumulate safety exposures. These data were not to be included in the placebo-controlled efficacy and safety analyses.

Blinding

The JAIO study is a double-blind study in which participants, care providers, investigators, and the sponsor were blinded to the study intervention.

Statistical methods

The SAP was amended six times; the most important changes include:

- Update to version 1.1: Inclusion of the final graphical testing procedure upon EMA advice and adding of per protocol, tipping point and sensitivity analysis (SAP version 1.1).
- Update to version 2.0: Due to major change. Adding of a new power analysis based on the updated testing strategy introduced in 1.1 is the mentioned, but no further changes are specified.
- Update to version 6.0: Updated as per protocol amendment f, update of week 52 scope and details of interim analysis.

The approval date of the final SAP 6.0 submitted by the Applicant is 22 May 2025. Database lock for primary analysis was on 01 November 2024, which is also listed as the final approval date of SAP version 4.0. SAP version 5.0 was finalised 6 December 2024 and mainly describes some additions to Tables and removal of variables not analysed/collected from the tables.

Populations and treatment groups

The following analysis sets were defined.

Table 7: Analysis Sets for Adolescents

Analysis Sets for Adolescents

Participant Analysis Set	Description
Intent-to-treat (ITT) Analysis Set for adolescent participants	All participants in age group 12 to <18 years randomly assigned in Study JAIO who are enrolled prior to stopping placebo enrollment for this age group will be included in this set. Participants will be analyzed according to the treatment group to which they were randomized at baseline (Visit 2).
Per-Protocol Set (PPS) for adolescent participants	The PPS for adolescents will include all participants in the adolescent ITT analysis set who are not deemed noncompliant with treatment, who do not have any important protocol deviations that exclude participants from the PPS, and are enrolled at clinical sites that do not have significant GCP deviations that require a report to regulatory agencies. The important protocol deviations, including the subset that result in exclusion from the PPS, will be determined while the study team remains blinded, prior to the primary outcome database lock.
Adolescent Placebo-controlled Safety Analysis Set (APSAS)	The Adolescent Placebo-controlled Safety Analysis Set is defined as all adolescents 12 to <18 who were randomized in Study JAIO before stopping placebo enrollment, who received at least 1 dose of IP, and who did not discontinue from the study for the reason "Lost to Follow-up" at the first post-baseline visit. Participants will be analyzed according to the treatment group to which they were randomized at baseline (Visit 2).
Adolescent Safety Population	The adolescent safety population is defined as all participants 12 to <18 years who were randomized in Study JAIO, including those randomized after stopping placebo enrollment, who received at least 1 dose of IP, and who did not discontinue from the study for the reason "Lost to Follow-up" at the first post-baseline visit. Participants will be analyzed according to the treatment group to which they were randomized at baseline (Visit 2).

Abbreviations: GCP = good clinical practice; IP = investigational product.

The ITT set for adolescent participants are used for the primary analysis for the efficacy endpoints.

Estimand strategy

The following estimand is defined for the primary outcome:

Population: Participants with severe or very severe AA as defined by the inclusion and exclusion criteria.

Treatment of interest: baricitinib high dose QD, baricitinib low dose QD, and placebo

Outcome variable at patient level: SALT ≤20 at week 36

Population level summary: OR for comparison between baricitinib high dose or low dose vs placebo

Intercurrent events of use of prohibited medication leading to permanent treatment discontinuation, use of prohibited medication leading to temporary treatment interruption and permanent treatment discontinuation for other reasons will be handled using a composite strategy. Subjects will be considered non-responders after first permanent treatment discontinuation or during treatment interruption.

A similar estimand is used for the other binary (key secondary) endpoints. The SAP also defined an estimand for the continuous endpoints where the targeted scenario is a hypothetical scenario in which all patients adhered to the treatment and concomitant medication was not available.

Statistical analyses

Primary analysis method for the binary responder endpoints, covering all primary and key secondary endpoints, was a logistic regression analysis with treatment group as independent variable and an adjustment for stratification variables and baseline value of the outcome, with the model derived odds ratio reported as effect size together with 95% confidence intervals. The p-value for the odds-ratio for the treatment group is used for primary statistical inference. In case of (quasi-)separation, Firth's correction will be applied, and in case that fails to converge the Fisher's exact test will be used. Differences in responder proportions will be reported as additional effect size with 95% confidence interval calculated with Newcombe-Wilson method without continuity correction.

Analysis method for secondary continuous endpoints will be an ANCOVA. Testing will be done using type III tests for the LS means. The LS mean differences will be reported as effect size with standard error, p-value and 95% confidence interval.

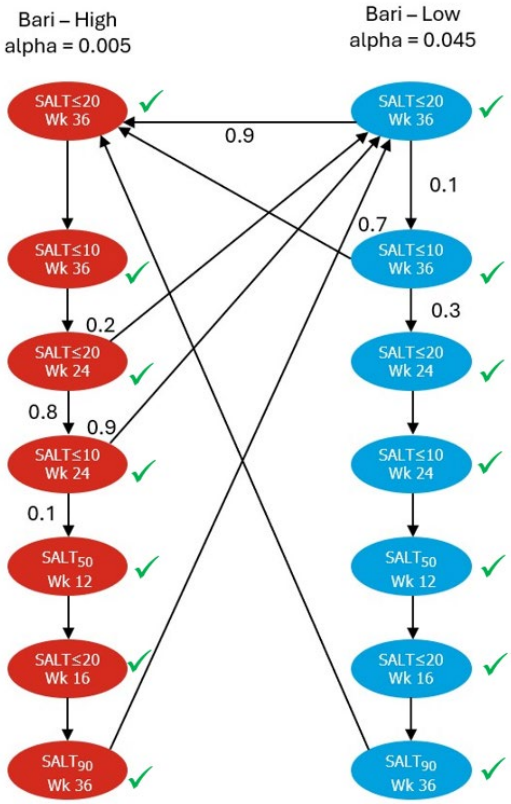
The SAP further describes the use of mixed model for repeated measures (MMRM) for comparison of repeatedly measured endpoint at different timepoints. Here data after intercurrent events will be set to missing, aligning the estimation to the targeted hypothetical scenario as if concomitant medication was not available and all adhered to the treatment assigned.

Additional analyses specified include time to event analysis using log-rank test and Cox regression, Fisher's exact test for comparing proportions of subjects with adverse events, discontinuations and safety endpoints, and ANCOVA for repeatedly measured vital signs, body weight and continuous safety variables.

Multiple testing strategy

The type I error was controlled at the 5% level (two-sided) over all primary and key secondary endpoints jointly over the two dose groups in the adolescent cohort using the following graphical testing procedure.

Figure 6: Results of graphical multiple-testing procedure in Study JAIO.



Abbreviations: Bari = baricitinib; SALT = Severity of Alopecia Tool; w/Wk = week
✓ Achieved statistical significance after adjustment for multiplicity.

Handling of missing data

Missing data for responder endpoints is imputed using non-responder imputation (NRI), in line with the composite strategy and considering participants with missing outcomes treatment failures.

Observations after permanent treatment discontinuation and between treatment interruption due to use of prohibited medication and reinitiation of the study drug were not used and imputed. For continuous endpoints a modified last-observation carried forward (mLOCF) imputation approach was used. The modified last observation carried forward approach used the last non-missing postbaseline observation prior to the occurrence of intercurrent event (permanent treatment discontinuation or treatment interruption due to use of prohibited medication). For patients without at least one postbaseline observation, missing continuous data was not to be imputed.

For binary outcome that defined based on continuous data, mLOCF will be applied on continuous version first then converted to binary outcome. This strategy is used as a sensitivity analyses performed for primary and key secondary endpoints for which NRI will be used in primary analysis.

Sensitivity analyses

The following sets of sensitivity analyses were prespecified in the SAP:

- Analyses in the per-protocol set;
- Placebo multiple imputation for outcomes after intercurrent events;
- Mixed Model for Repeated Measures (MMRM) where observations after an intercurrent event are set to missing and making a missingness at random assumption;
- Worst observation carried forward as a composite strategy for continuous endpoints;

- Tipping point analysis for the primary endpoint.

Subgroup analyses

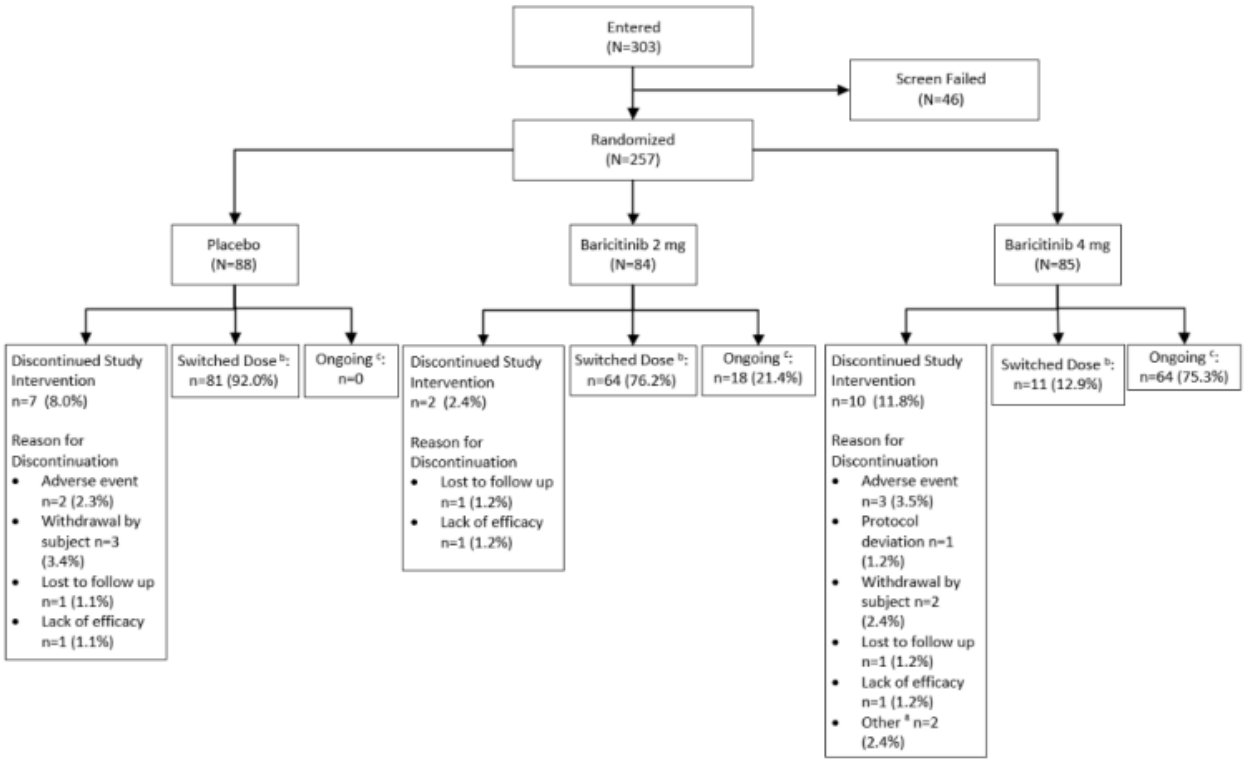
Exploratory subgroup analyses for the primary endpoint were prespecified for: gender, geographic region, race, ethnicity, weight group, BMI group, renal function status at screening, baseline SALT severity and duration of current AA episode.

Results

Participant flow

A total of 303 patients between 12 and 18 years of age were screended and 257 were subsequently enrolled in the JAIO study and randomised to either placebo (n = 88), baricitinib lowe dose (n = 84), or baricitnib high dose (n = 85) (Figure 7). A total of 243 patients completed up to week 36 and entered the JAIO LTE period.

Figure 7: Study participant disposition figure for the Adolescent Placebo-Controlled Set



Abbreviations: n = number of participants in the subgroup; N = number of participants in the group.
[a] Participants meeting Week 76 nonresponder criteria for permanent discontinuation.
[b] "Switched Dose" includes participants who have switched treatment at any point from initial randomized treatment.
[c] Participants included are those ongoing under the treatment they are reported at the time of the data cut-off date.
Sources: Table JAIO.8.1 and Table JAIO.8.2.

Only 4 patients in the placebo group reached spontaneous remission and remained on placebo beyond week 36. A total of 82 patients in the baricitinib 2 mg group and 80 patients at the baricitinib 4 mg group stayed in the study after the 36 weeks visit; a total of 82 patients (97.6%) in the 2 mg group and 80 patients (94.1%) in the 4 mg group ultimately completed the week 52 visits (data cut-off date 15 April 2025).

Recruitment

First patient first visit was on 27 February 2023. The current analyses are based on database cutoff date of April 15, 2025.

Conduct of the study

Sites in 10 countries enrolled participants (Australia, Canada, France, Hungary, Japan, Poland, South Korea, Spain, Taiwan and the United States of America). Most participants enrolled in Study JAIO were from Poland and US sites.

Protocol deviations

A total of 74 patients (29%) had at least 1 important protocol deviation. Most (14%) were due to discrepancies between the duration of the current episode (less than 4 years or 4 years or more) entered in the IWRS for stratification and the later date of current episode entered in the CRF. Despite this, the distribution of patients stratified by current episode duration was similar across the three study arms. In 10 patients dosing non-compliance was observed (< 80% in 7 and > 120% in 3). Other deviations observed were in- and exclusion issues (n = 4), laboratory assessments missing at baseline (n = 5), prohibited concomitant medication (n = 1).

Baseline data

Patient demographics

Mean age in the JAIO study varied between 14.7 and 14.9 years across the three groups, with almost equal percentages of males (51%) and females (49%). Most patients were of white race (58% – 62%), with average weight and height compared to the general population. Most patients originated from Europe (42% - 43%) and North America (27% - 31%). See Table 8 below.

Table 8: Summary of Selected Baseline Characteristics

Attribute	PBO N = 88 n (%)	BARI 2 mg N = 84 n (%)	BARI 4 mg N = 85 n (%)
Age (years), mean (SD)	14.68 (1.72)	14.94 (1.61)	14.56 (1.78)
Female, n (%)	47 (53.4)	39 (46.4)	41 (48.2)
Male, n (%)	41 (46.6)	45 (53.6)	44 (51.8)
Race, n (%)			
American Indian or Alaska Native	Redacted	Redacted	Redacted
Asian	26 (29.5)	23 (27.4)	23 (27.1)
Black or African American	6 (6.8)	5 (6.0)	8 (9.4)
Native Hawaiian or Other Pacific Islanders	Redacted	Redacted	Redacted
White	51 (58.0)	52 (61.9)	52 (61.2)
Multiple	3(3.4)	3 (3.6)	1 (1.2)
Not reported	Redacted	Redacted	Redacted
Height (Z-Score), mean (SD)	0.13 (0.95)	0.20 (0.91)	0.06 (1.11)
Height percentile, mean (SD)	54.48 (27.74)	55.38 (26.34)	52.08 (30.77)
Weight (Z-Score), mean (SD)	0.25 (1.07)	0.61 (0.96)	0.25 (1.32)
Weight percentile, mean (SD)	56.98 (28.92)	66.01 (25.90)	56.59 (31.01)
BMI (Z-Score), mean (SD)	0.17 (1.07)	0.54 (0.89)	0.21 (1.23)
BMI percentile, mean (SD)	54.77 (30.26)	65.36 (25.61)	55.41 (30.90)
Geographic region			
North America[a], n (%)	24 (27.3)	26 (31.0)	26 (30.6)
Europe[b], n (%)	38 (43.2)	35 (41.7)	36 (42.4)
Japan, n (%)	7 (8.0)	5 (6.0)	4 (4.7)
Rest of the world[c], n (%)	19 (21.6)	18 (21.4)	19 (22.4)

Abbreviations: BARI = baricitinib; BMI = body mass index; N = number of participants in the analysis population; n = number of participants in the specified category with nonmissing values; PBO = placebo; SD = standard deviation.

a Includes United States and Canada.

b Includes France, Hungary, Poland, and Spain.

c Includes Australia, South Korea, and Taiwan.

Baseline disease characteristics

The mean duration from onset of AA was 6.4 years and the mean duration of the current AA episode was 3.2 years. Sixty-three to 66% of the patients across treatment arms presented with very severe AA (SALT scores 95-100) at baseline and 49% - 59% as Alopecia Universalis (highest percentage in high dose baricitinib group, lowest in placebo). Median SALT score was 100, 65% of participants had significant or complete EB hair loss at baseline, and 57% had significant or complete EL hair loss at baseline, as measured by ClinRO Measures for EB and EL hair loss scores of 2 or 3. The best (0) *and* worst ClinRO baseline scores (3) were highest in the high dose baricitinib group. See Table 9 below.

Table 9: Summary of Selected Baseline Disease Characteristics

Baseline Attribute	PBO N = 88	BARI 2 mg N = 84	BARI 4 mg N = 85
Duration from onset of AA (years), mean (SD)	6.62 (3.94)	6.35 (3.89)	6.08 (3.95)
<1 year	0	0	0
1 to <5 years	41 (46.6)	37 (44.0)	44 (51.8)
5 to <10 years	25 (28.4)	26 (31.0)	28 (32.9)
≥10 years	22 (25.0)	21 (25.0)	13 (15.3)
Duration of the current episode of AA (years), mean (SD)	3.08 (1.84)	3.18 (1.85)	3.27 (2.17)
Duration of current episode of AA in years, n (%)			
<4	61 (69.3)	54 (64.3)	54 (63.5)
≥4	26 (29.5)	29 (34.5)	31 (36.5)
Immunoglobulin E (IU/mL), n (%)			
<200	42 (47.7)	38 (45.2)	45 (52.9)
≥200	46 (52.3)	45 (53.6)	38 (44.7)
Disease severity			
SALT score, mean (SD)	88.0 (17.1)	90.4 (15.1)	88.8 (16.6)
Severe (SALT score of 50-94), n (%)	32 (36.4)	29 (34.5)	31 (36.5)
Very severe (SALT score of 95-100), n (%)	55 (62.5)	55 (65.5)	54 (63.5)
Classified as universalis, n (%)			
Yes	43 (48.9)	45 (53.6)	50 (58.8)
No	45 (51.1)	39 (46.4)	35 (41.2)
Classified as ophiasis, n (%)			
Yes	8 (9.1)	4 (4.8)	11 (12.9)
No	80 (90.9)	80 (95.2)	74 (87.1)
Clinician-Reported Outcome Measure for EB Hair Loss™, n (%)			
0	18 (20.5)	16 (19.0)	21 (24.7)
1	8 (9.1)	13 (15.5)	10 (11.8)
2	25 (28.4)	20 (23.8)	15 (17.6)
3	35 (39.8)	34 (40.5)	39 (45.9)
Clinician-Reported Outcome Measure for EL Hair Loss™, n (%)			
0	27 (30.7)	20 (23.8)	26 (30.6)
1	9 (10.2)	16 (19.0)	10 (11.8)
2	22 (25.0)	19 (22.6)	18 (21.2)
3	28 (31.8)	28 (33.3)	31 (36.5)
Clinician-Reported Outcome Measure for Nail Appearance™, n (%)			
0	40 (45.5)	35 (41.7)	31 (36.5)
1	32 (36.4)	25 (29.8)	33 (38.8)
2	13 (14.8)	16 (19.0)	15 (17.6)
3	1 (1.1)	6 (7.1)	6 (7.1)

Abbreviations: AA = alopecia areata; BARI = baricitinib; EB = eyebrow; EL = eyelash; N = number of participants in the analysis population; n = number of participants in the specified category with nonmissing values; PBO = placebo; SALT = Severity of Alopecia Tool; SD = standard deviation.

Most common comorbidities were allergic rhinitis (24 – 26%), atopic dermatitis (18 – 28%), and asthma (8 – 15%). Depression and anxiety were reported by 3.6 – 5.7% and 1.1 – 3.6% of the patients respectively.

Prior Alopecia Areata therapy

As per protocol requirement, all participants enrolled in Study JAIO reported prior AA therapy:

- >80% had used topical therapies,
- >51% had used systemic therapy, and
- >21% had used phototherapies.

Among systemic therapies

- 35% had used systemic corticosteroids,
- 3.9% had used a JAK inhibitor,
- 27% had used other immunosuppressants, the most common of which were ciclosporin (15%) and methotrexate (12%), and
- 17% used other systemic non-immunosuppressants.

Differences between the three groups were small. Fewer patients in the high dose baricitinib group had used systemic corticosteroids, JAKis, or topical immunotherapy than those in low dose baricitinib or placebo. See Table 10 below.

Table 10: Summary of Prior AA Treatment

Prior therapy	PBO N = 88 n (%)	BARI 2 mg N = 84 n (%)	BARI 4 mg N = 85 n (%)
Prior AA Therapy			
Naïve	0	0	0
Systemic Agents [All Immunosuppressant/Immunomodulator]	46 (52.3)	43 (51.2)	44 (51.8)
Systemic Agents [Corticosteroids]	32 (36.4)	32 (38.1)	27 (31.8)
Systemic Agents [JAK inhibitor]	4 (4.5)	4 (4.8)	2 (2.4)
Systemic Agents [Other immunosuppressant]	23 (26.1)	23 (27.4)	24 (28.2)
Other Systemic [Non-immunosuppressant]	17 (19.3)	14 (16.7)	13 (15.3)
Intralesional Therapy	12 (13.6)	12 (14.3)	14 (16.5)
Topical Therapy excluding Immunotherapy	72 (81.8)	66 (78.6)	69 (81.2)
Topical Immunotherapy	20 (22.7)	20 (23.8)	15 (17.6)
Procedures	2 (2.3)	2 (2.4)	1 (1.2)
Phototherapy	20 (22.7)	16 (19.0)	20 (23.5)

Abbreviations: AA = alopecia areata; BARI = baricitinib; JAK = Janus kinase; N = number of participants in the analysis population; n = number of participants in the specified category with non-missing values; PBO = placebo

Concomitant AA therapy

A total of seven patients reported concomitant use of AA medication during the study, including minoxidil, pimecrolimus, an anilide, fexofenadine and levocetirizine.

Concomitant therapy other than for AA

Up to 65% of the patients used concomitant therapy for other indications than AA. Most common were anilides (mainly paracetamol), antihistaminics, proprionic acid derivatives (mostly ibuprofen), antibiotics, and topical acne treatments which do not impact AA.

Treatments that may have affected AA reported by 1 or more patients, were corticosteroid use, TCI/JAKi's, HMG COA reductase inhibitors, and cryotherapy. These were most often prescribed for

treatment of AEs (9.7% of the patients; systemic use in one patient) and pre-existing conditions (12.8%; systemic use in two patients). The remainder of patients used non-systemic routes of administration, mainly including topical formulations which could not be applied to the scalp, eyebrow, or eyelash, with a reasonable short duration (data not further specified).

Patient compliance

From week 0 to 36, 7 patients (8%) in the placebo, and 4 (2.4%) in the baricitinib group were non-compliant (< 80% compliant). Altogether, 245/257 patients (i.e. 95%) were compliant during the placebo-controlled period.

Numbers analysed

A total of 257 patients constituted the ITT analysis set of adolescents and 213 patients were enclosed in the Per Protocol analysis set. The PP analysis set included patients from the ITT set who were not non-compliant, who did not have any important protocol deviations that exclude participants from the PPS, and were enrolled at clinical sites that did not have significant GCP deviations that required a report to regulatory agencies.

Outcomes and estimation

Primary endpoint

The primary endpoint (SALT ≤20 at week 36) was met; 27% and 42% of the patients in the low and high dose baricitinib groups reached the primary endpoint compared to 4.5% in the placebo group; corresponding response rate differences with placebo were 22.8% and 37.8% respectively. Comparison for both doses individually versus placebo were both statistically significant (p = 0.001; see Table 11 below).

Table 11: Results for Primary Endpoint in Study JAIO ITT Population

	PBO **N = 88** **n (%)**	**BARI 2 mg** **N = 84** **n (%)**	**BARI 4 mg** **N = 85** **n (%)**
Proportion of Participants Achieving SALT ≤20 at Week 36			
Response, n (%)	4 (4.5)	23 (27.4)	36 (42.4)
(95% CI)	(1.8, 11.1)	(19.0, 37.7)	(32.4, 53.0)
Difference (95% CI) vs. PBO[a]	NA	22.8 (12.2, 33.6)	37.8 (25.9, 48.8)
Odds Ratio (95% CI) vs. PBO[b]	NA	17.3 (4.5, 66.1)	35.8 (9.4, 136.3)
p-Value vs. PBO[b]	NA	0.001	0.001

Abbreviations: BARI = baricitinib; CI = confidence interval; ITT = intent to treat; n = number of patients in the specified category; N = number of patients in the analysis population; NA = not applicable; p = probability value; PBO = placebo; SALT = Severity of Alopecia Areata Tool; vs. = versus.

[a] Difference CIs are constructed using Newcombe-Wilson method, without continuity correction. Response CIs are constructed using Wilson method, without continuity correction.

[b] Logistic regression analysis with treatment group, geographic region, duration of current episode at baseline (4 years or less vs. 4 years or more), disease severity (SALT 50-94 vs. SALT 95-100), and baseline SALT score as factors.

Key secondary endpoints

For all secondary endpoints, hierarchically tested, baricitinib low and high dose, resulted in statistically significantly higher response rates compared to placebo (see Table 12 below).

Table 12: Key secondary endpoints in study JAIO

	PBO N = 88 n (%)	BARI 2 mg N = 84 n (%)	BARI 4 mg N = 85 n (%)
Proportion of Participants Achieving SALT ≤20 at Weeks 16 and 24			
Week 16			
Response, n (%)	0	11 (13.1)	17 (20.0)
(95% CI)	(0.0, 4.2)	(7.5, 21.9)	(12.9, 29.7)
Difference (95% CI) vs. PBO[a]	NA	13.1 (6.1, 21.9)	20.0 (11.7, 29.7)
Odds Ratio (95% CI) vs. PBO[b]	NA	44.7 (2.7, 750.4)	72.5 (4.4, 1194.8)
p-Value vs. PBO[b]	NA	0.009	0.003
Week 24			
Response, n (%)	3 (3.4)	14 (16.7)	27 (31.8)
(95% CI)	(1.2, 9.5)	(10.2, 26.1)	(22.8, 42.3)
Difference (95% CI) vs. PBO[a]	NA	13.3 (4.3, 22.9)	28.4 (17.5, 39.1)
Odds Ratio (95% CI) vs. PBO[b]	NA	15.8 (3.1, 80.3)	44.3 (8.8, 223.3)
p-Value vs. PBO[b]	NA	0.001	0.001
Proportion of Participants Achieving a $SALT_{50}$ at Week 12			
Response, n (%)	3 (3.4)	13 (15.5)	17 (20.0)
(95% CI)	(1.2, 9.5)	(9.3, 24.7)	(12.9, 29.7)
Difference (95% CI) vs. PBO[a]	NA	12.1 (3.3, 21.6)	16.6 (7.2, 26.6)
Odds Ratio (95% CI) vs. PBO[b]	NA	6.9 (1.8, 27.0)	9.3 (2.4, 35.4)
p-Value vs. PBO[b]	NA	0.006	0.002
Proportion of Participants Achieving a $SALT_{90}$ at Week 36			
Response, n (%)	1 (1.1)	17 (20.2)	28 (32.9)
(95% CI)	(0.2, 6.2)	(13.0, 30.0)	(23.9, 43.5)
Difference (95% CI) vs. PBO[a]	NA	19.1 (10.3, 28.9)	31.8 (21.4, 42.4)
Odds Ratio (95% CI) vs. PBO[b]	NA	32.2 (4.0, 259.0)	64.3 (8.1, 510.1)
p-Value vs. PBO[b]	NA	0.002	0.001
Proportion of Participants Achieving an Absolute SALT ≤10 at Weeks 24 and 36			
Week 24			
Response, n (%)	0	9 (10.7)	18 (21.2)
(95% CI)	(0.0, 4.2)	(5.7, 19.1)	(13.8, 31.0)
Difference (95% CI) vs. PBO[a]	NA	10.7 (4.2, 19.1)	21.2 (12.7, 31.0)
Odds Ratio (95% CI) vs. PBO[b]	NA	36.0 (2.1, 611.9)	81.9 (4.9, 1355.9)
p-Value vs. PBO[b]	NA	0.014	0.003
Week 36			
Response, n (%)	2 (2.3)	18 (21.4)	31 (36.5)
(95% CI)	(0.6, 7.9)	(14.0, 31.3)	(27.0, 47.1)
Difference (95% CI) vs. PBO[a]	NA	19.2 (9.8, 29.2)	34.2 (23.2, 44.9)
Odds Ratio (95% CI) vs. PBO[b]	NA	39.8 (4.9, 325.8)	89.8 (11.0, 729.5)
p-Value vs. PBO[b]	NA	0.001	0.001

Abbreviations: BARI = baricitinib; CI = confidence interval; ITT = intent to treat; n = number of patients in the specified category; N = number of patients in the analysis population; NA = not applicable; p = probability value; PBO = placebo; SALT = Severity of Alopecia Areata Tool; vs. = versus.

[a] Difference CIs are constructed using Newcombe-Wilson method, without continuity correction. Response CIs are constructed using Wilson method, without continuity correction.

[b] Logistic regression analysis with treatment group, geographic region, duration of current episode at baseline (4 years or less vs. 4 years or more), disease severity (SALT 50-94 vs. SALT 95-100), and baseline SALT score as factors.

Sensitivity analyses were conducted to evaluate the impact of protocol deviations and differences among analysis populations on the primary and key secondary endpoints. Results were consistent across all censoring rules and analysis methods, i.e., statistically significant improvement compared to placebo with both baricitinib 2 mg and 4 mg.

Also, when comparing the analyses for the ITT with the PP population, no differences were observed for both the primary (Table 13) as well as the secondary endpoints (data not shown).

Table 13: Comparison of ITT and PP for the primary endpoint of study JAIO

Abbreviations: BARI = baricitinib; CI = confidence interval; ITT = intent to treat; n = number of participants in the specified

	Per Protocol Set			ITT Set		
	PBO N = 68 n (%)	**BARI 2 mg N = 66 n (%)**	**BARI 4 mg N = 79 n (%)**	**PBO N = 88 n (%)**	**BARI 2 mg N = 84 n (%)**	**BARI 4 mg N = 85 n (%)**
Primary Endpoint						
Proportion of Participants Achieving SALT ≤20 at Weeks 36						
Week 36						
Response, n (%)	4 (5.9)	18 (27.3)	34 (43.0)	4 (4.5)	23 (27.4)	36 (42.4)
95% CI	(2.3, 14.2)	(18.0, 39.0)	(32.7, 54.0)	(1.8, 11.1)	(19.0, 37.7)	(32.4, 53.0)
Difference (95% CI) vs. PBO[a]		21.4 (9.0, 33.7)	37.2 (23.9, 48.7)		22.8 (12.2, 33.6)	37.8 (25.9, 48.8)
Odds Ratio (95% CI) vs. PBO[b]		13.5 (3.4, 53.6)	30.5 (7.8, 119.4)		17.7 (4.6, 67.8)	38.3 (9.9, 147.4)
p-Value vs. PBO[b]		0.001	0.001		0.001	0.001

category; N = number of participants in the analysis population; NA = not applicable; p = probability value; PBO = placebo; SALT = Severity of Alopecia Tool; vs. = versus.

a Difference CIs are constructed using Newcombe-Wilson method, without continuity correction. Response CIs are constructed using Wilson method, without continuity correction.

b Logistic regression analysis with treatment group, geographic region, duration of current episode at baseline (4 years or less vs. 4 years or more), disease severity (SALT 50-94 vs. SALT 95-100), and baseline SALT score as factors.

Other secondary outcomes

Below, other secondary endpoints are first presented for the **placebo-controlled period** (up to week 36), followed by an overview of **preliminary LTE data up to 52 weeks** including a graphical presentation over time for SALT and ClinROs. The other secondary endpoints were not controlled for multiplicity.

Placebo-controlled period

SALT

Multiple alternative SALT scores at variable endpoints up till week 52 were calculated and compared between the three groups, without controlling for multiplicity.

Table 14: Proportion of Participants Achieving $SALT_{50}$ at Weeks 16, 24, and 36

	PBO (N = 88)	BARI 2 mg (N = 84)	BARI 4 mg (N = 85)
Week 16			
Response, n (%) (95% CI)	3 (3.4) (1.2, 9.5)	14 (16.7) (10.2, 26.1)	31 (36.5) (27.0, 47.1)
Difference (95% CI) vs. PBO[a]	NA	13.3 (4.3, 22.9)	33.1 (21.8, 43.9)
Odds Ratio (95% CI) vs. PBO[b]	NA	7.6 (2.0, 29.3)	25.2 (6.7, 94.3)
p-Value vs. PBO[b]	NA	0.004	0.001
Week 24			
Response, n (%) (95% CI)	3 (3.4) (1.2, 9.5)	21 (25.0) (17.0, 35.2)	45 (52.9) (42.4, 63.2)
Difference (95% CI) vs. PBO[a]	NA	21.6 (11.5, 32.0)	49.5 (37.4, 60.0)
Odds Ratio (95% CI) vs. PBO[b]	NA	12.7 (3.4, 47.2)	51.5 (13.7, 192.7)
p-Value vs. PBO[b]	NA	0.001	0.001
Week 36			
Response, n (%) (95% CI)	5 (5.7) (2.5, 12.6)	31 (36.9) (27.4, 47.6)	51 (60.0) (49.4, 69.8)
Difference (95% CI) vs. PBO[a]	NA	31.2 (19.4, 42.4)	54.3 (41.6, 64.6)
Odds Ratio (95% CI) vs. PBO[b]	NA	14.4 (4.8, 43.0)	41.8 (13.6, 128.0)
p-Value vs. PBO[b]	NA	0.001	0.001

Abbreviations: BARI = baricitinib; CI = confidence interval; N = number of participants in the analysis population; n = number of participants in the specified category; NA = not applicable; p-value = probability value; PBO = placebo; SALT = Severity of Alopecia Tool; $SALT_{50}$ = at least 50% improvement from baseline in SALT score

[a] Difference CI are constructed using the Newcombe-Wilson method, without continuity correction. Response CI are constructed using the Wilson method, without continuity correction.

[b] Logistic regression analysis with treatment group, geographic region, duration of current episode at baseline (<4 years vs. ≥4 years), disease severity (SALT 50-94 vs. SALT 95-100), and baseline SALT score as factors.

Table 15: Proportion of Participants Achieving $SALT_{75}$ at Weeks 24 and 36

	PBO (N = 88)	BARI 2 mg (N = 84)	BARI 4 mg (N = 85)
Week 24			
Response, n (%) (95% CI)	1 (1.1) (0.2, 6.2)	15 (17.9) (11.1, 27.4)	28 (32.9) (23.9, 43.5)
Difference (95% CI) vs. PBO[a]	NA	16.7 (8.3, 26.3)	31.8 (21.4, 42.4)
Odds Ratio (95% CI) vs. PBO[b]	NA	27.8 (3.4, 226.4)	69.7 (8.7, 559.9)
p-Value vs. PBO[b]	NA	0.002	0.001
Week 36			
Response, n (%) (95% CI)	3 (3.4) (1.2, 9.5)	22 (26.2) (18.0, 36.5)	41 (48.2) (37.9, 58.7)
Difference (95% CI) vs. PBO[a]	NA	22.8 (12.5, 33.3)	44.8 (32.8, 55.5)
Odds Ratio (95% CI) vs. PBO[b]	NA	14.0 (3.8, 51.9)	39.8 (10.8, 147.2)
p-Value vs. PBO[b]	NA	0.001	0.001

Abbreviations: BARI = baricitinib; CI = confidence interval; N = number of participants in the analysis population; n = number of participants in the specified category; NA = not applicable; p-value = probability value; PBO = placebo; SALT = Severity of Alopecia Tool; $SALT_{75}$ = at least 75% improvement from baseline in SALT score

[a] Difference CI are constructed using the Newcombe-Wilson method, without continuity correction. Response CI are constructed using the Wilson method, without continuity correction.

[b] Logistic regression analysis with treatment group, geographic region, duration of current episode at baseline (<4 years vs. ≥4 years), disease severity (SALT 50-94 vs. SALT 95-100), and baseline SALT score as factors.

Table 16: Proportion of Participants Achieving $SALT_{90}$ at Weeks 24

Week 24	PBO (N = 88)	BARI 2 mg (N = 84)	BARI 4 mg (N = 85)
Response, n (%) (95% CI)	0 (0.0, 4.2)	9 (10.7) (5.7, 19.1)	16 (18.8) (11.9, 28.4)
Difference (95% CI) vs. PBO[a]	NA	10.7 (4.2, 19.1)	18.8 (10.8, 28.4)
Odds Ratio (95% CI) vs. PBO[b]	NA	31.0 (1.9, 506.7)	57.7 (3.6, 915.6)
p-Value vs. PBO[b]	NA	0.016	0.005

Abbreviations: BARI = baricitinib; CI = confidence interval; N = number of participants in the analysis population; n = number of participants in the specified category; NA = not applicable; p-value = probability value; PBO = placebo; SALT = Severity of Alopecia Tool; $SALT_{90}$ = at least 90% improvement from baseline in SALT score

[a] Difference CI are constructed using the Newcombe-Wilson method, without continuity correction. Response CI are constructed using the Wilson method, without continuity correction.

[b] Logistic regression analysis with treatment group, geographic region, duration of current episode at baseline (<4 years vs. ≥4 years), disease severity (SALT 50-94 vs. SALT 95-100), and baseline SALT score as factors.

Table 17: Proportion of Participants Achieving $SALT_{100}$ at Weeks 24 and 36

	PBO (N = 88)	BARI 2 mg (N = 84)	BARI 4 mg (N = 85)
Week 24			
Response, n (%) (95% CI)	0 (0.0, 4.2)	6 (7.1) (3.3, 14.7)	4 (4.7) (1.8, 11.5)
Difference (95% CI) vs. PBO[a]	NA	7.1 (1.5, 14.7)	4.7 (-0.4, 11.5)
Odds Ratio (95% CI) vs. PBO[b]	NA	18.7 (1.2, 288.2)	11.1 (0.7, 175.6)
p-Value vs. PBO[b]	NA	0.036	0.087
Week 36			
Response, n (%) (95% CI)	0 (0.0, 4.2)	7 (8.3) (4.1, 16.2)	10 (11.8) (6.5, 20.3)
Difference (95% CI) vs. PBO[a]	NA	8.3 (2.4, 16.2)	11.8 (5.1, 20.3)
Odds Ratio (95% CI) vs. PBO[b]	NA	23.1 (1.4, 374.4)	31.2 (2.0, 492.1)
p-Value vs. PBO[b]	NA	0.027	0.015

Abbreviations: BARI = baricitinib; CI = confidence interval; N = number of participants in the analysis population; n = number of participants in the specified category; NA = not applicable; p-value = probability value; PBO = placebo; SALT = Severity of Alopecia Tool; $SALT_{100}$ = at least 100% improvement from baseline in SALT score

[a] Difference CI are constructed using the Newcombe-Wilson method, without continuity correction. Response CI are constructed using the Wilson method, without continuity correction.

[b] Logistic regression analysis with treatment group, geographic region, duration of current episode at baseline (<4 years vs. ≥4 years), disease severity (SALT 50-94 vs. SALT 95-100), and baseline SALT score as factors.

Table 18: Percent Change from Baseline in SALT Score at Weeks 12, 16, 24 and 36 (mLOCF)

	PBO (N = 88)	BARI 2 mg (N = 84)	BARI 4 mg (N = 85)
Baseline mean	88.0	90.4	88.8
Week 12			
Number of participants	86	83	84
LSM (SE)	-5.6 (2.8)	-17.8 (2.7)	-26.5 (2.7)
LSM Diff (SE) vs. PBO	NA	-12.1 (3.6)	-20.8 (3.6)
95% CI vs. PBO	NA	(-19.3, -5.0)	(-27.9, -13.7)
p-Value vs. PBO	NA	0.001	0.001
Week 16			
Number of participants	86	83	84
LSM (SE)	-6.1 (3.1)	-21.4 (3.1)	-37.1 (3.1)
LSM Diff (SE) vs. PBO	NA	-15.2 (4.1)	-31.0 (4.1)
95% CI vs. PBO	NA	(-23.3, -7.2)	(-39.0, -23.0)
p-Value vs. PBO	NA	0.001	0.001
Week 24			
Number of participants	86	83	84
LSM (SE)	-8.2 (3.8)	-28.8 (3.7)	-50.5 (3.7)
LSM Diff (SE) vs. PBO	NA	-20.6 (4.9)	-42.3 (4.9)
95% CI vs. PBO	NA	(-30.3, -10.9)	(-51.9, -32.7)
p-Value vs. PBO	NA	0.001	0.001
Week 36			
Number of participants	86	83	84
LSM (SE)	-6.6 (4.2)	-38.6 (4.1)	-59.1 (4.1)
LSM Diff (SE) vs. PBO	NA	-32.0 (5.4)	-52.5 (5.4)
95% CI vs. PBO	NA	(-42.7, -21.4)	(-63.1, -41.8)
p-Value vs. PBO	NA	0.001	0.001

Abbreviations: BARI = baricitinib; CI = confidence interval; Diff = difference; LSM = least squares mean; mLOCF= modified last observation carried forward; N = number of participants in the analysis population; NA = not applicable; p-value = probability value; PBO = placebo; SALT = Severity of Alopecia Tool; SE = standard error

ClinRO's

The ClinRO's were presented over time at week 16, 24, and 36 for the proportion of patients with a score 0 or 1 including at least 2 points improvement as from baseline. For EB and EL Hair Loss, an increase in proportion of responding patients is seen between week 16 and 36 in both baricitinib dose groups, with the largest increase for the high dose baricitinib group compared to the low dose and the placebo group. In the placebo group, there were no responders for the ClinRO EB hair loss, while for EL hair loss proportions up to 14% were seen over time. At every time point, however, these percentages were substantially lower than observed for the baricitinib groups. For ClinRO Nail Appearance numbers were small and no trend was observed.

Table 19: Proportion of participants reaching ClinRO measures for EL and EB Hair Loss and Nail Appearance scores 0 or 1 with at least 2 point improvement from baseline to week 16, 24, and 36

ClinRO EB Hair Loss	**PBO (n=60)**	**Bari 2 mg (n=54)**	**Bari 4mg (n=54)**
Week 16			
Response, n (%)	0	4 (7.4)	11 (20.4)
(95% CI)	(0.0 – 0.6)	(2.9 – 17.6)	(11.8 – 32.9)
Week 24			
Response, n (%)	0	6 (11.1)	23 (42.6)
(95% CI)	(0.0 – 0.6)	(5.2 – 22.2)	(30.3 – 55.8)
Week 36			
Response, n (%)	0	13 (24.1)	27 (50.0)
(95% CI)	(0.0 – 0.6)	(14.6 – 36.9)	(37.1 – 62.9)
ClinRO EL Hair Loss	**PBO (n=50)**	**Bari 2 mg (n=47)**	**Bari 4mg (n=49)**
Week 16			
Response, n (%)	2 (4.0)	6 (12.8)	10 (20.4)
(95% CI)	(1.1 – 13.5)	(6.0 – 25.2)	(11.5 – 33.6
Week 24			
Response, n (%)	3 (6.0)	9 (19.1)	20 (40.8)
(95% CI)	(2.1 – 16.2)	(10.4 – 32.5)	(28.2 – 54.8)
Week 36			
Response, n (%)	7 (14.0)	12 (25.5)	21 (42.9)
(95% CI)	7.0 – 26.2	15.3 – 39.5	(30.0 – 56.7)
ClinRO Nail Appearance	PBO (n = 14)	Bari 2 mg (n = 22)	Bari 4 mg (n = 21)
Week 16			
Response, n (%)	1 (7.1)	3 (13.6)	3 (14.3)
(95% CI)	(1.3 – 31.5)	(4.7 – 33.3)	(5.0 – 34.6)
Week 24			
Response, n (%)	2 (14.3)	2 (9.1)	5 (23.8)
(95% CI)	(4.0 – 39.9)	(2.5 – 27.8)	(10.6 – 45.1)
Week 36			
Response, n (%)	3 (13.6)	3 (13.6)	5 (23.8)
(95% CI)	(7.6 – 47.6)	(4.7 – 33.3)	(10.6 – 45.1)

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PRO's

The PRO's were presented over time at week 16, 24, and 36 for the proportion of patients with a score 0 or 1 including at least 2 points improvement as from baseline. Except for the PRO Nail Appearance, as from week 16 onwards, the proportions responders in the high dose baricitinib group is higher than the low dose baricitinib and placebo group, and low dose higher than placebo. Over time, a gradual increase in proportion responders is seen from week 16 to week 36 in both baricitinib dose groups, with the largest proportions in the high dose group. For PRO Nail Appearance numbers were small and no trend was observed.

Table 20: Proportion of participants reaching PRO measures for Scalp Hair, EB and EL Hair Loss, and Nail Appearance 0 or 1 with at least 2 point improvement from baseline at week 16, 24, and 36

PRO Scalp hair assessment score	PBO (n=74)	Bari 2 mg (n=69)	Bari 4mg (n=77)
Week 16			
Response, n (%)	6 (8.1)	8 (11.6)	10 (13.0)
(95% CI)	3.8 – 16.6	6.0 – 21.2	7.2 – 22.3
Week 24			
Response, n (%)	5 (6.8)	11 (15.9)	22 (28.6)
(95% CI)	2.9 – 14.9	9.1 – 26.3	19.7 – 39.5
Week 36			
Response, n (%)	8 (10.8)	16 (23.2)	30 (39.0)
(95% CI)	5.6 – 19.9	14.8 – 34.4	28.8 – 50.1
PRO EB Hair Loss	**PBO (n=61)**	**Bari 2 mg (n=57)**	**Bari 4mg (n=52)**
Week 16			
Response, n (%)	1 (1.6)	6 (10.5)	18 (34.6)
(95% CI)	0.3 – 8.7	4.9 – 21.1	23.2 – 48.2
Week 24			
Response, n (%)	0	8 (14.0)	21 (40.4)
(95% CI)	(0.0 – 5.9)	7.3 – 25.3	28.2 – 53.9
Week 36			
Response, n (%)	2 (3.3)	10 (17.5)	30 (57.7)
(95% CI)	0.9 – 11.2	9.8 – 29.4	44.2 – 70.1
PRO EL Hair Loss	**PBO (n=44)**	**Bari 2 mg (n=44)**	**Bari 4mg (n=46)**
Week 16			
Response, n (%)	4 (9.1)	5 (11.4)	11 (23.9)
(95% CI)	3.6 – 21.2)	5.0 – 24.0	13.9 – 37.9
Week 24			
Response, n (%)	2 (4.5)	9 (20.5)	23 (50.0)
(95% CI)	1.3 – 15.1	11.2 – 34.5	36.1 – 63.9
Week 36			
Response, n (%)	6 (13.6)	9 (20.5)	27 (58.7)
(95% CI)	6.4 – 26.7	11.2 – 34.5	44.3 – 71.7
PRO Nail Appearance	**PBO (n = 18)**	**Bari 2 mg (n = 19)**	**Bari 4 mg (n = 17)**
Week 16			
Response, n (%)	2 (11.1)	1 (5.3)	2 (11.8)
(95% CI)	3.1 – 32.8	0.9 – 24.6	3.3 – 34.3
Week 24			
Response, n (%)	2 (11.1)	4 (21.1)	5 (29.4)
(95% CI)	3.1 – 32.8	8.5 – 43.3	13.3 – 53.1
Week 36			
Response, n (%)	2 (11.1)	4 (21.1)	3 (17.6)
(95% CI)	3.1 – 32.8	8.5 – 43.3	6.2 – 41.0

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HADS and PROMIS

Changes in HADS and subscale scores between baseline and week 36 were numerically largest for high dose baricitinib compared to placebo and low dose baricitinib, without a clear numerical difference between the latter two groups.

Changes in PROMIS subscale scores between baseline and week 36 were larger for baricitinib compared to placebo, with a tendency for the largest improvement in the high dose baricitinib group.

Table 21: **HADS and PROMIS scores at baseline and week 36. Mean Change from Baseline in Additional Efficacy Assessments at Week 36**

	PBO (N = 88)	BARI 2 mg (N = 84)	BARI 4 mg (N = 85)
HADS-Anxiety total score (mLOCF)			
Baseline mean	4.8	4.6	5.5
Number of participants	84	83	83
LSM (SE)	-1.3 (0.3)	-1.1 (0.3)	-1.9 (0.3)
LSM Diff (SE) vs. PBO	NA	0.2 (0.4)	-0.6 (0.4)
95% CI vs. PBO	NA	(-0.6, 1.0)	(-1.4, 0.2)
HADS-Depression total score (mLOCF)			
Baseline mean	3.1	3.5	3.2
Number of participants	84	83	83
LSM (SE)	-0.9 (0.3)	-0.7 (0.3)	-1.1 (0.3)
LSM Diff (SE) vs. PBO	NA	0.2 (0.4)	-0.2 (0.4)
95% CI vs. PBO	NA	(-0.5, 0.9)	(-0.9, 0.5)
PROMIS depression score (mLOCF)			
Baseline mean	46.36	46.63	46.05
Number of participants	80	82	79
LSM (SE)	-1.96 (0.87)	-2.57 (0.85)	-3.65 (0.87)
LSM Diff (SE) vs. PBO	NA	-0.61 (1.17)	-1.69 (1.18)
95% CI vs. PBO	NA	(-2.92, 1.70)	(-4.03, 0.64)
PROMIS anxiety score			
Baseline mean	46.74	45.73	47.28
Number of participants	80	82	79
LSM (SE)	-2.60 (0.82)	-3.35 (0.80)	-4.29 (0.82)
LSM Diff (SE) vs. PBO	NA	-0.75 (1.10)	-1.68 (1.11)
95% CI vs. PBO	NA	(-2.92, 1.42)	(-3.87, 0.50)

Abbreviations: BARI = baricitinib; CI = confidence interval; Diff = difference; HADS = Hospital Anxiety and Depression Scale; LSM = least squares mean; mLOCF = modified last observation carried forward; N = number of participants in the analysis population; NA = not applicable; PBO = placebo; PROMIS = Patient-Reported Outcomes Measurement Information System; SE = standard error.

For FDLQI and the NeuroQoL numerically larger improvement was seen for the high dose baricitinib group compared to placebo and the low dose baricitinib group.

Table 22: FLDQI and NeuroQoL scores at baseline and change from baseline at week 36

FDLQI	PBO (n = 75)	Bari 2 mg (n = 78)	Bari 4 mg (n = 76)
Baseline mean	8.0	8.3	7.9
LSM (SE) at week 36	-1.0 (0.5)	-1.6 (0.5)	-2.8 (0.5)
NEURO-QoL	PBO (n = 38)	Bari 2 mg (n = 33)	Bari 4 mg (n = 40)
Baseline mean	50.4	51.42	51.39
LSM (SE) at week 36	-4.9 (1.51)	-4.34 (1.67)	-7.13 (1.45)

Drafted by assessor

Skindex-16 AA domain scores

The largest numerical changes at the Skindex-16 AA domain scores were seen for the high dose baricitinib group; the low dose baricitinib group also had numerically larger increases compared to placebo.

Table 23: Skindex-16 AA scores at baseline and change from baseline at week 36

Skindex-16 AA Symptoms	**PBO (n = 79)**	**Bari 2 mg (n = 82)**	**Bari 4 mg (n = 79)**
Baseline mean	11.16	11.51	12.20
LSM (SE) at week 36	2.89 (1.58)	0.68 (1.53)	0.39 (1.56)
Skindex-16 AA Emotions	**PBO (n = 79)**	**Bari 2 mg (n = 82)**	**Bari 4 mg (n = 79)**
Baseline mean	41.24	46.09	40.14
LSM (SE) at week 36	-3.98 (2.63)	-12.87 (2.55)	-18.22 (2.60)
Skindex-16 AA Functioning	**PBO (n = 79)**	**Bari 2 mg (n = 82)**	**Bari 4 mg (n = 79)**
Baseline mean	20.31	26.67	20.63
LSM (SE) at week 36	-4.96 (2.17)	-6.82 (2.10)	-9.40 (2.14)

Drafted by assessor

EQ5D-Y and EQ-5D-5L

Numerical changes for the EQ5D assessments were small over time without a clear trend.

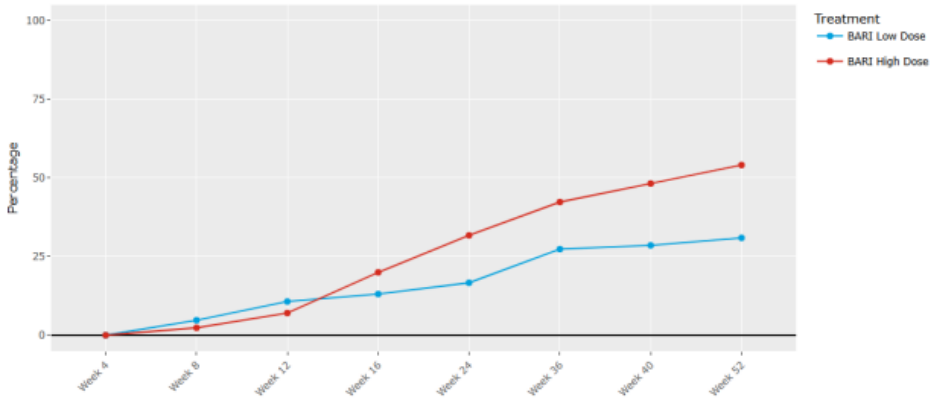
EQ-5D-Y Health State (UK)	**PBO (n = 62)**	**Bari 2 mg (n = 57)**	**Bari 4 mg (n = 58)**
Baseline mean	0.93	0.92	0.91
LSM (SE) at week 36	0.03 (0.0111)	0.01 (0.0112)	0.04 (0.0113)
EQ-5D-Y VAS	**PBO (n = 62)**	**Bari 2 mg (n = 57)**	**Bari 4 mg (n = 58)**
Baseline mean	85.0	83.3	83.2
LSM (SE) at week 36	2.4 (1.5)	4.0 (1.5)	3.0 (1.5)
EQ-5D-5L Health State (UK)	**PBO (n = 17)**	**Bari 2 mg (n = 23)**	**Bari 4 mg (n = 21)**
Baseline mean	0.88	0.91	0.93
LSM (SE) at week 36	0.03 (0.0346)	0.00 (0.0294)	-0.00 (0.0326)
EQ-5D-5L VAS	**PBO (n = 17)**	**Bari 2 mg (n = 23)**	**Bari 4 mg (n = 21)**
Baseline mean	82.4	85.8	84.4
LSM (SE) at week 36	1.5 (2.6)	-0.4 (2.2)	1.0 (2.4)

Drafted by assessor

Preliminary LTE data up to 52 weeks

Changes over time for SALT ≤20, mean change from baseline over time for SALT, and proportions of patients achieving ClinRO measures EL and EB Hair Loss scores 0 or 1 with at least 2 points improvement over time, are presented below.

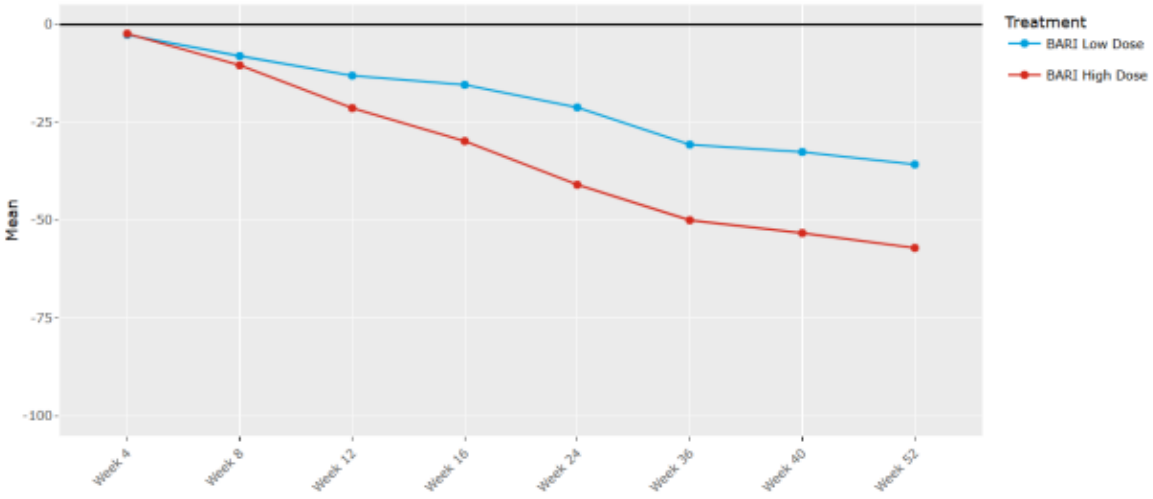
Figure 8: Proportion of participants achieving SALT score ≤20 through Week 52 in the Adolescent ITT Set using primary censoring rule (NRI)



Abbreviations: BARI = baricitinib, ITT = intent-to-treat; NRI = nonresponder imputation; SALT = Severity of Alopecia Tool.

At week 52, response rates for 2 mg (n = 84) and 4 mg (n = 85) baricitinib were 31% (95% CI 22 – 42) and 54% (44 – 64).

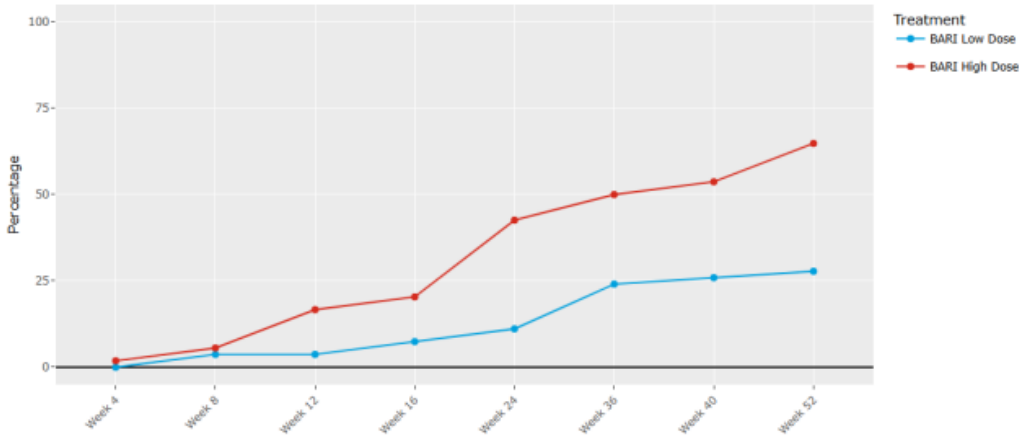
Figure 9: Mean change from baseline in SALT score through Week 52 in the Adolescent ITT Set using primary censoring rule (ANCOVA mLOCF)



Abbreviations: ANCOVA = analysis of covariance; BARI = baricitinib, ITT = intent-to-treat; mLOCF = modified last observation carried forward; NRI = nonresponder imputation; SALT = Severity of Alopecia Tool.

Mean change (LSM (SE)) in SALT score at week 52 was -37.9 (4.1) for baricitinib 2 mg (n = 83) and -58.3 (4.2) for baricitinib 4 mg (n = 84).

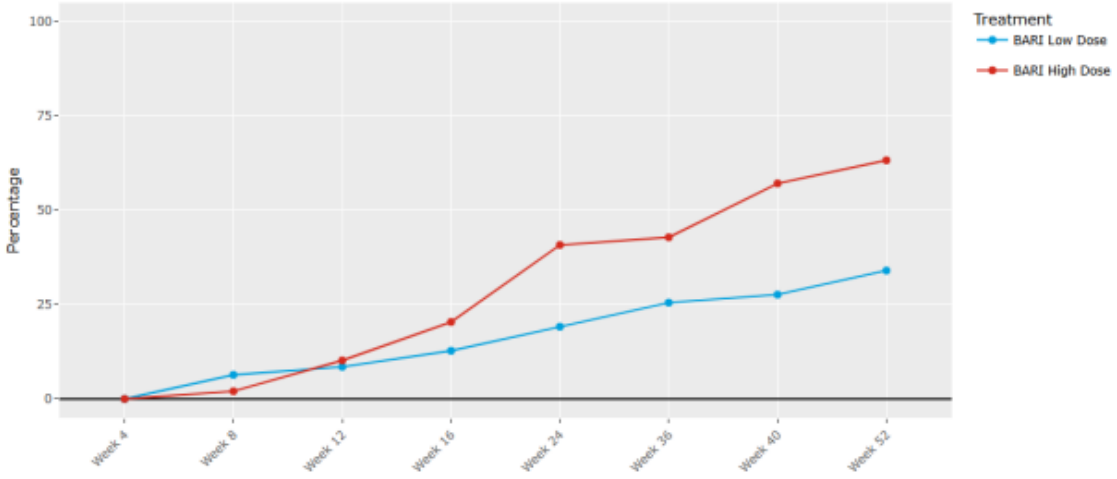
Figure 10: Proportion of participants achieving ClinRO measure for EB hair loss 0 or 1 with ≥2-point improvement from baseline through Week 52 in the Adolescent ITT Set among participants with score ≥2 at baseline, using primary censoring rule (NRI)



Abbreviations: BARI = baricitinib, ClinRO = clinician-reported outcome; EB = eyebrow; ITT = intent-to-treat; NRI = nonresponder imputation; SALT = Severity of Alopecia Tool.

At week 52, response rates for 2 mg (n = 54) and 4 mg baricitinib (n = 54) were 28% (95% CI 18 – 41) and 65% (52 – 76).

Figure 11: Proportion of participants achieving ClinRO measure for EL hair loss 0 or 1 with ≥2-point improvement from baseline through Week 52 in the Adolescent ITT Set among participants with score ≥2 at baseline, primary censoring rule (NRI).



Abbreviations: BARI = baricitinib, ClinRO = clinician-reported outcome; EL = eyelash; ITT = intent-to-treat; NRI = nonresponder imputation; SALT = Severity of Alopecia Tool.

At week 52, response rates for 2 mg (n = 47) and 4 mg (n = 49) baricitinib were 34% (95% CI 22 – 48) and 63% (49 – 75).

For the other endpoints:

- Mean changes in HADS and PROMIS (subscales) compared to baseline showed improvements at week 52, with numerically larger improvements for the high dose baricitinib;

- Mean changes in FDLQI, Skindex-16 AA-Y subscales, and Neuro-Qol paediatric compared to baseline generally showed improvements at week 52, with numerically larger improvements for the high dose baricitinib;

Mean changes in EQ-5D subscales generally did not show numerical changes over time, nor differences between low and high dose baricitinib.

Ancillary analyses

Subgroup analyses

Subgroup analyses for the primary endpoint SALT score ≤ 20 at week 36 were explored by forest plots comparing the 2 mg baricitinib group with placebo and the 4 mg baricitinib group with placebo for the strata for gender, BMI, race, ethnicity, geographic region, baseline SALT category (disease severity), and current AA episode duration.

Figure 12: Subgroup analyses for the primary endpoint SALT score ≤ 20 at week 36 (race, gender).

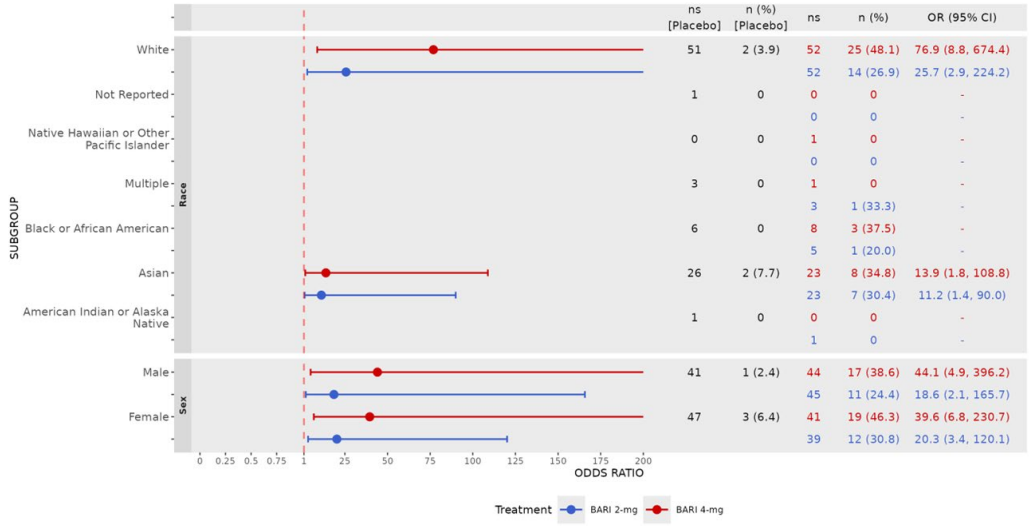


Figure 13: Subgroup analyses for the primary endpoint SALT score ≤ 20 at week 36 (ethnicity, geographical region, weight).

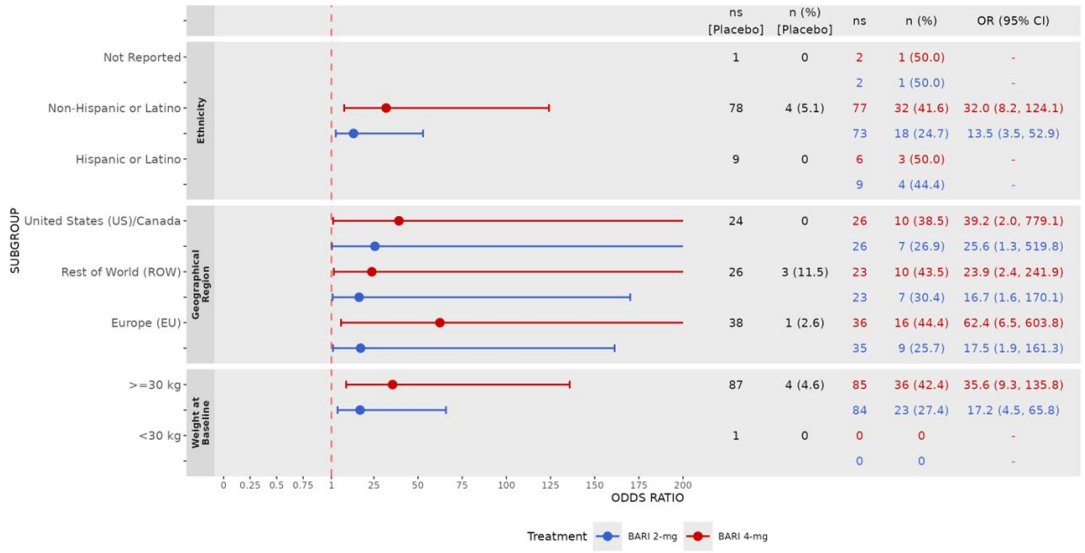
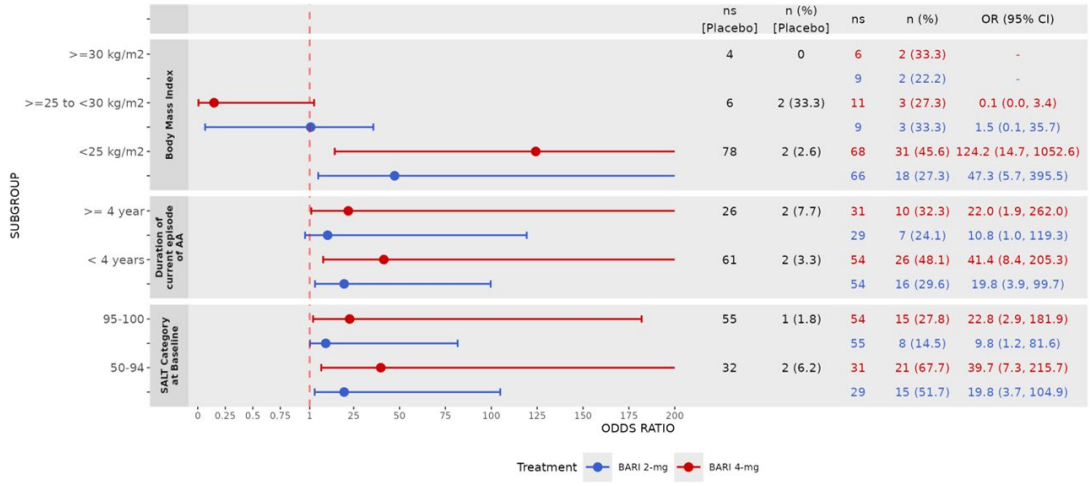


Figure 14: Subgroup analyses for the primary endpoint SALT score ≤ 20 at week 36 (BMI, duration of AA episode, SALT category).



2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical programme supporting this application consists of one phase 3 pivotal study, study JAIO (brief title: BRAVE-AA-PEDS), performed in children and adolescents (6-18 years) with AA. Data from adolescents (12-18 years) are presented. In addition, data from studies of the approved paediatric indications Atopic Dermatitis (I4V-MC-JAIP) and Juvenile Idiopathic Arthritis (I4V-MC-JAHV), as well as the adult AA indication (studies I4V-MC-JAIR and I4V-MC-JAHO) are considered relevant.

No separate dose-response study has been performed. The 2 mg and 4 mg doses were selected based on the phase 3 studies performed in adults with AA (studies I4V-MC-JAIR and I4V-MC-JAHO), and the paediatric studies in Atopic Dermatitis (I4V-MC-JAIP) and juvenile idiopathic arthritis (I4V-MC-JAHV).

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.

Study design

Study JAIO is designed as a phase 3, double-blind, randomised, placebo-controlled trial to evaluate the efficacy, safety, and pharmacokinetics of baricitinib in children from 6 years to less than 18 years of age with Alopecia Areata. After the 36 weeks double-blind period, patients can enter the long-term extension treatment phase up to 2 years, with possible re-allocations at week 36 (after end of placebo-controlled phase; non-responders on placebo are assigned to baricitinib), week 52 (placebo and low dose baricitinib treated patients are transitioned to high dose baricitinib when satisfying uptitration criteria), and week 76 (non-responders discontinue).

Overall, the design of the JAIO study is acceptable. Placebo as a comparator is agreed, as at time of approval there were no other authorised medicines for the treatment of AA in adolescents. Of note, since then, ritlecitinib has been authorised in the EU/UK/US for adolescents (≥12 years of age) with severe AA. The LTE will eventually provide additional data on long-term efficacy and safety up to 136 weeks.

No data on down-titration and / or stopping in case of maintained good response is gathered, but a recommendation (discontinuation after 36 weeks in the absence of therapeutic benefit) is included based on the adult AA and the paediatric AD posology texts. Further, a stopping / down-titration rule (consideration of 2 mg once daily for patients who have achieved sustained control of disease activity with 4 mg once daily) is included in the SmPC section 4.2 based on adult AA data in case of absence of treatment response. This is acceptable, also for safety reasons, in order to reduce lengthy exposure.

After the patient inclusion for the placebo-controlled period was completed, another 160 patients were planned to be randomly assigned to baricitinib 2 mg or 4 mg, mainly to further support the safety data set, but also in support of efficacy.

The single pivotal trial in support of this Application, and its basic design elements including placebo comparator, duration of the placebo-controlled period, the LTE period, as well as the staggered inclusion approach (adolescents first) were agreed with PDCO as laid down in the PIP (EMA/PDCO Summary Report EMA/13938/2021). In particular, the study duration is considered acceptable as AA is a chronic, relapsing disease. The duration is also aligned with the adult AA application. Although it is reported that up to 50% of patients who present with patchy AA experience spontaneous hair regrowth within one year, most will relapse within months or years after remission. Long-term efficacy is demonstrated in adults with AA; given the similar pathophysiological mechanism in adolescents compared to adults, it is accepted that LTE data are not formally completed during this Application. At the date of data cut-off (15 April 2025), the placebo-controlled period was completed and final data were presented. The LTE was completed up to 52 weeks; preliminary data were provided for efficacy. Data from the additionally assigned patients to baricitinib 2 mg or 4 mg after completed enrolment of the placebo-controlled period, were preliminary and therefore not included in the current efficacy assessment. Final data will be provided post-authorisation; the current sample size is sufficient for assessment.

Patient population

Given the claimed indication, the focus of the current assessment is on the patient population aged from 12 to 18 years with severe AA; patients with other types of alopecia were excluded, and this is in line with the intended indication of patients with at least severe AA. Adolescent patients had to weigh at least 30 kg; this aligns with section 4.2 of the SmPC, stating that 'The safety and efficacy of baricitinib in children less than 12 years of age or weighing < 30 kg with alopecia areata have not yet been established.'

The inclusion criteria, as requested by the PDCO (*EMA/PDCO Summary Report EMA/13938/2021*), are acceptable from a methodological and ethical standpoint and ensured appropriate enrichment of the study population. Although all patients were required to have had one prior treatment, it is considered that inclusion of the line of indication is not required because 1) the line of treatment is unlikely to affect efficacy outcome, and 2) for adult AA the line of treatment was also not included in the indication for Olumiant and 3) this is in line with the (adolescent) AA indication for another JAK inhibitor, ritlecitinib.

The enrichment of the study population by psychological-impact/counselling is considered not an issue for the generalisability of the study data to the broader adolescent population, as the vast majority of adolescents with AA experience psychological impact of their disease. Further, the absence or presence of psychological burden in itself is unlikely to affect reported efficacy of the product, especially not the objective or physician-related endpoints. Therefore, the JAIO study data can be generalised to the target population of adolescents with severe AA. The exclusion criteria are in line with the posology and warnings stated in the SmPC.

Endpoints and outcomes

The primary endpoint, SALT ≤20 at week 36 (i.e. scalp hair loss of ≤20% or at least 80% scalp hair coverage) used in the primary adult AA Application is validated, clinically relevant, assessed at a sufficient time interval to detect treatment effect, and agreed by the PDCO.

Key secondary endpoints were derived from the SALT (SALT assessments at earlier timepoints which enable the investigation of onset of treatment benefit and more stringent SALT scores to study the percentage of patients reaching best clinical outcome) and were multiplicity controlled. The proportion of participants reaching an absolute SALT score ≤10 at week 36 was an agreed key secondary endpoint according to the PDCO report, but mean change in SALT score, mean change in PROMIS scores, and mean change in HADS scores at week 36 were not included as secondary endpoints while previously agreed by the PDCO. The change in SALT score was removed from the hierarchically tested endpoints by the Applicant as per FDA communication in December 2022; for this endpoint, however, a significant difference was seen between both baricitinib doses and placebo, so removal of this key secondary endpoint had not affected interpretation of data. The HADS and PROMIS were removed as key secondary endpoints as these had shown only minor differences in the adult AA program and it was anticipated that this would also be the case for adolescents. Altogether, the key secondary endpoints were considered acceptable.

The most relevant other secondary endpoints are considered the PROs and ClinROs, and the HADS and PROMIS. The ClinROs and PROs for eyebrow hair loss, eyelash hair loss, nail appearance, and the PRO for scalp hair assessment have been developed by the Applicant and were also previously applied in the type 2 variation for adult AA. Although acceptably validated in adults, a formal validation procedure was not performed in adolescents and data on psychometric properties more generally in adolescents were not submitted. This was considered not problematic for the ClinROs because these are scored by the physician and disease presentation between adults and adolescents is comparable. Further, it is acknowledged that ClinROs are potentially relevant to patients and prescribers, and these are also included in the adult AA section of the SmPC, which justifies their inclusion in the adolescent part as well. The inclusion of the Skindex-16 AA-Y was also justified, given the minor change in the adolescent versus the adult version (1 word) and the fact that the scale was included in the SmPC for the adult AA indication as well, providing comparative, informative data for prescribers.

The HADS is widely used in chronic disease, also in adolescents. There is sufficient validation data in adolescents. The cut-off points used for the adolescent population in this Application were based on Terluin et al. (2009) and Chan et al. (2010), the latter defined based on adolescent data. The cut-offs

used, although not specifically for AA, can be accepted but results are to be interpreted with caution due to the caveats mentioned before.

The PROMIS (short forms for anxiety, depression) was also used as secondary outcome measure in the type 2 variation for extension of the indication to adolescents with AD and have not formally been validated in AA. However, they were validated in adolescents generally and developed as universal assessment rather than disease-specific. As such, the use of the PROMIS for assessment of anxiety and depression in adolescents is justified.

For the FDQLI and the EQ-5D no psychometric data were provided by the Applicant. The issue is not further pursued as the FDLQI is not among the key secondary endpoints and inclusion in the SmPC is not applied for.

X-ray and MRI for the assessment of growth, as well as the assessment of potential impact on bone, are aligned with the requirement in the PIP and are supported.

Treatment

In the JAIO study, baricitinib dose was 2 mg or 4 mg, compared to placebo. Dosing was based on the adult AA data and paediatric data in the AD and JIA trials. The high dose is ultimately included in the posology, i.e. 'The recommended dose of baricitinib is 4 mg once daily for patients weighing 30 kg or more.' Inherent to the target population in this Application, no except 1 patient < 30 kg were included.

Allowed concomitant treatments were mainly topical treatments and all-but-systemic corticosteroids. These were aligned with the adult AA application and can be accepted as these are basic treatments described in guidelines on the treatment of AA.

Sample size and randomisation

The sample size and the stratified randomisation procedure methods to preserve blinding were appropriate. 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.

Statistical analysis

Overall, the statistical analyses are considered acceptable. The primary analyses use a non-responder imputation for outcomes after the intercurrent events of treatment discontinuations and initiation of prohibited concomitant medication, which aligns with the composite strategy and is considered acceptable for binary (responder) endpoints. For continuous endpoints, the intercurrent events of treatment discontinuations and interruptions due to prohibited medication were handled using a composite strategy implemented by imputing the last available pre-interruption/pre-discontinuation value for observations during interruption or after discontinuations. On-treatment outcomes collected after reinitiation of study treatment after such interruptions were used in the analysis. Several sensitivity analyses were planned that assess the robustness of the conclusions. Missing post-baseline data, modified Last Observation Carried Forward was used to impute values based on the most recent available post-baseline observation. The sensitivity analysis mainly considered different imputation strategies for outcomes after an intercurrent event, and were performed under a missingness at random assumption and a placebo-based imputation method. A graphical testing procedure controls the type I error over the study in which multiple endpoints were evaluated for two different doses. There were several amendments to the SAP, including a change of graphical testing procedure based on EMA request, and adding of per protocol set and sensitivity analysis, with major changes that affecting analysis in clinical study report all made before database lock and unblinding. This is acceptable.

Performance

The study included mainly patients from the US and Poland (EU), and may thus be considered representative for the EU population. Protocol deviations were mostly due to misspecification of the length of the current episode of AA, which was used for stratification, but this did not result in imbalances between the groups.

Patient flow

A total of 81/88 patients in the placebo group, 82/84 in the low dose baricitinib group (2 mg), and 80/85 in the high dose baricitinib group (4 mg) completed the 36 weeks double-blind period. A total of 77 patients (93%) in the 2 mg group and 79 patients (95%) in the 4 mg group completed the week 52 visit. Discontinuation rates were thus low. No clear pattern in reasons for discontinuation was identified, nor were there apparent differences between placebo and baricitinib groups that might have affected efficacy analyses. Data from patients initially assigned to placebo but re-randomised to baricitinib during the course of the JAIO study, were not provided. It is anticipated that these data are included in the final reporting on the LTE; the current database is of sufficient size.

Efficacy data and additional analyses

Patient population

Overall, demographic characteristics were comparable between the three treatment groups. Mean age was 14 years in line with the adolescent population, with about 50% female; this reflects the equal sex-ratio of AA in adolescents and adults. Most patients originated from the EU (and North- America), and were of white race, which makes that the results are considered relevant for the EU population.

Disease characteristics at baseline

Fewer patients in the high dose baricitinib group had a disease duration of 10 years or longer (15% versus 25% in the placebo and low dose groups). Probably related to this, these patients had fewer prior therapies as there was simply less time for that. In general, a history of more ineffective therapy increases the risk of another failed therapy in the future, and vice versa; this indeed was true but stratified analyses supported the superiority of 4 mg baricitinib irrespective of disease duration. For ClinRO's baseline scores EL and EB hair loss, the high dose baricitinib group showed more patients in the extreme scoring categories compared to the other two groups. However, it is unlikely that this may have affected efficacy outcome, as analyses of success rates include and control for, baseline scores.

Depression and anxiety were reported by up to 7% of the patients, although one of the inclusion criteria was that patients had to have a '*history of psychological counselling related to AA*', and '*history of psychological impact from refractory AA as reported by the investigator, parent, or participant*'. Psychological impact of AA may be due to other reasons than depression and anxiety, and depressive symptoms and feelings of anxiety may not ultimately lead to a clinical diagnosis of depression and anxiety. However, as no impact on efficacy or safety endpoints are expected, the issue is not considered significant (see also discussion on safety).

All patients had used prior AA therapy according to protocol, without clear differences between the three groups.

Concomitant therapies for AA were scarce and only used in the baricitinib groups (n = 2 in low dose and n = 4 in high dose). Sensitivity analyses, performed without these seven patients for the primary and key secondary endpoints, indicated that this did not affect outcome and thus interpretation of the data (data not shown). Concomitant therapies other than for AA were also unlikely to have impacted efficacy outcome.

Efficacy outcomes

For efficacy analyses, the ITT set consisted of 257 patients, which is in line with the targeted sample size in the power calculation. A total of 43 patients of these 257 were not included in the PP due to acceptable reasons. The main analyses are performed using the ITT set; the PP analyses for the primary and key secondary endpoints were compared with the ITT analyses.

The primary outcome SALT ≤20 at Week 36 was met ($p<0.001$) in both baricitinib treatment groups (4 mg and 2 mg); response rates were 27% and 42% in the low and high dose groups versus 4.5% in the placebo group. Sensitivity analysis confirmed robustness of the data. The response rate in the high dose group was larger than the anticipated 34% used for the power calculation. The response rates in adolescents (current JAIO study) were higher than the pooled response rates found in the adults AA studies (JAHO and JAIR); 16% in the low dose baricitinib group and 30% in the high dose baricitinib group, which were considered clinically relevant. The response rate in the placebo group was around 5%, which was comparable to the response in adolescents in the JAIO study. The most frequent important protocol deviations occurred in 14.4% of participants and was related to discrepancies between the duration of current episode entered into IWRS for stratification. The Applicant used the corrected category for duration of episode (<4 versus >= 4) in primary analyses.

The key secondary outcomes, hierarchically tested, were all significant and in favour of baricitinib treatment. For each key secondary endpoint, high dose baricitinib (4 mg) resulted in higher response rates than de low dose baricitinib (2 mg).

Other secondary outcomes, including ClinRO's and PRO's, as well as HADS and PROMIS, were generally numerically aligned with these findings up to week 36; preliminary data up to week 52 seem to align with this as well.

ClinRO data for EB and EL hair loss are included in section 5.1 of the SmPC. For the Skindex-16 AA-Y, inclusion in the SmPC was considered justified given the inclusion of this scale for the adult AA indication.

The results for the primary and key secondary endpoints are in support of the claimed posology of 4 mg for the intended indication (proposed SmPC section 4.2) from an efficacy perspective. The fact that primary, key secondary, and secondary endpoints including ClinRO's and PRO's were rather consistent with regard to the higher response rates in the high dose baricitinib group compared to low dose and placebo, further supports the strength of evidence for baricitinib for the treatment of severe AA in adolescents.

Differences between baricitinib and placebo were already seen as early as from week 8, with further improvement over time until week 36; this supports the assumption that 36 weeks is a more appropriate time point to stop treatment in non-responders than an earlier timepoint. Preliminary data up to 52 weeks suggests further improvement with continued treatment.

Subgroup analyses

The 4 mg baricitinib dose resulted in consistently higher primary endpoint response rates for higher disease severity and longer disease duration compared to placebo, across strata of relevant variables. The odds for a treatment response seemed to be lower in the BMI 25-30 kg/m^2 group in both baricitinib groups compared to placebo, but as the numbers were low and dose adjustment previously was not considered required in patients with a higher BMI, the issue is not further pursued.

2.4.4. Conclusions on the clinical efficacy

The primary outcome (SALT ≤20 at week 36) was met (p<0.001) in both baricitinib treatment groups (4 mg and 2 mg dosing regimens) compared to placebo. The response rate differences of 38% (26% – 49%) and 23% (95% CI 12% - 34%) for 4 mg and 2 mg baricitinib versus placebo both considered clinically relevant. Across all endpoints, high dose baricitinib (4 mg once daily) was generally superior to low dose (2 mg once daily) treatment and placebo.

The onset of treatment effect emerged as from 8 weeks after treatment initiation with continuous improvement through week 36 and no clear plateau; suggesting that treatment benefit may further increase beyond this timepoint. LTE study data will provide more evidence on this issue.

In the management of AA and hair loss, the acceptability of the amount of hair that grows back is clinically relevant. If the amount of hair growth is insufficient, treatment will not be satisfactory for the patients. The relevance of treatment outcome to patients was supported by numerical changes in the ClinROs (scalp, eyebrow, eyelash) and SKINDEX-16 AA-Y.

2.5. Clinical safety

Introduction

Safety data sets

The safety evaluation includes the data from baricitinib-treated adolescent participants 12 to <18 years old with severe AA from multicentre 'phase 3', double blind, randomised, placebo-controlled study I4V-MC-JAIO (JAIO). Safety data are included from the 36-week placebo-controlled period and from the 2-year extension period up to the database cutoff date of 15 April 2025. All randomised patients who reached week 36 or dropped out before that time and received at least one dose of study medication and were not 'lost to follow-up' before the first post-baseline visit, were included in the placebo-controlled safety analysis set (Table 24). After 36 weeks, patients could enter the extension phase of up to 2 years. This part of the study is still **ongoing**.

Table 24: Overview of safety analysis sets of study JAIO.

	PC BARI AA Adolescents	Ext BARI AA Adolescents	All BARI AA Adolescents
Time period	Starting from randomisation up to the primary endpoint.	Starting from randomisation up to the data cutoff date. Includes all participants who were exposed to BARI 2 mg or BARI 4 mg dose from randomisation until dose or treatment change.	Includes all participants who were exposed to any BARI dose at any time during the study, either from randomisation or from switch from PBO.
Purpose	Enable PBO comparison with BARI 2 mg and 4 mg. Enable dose comparison between 2 mg and 4 mg; based on the 36-week data.	Enable an assessment of long-term exposure to BARI 2 mg or 4 mg. Enable dose comparison between BARI 2 mg and 4 mg.	Enable the identification of more unusual or rare events in participants treated with any dose of baricitinib that might require further evaluation and discussion.
Treatment groups	PBO BARI 2 mg BARI 4 mg	BARI 2 mg BARI 4 mg Data censored at dose or treatment change.	All BARI (all doses) All BARI 2 mg[a] All BARI 4 mg[a]

Abbreviations: AA = alopecia areata; All BARI AA Adolescents = All baricitinib alopecia areata adolescents; Ext BARI AA Adolescents = Extended baricitinib alopecia areata adolescents; NA = not applicable; PC BARI AA Adolescents = Placebo-controlled baricitinib alopecia areata adolescents; vs = versus.

[a] All BARI 2-mg and All BARI 4-mg groups are displayed in source tables but will not be included or discussed in this document.

Note: Baricitinib doses were administered once daily.

Patient exposure

At 10 Sept 2024, the clinical trial safety database of baricitinib contains data of 7710 adults, with 22,750.3 patient-years of exposure in AA, AD, and RA, and of 687 paediatric patients, with 1076.4 patient-years of exposure in AD and JIA.

For the adolescent AA development program, at **data cut-off date 15 April 2025**, the PC BARI AA Adolescent safety dataset was completed and consisted of a total of 257 participants randomised to a treatment group; 243 participants completed the week 36 treatment visit and entered the JAIO long-term extension period (92%, 98%, and 94% in Placebo, 2-mg, and 4-mg groups, respectively). A total of 398 patients completed the 52 weeks visit (i.e. those from the placebo-controlled study as well as those from the Baricitinib Exposure Set additionally included after completion of enrolment for the placebo-controlled study part). Overall exposure was 478.9 patient years (PY).

Table 25: Exposure by treatment group and analysis set in study JAIO.

	PC BARI AA Adolescents			Ext BARI AA Adolescents		All BARI AA Adolescents
	PBO N = 88	BARI 2 mg N = 83	BARI 4 mg N = 85	BARI 2 mg N = 166	BARI 4 mg N = 168	All Doses N = 415
Mean weeks of exposure (SD)	34.56 (5.23)[a]	35.85 (1.61)[a]	35.05 (4.48)[a]	55.02 (10.44)[a]	63.50 (13.89)[a]	60.22 (16.36)[b]
Total patient-years[c] mean (SD)	58.3 0.66 (0.10)	57.0 0.69 (0.03)	57.1 0.67 (0.09)	175.1 1.05 (0.20)	204.4 1.22 (0.27)	478.9 1.15 (0.31)

Abbreviations: All BARI AA Adolescents = All baricitinib alopecia areata adolescents; BARI = baricitinib; Ext BARI AA Adolescents = Extended baricitinib alopecia areata adolescents; N = number of participants in the analysis population; PC BARI AA Adolescents = Placebo-controlled baricitinib alopecia areata adolescents;
PBO = Placebo; SD = standard deviation.

a Duration of exposure is calculated as duration of exposure (in weeks) to the study drug, excluding exposure posttreatment change or rescue to baricitinib: (date of last dose of study drug - date of first dose of study drug + 1)/7.
b Duration of exposure is calculated as duration of exposure (in weeks) to study drug: (date of last dose of study drug - date of first dose of study drug + 1)/7.
c Total patient-years is calculated as the sum of duration of exposure in days for all participants in the dosing regimen/365.25.
d Mean (SD) is not available in weeks.
Time spent within any temporary study drug interruption is included within exposure time.
Time after permanent study drug discontinuation is not included within exposure time.
Sources: JAIO Week 36 Summary of Clinical Safety and JAIO Week 52 Summary of Clinical Safety

Adverse events

AEs were classified based on MedDRA Version 27.0. Treatment-emergent AEs were defined as AEs that first occurred or worsened in severity after the first dose of study drug. The analysis period is defined as the treatment period plus up to 30 days off-drug follow-up time. Common TEAEs were defined as those reported at a frequency of ≥2%, before rounding, of the number of participants in any group, including placebo.

Overview of Adverse Events

A numerically higher proportion of participants in the baricitinib groups reported TEAEs compared to the placebo group. Also, a higher proportion of participants in the baricitinib 4-mg group reported TEAEs and SAEs compared with participants in the baricitinib 2-mg group.

Most AEs were of mild or moderate severity. A similar proportion of participants in the baricitinib 4 mg treatment group reported severe AEs or SAEs compared to the placebo group. No SAEs were reported in the baricitinib 2 mg group.

One participant in baricitinib group and 2 in the placebo group had an AE leading to permanent discontinuation from study drug. No deaths were reported in the adolescent placebo-controlled cohort.

Table 26: Summary of AEs in the safety sets of study JAIO (data cutoff date 15 April 2025).

	PC BARI AA Adolescents			Ext BARI AA Adolescents		All BARI AA Adolescents
	PBO N = 88 PYE = 58.3 n (%) [IR]	BARI 2 mg N = 83 PYE = 57.0 n (%) [IR]	BARI 4 mg N = 85 PYE = 57.1 n (%) [IR]	BARI 2 mg N = 166 PYE = 175.1 n (%) [IR]	BARI 4 mg N = 168 PYE = 204.4 n (%) [IR]	All Doses N = 415 PYE = 478.9 n (%) [IR]
Deaths	0	0	0	0	0	0
SAE	Redacted	Redacted	Redacted	2 (1.2) [1.1]	8 (4.8) [4.0]	15 (3.6) [3.2]
TEAE[a]	47 (53.4) [129.1]	50 (60.2) [160.1]	60 (70.6) [199.7]	115 (69.3) [145.1]	135 (80.4) [185.9]	284 (68.4) [134.1]
Mild	27 (30.7) [56.3]	37 (44.6) [96.6]	43 (50.6) [116.4]	66 (39.8) [54.9]	70 (41.7) [52.4]	154 (37.1) [46.2]
Moderate	18 (20.5) [36.3]	12 (14.5) [23.3]	15 (17.6) [28.5]	46 (27.7) [31.2]	56 (33.3) [33.3]	115 (27.7) [28.5]
Severe	2 (2.3) [3.5]	1 (1.2) [1.8]	2 (2.4) [3.6]	3 (1.8) [1.7]	9 (5.4) [4.5]	15 (3.6) [3.2]
Permanent DC from study drug due to AE	Redacted	Redacted	Redacted	1 (0.6) [0.6]	3 (1.8) [1.5]	5 (1.2) [1.0]
Temporary interruption from study drug due to AE	9 (10.2) [16.4]	5 (6.0) [9.1]	8 (9.4) [14.7]	21 (12.7) [12.9]	24 (14.3) [12.8]	53 (12.8) [11.9]
DC from study due to AE	Redacted	Redacted	Redacted	1 (0.6) [0.6]	3 (1.8) [1.5]	5 (1.2) [1.0]

Abbreviations: AE = adverse event; All BARI AA Adolescents = All baricitinib alopecia areata adolescents; BARI = baricitinib; DC = discontinuation; Ext BARI AA Adolescents = Extended baricitinib alopecia areata adolescents; IR = incidence rate; N = number of participants in the analysis population;
n = number of participants in the specified category; PC BARI AA Adolescents = Placebo-controlled baricitinib alopecia areata adolescents; PBO = Placebo; PYE = participant-years of exposure; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

a Participants with multiple occurrences of the same event are counted under the highest severity.

b IR not available.

IRs are calculated based on participant-years at risk.
Classifications of AEs are based on MedDRA Version 27.0.
Percentages (%) are based on the number of participants in the APSAS in each treatment group (N).
A TEAE was defined as any event that occurred on or after the first dose of study drug administration or any preexisting event that worsened in severity after dosing.

Common Adverse Events

There was an overall higher frequency of treatment-emergent AEs in the baricitinib 4 mg group compared with placebo.

On level of **SOC**, differences between the baricitinib 4 mg group as compared to the placebo group were seen with: infections and infestations (40% *versus* 32%), skin and subcutaneous tissue disorders (19% *versus* 11%), investigations (12% *versus* 4.5%), blood and lymphatic system disorders (11% *versus* 1.1%), psychiatric disorders (5.9% *versus* 1.1%). Neoplasms occurred in the baricitinib group (n=2, 2.4%). The 5 instances of psychiatric disorders in the baricitinib group were cases of: anxiety, depression, flat affect, nervousness.

On the **PT** level, the largest differences between the baricitinib 4 mg group as compared to the placebo group were seen with (Table 27): acne (9.4% *versus* 4.5%), headache (8.2% *versus* 5.7%), upper respiratory tract infections (8.2% *versus* 6.8%) and rhinitis (7.1% *versus* 3.4%) but not nasopharyngitis, blood CPK increased (5.9% *versus* 2.3%), influenza (5.9% *versus* 3.4% and Covid19 (redacted), eosinophilia (4.7% *versus* 1.1%), neutropenia (redacted), ALT increased (redacted), blood cholesterol increased (2.4% *versus* 0). Influenza and urinary tract infections occurred more frequently in the baricitinib 2 mg group as compared to the placebo group and the 4 mg group.

Table 27: Common (≥2%) treatment-emergent AEs in study JAIO.

	PC BARI AA Adolescents			Extended BARI AA Adolescents		All BARI AA Adolescents
n (%) [IR]	**PBO N =88 PYE = 58.3 n (%) [IR]**	**BARI 2 mg N = 83 PYE = 57.0 n (%) [IR]**	**BARI 4 mg N = 85 PYE = 57.1 n (%) [IR]**	**BARI 2 mg N = 166 PYE = 175.1 n (%) [IR]**	**BARI 4 mg N = 68 PYE = 204.4 n (%) [IR]**	**All Doses N = 415 PYE = 478.9 n (%) [IR]**
Participants with at least 1 TEAE	47 (53.4) [129.1]	50 (60.2) [160.1]	60 (70.6) [199.7]	115 (69.3) [145.1]	135 (80.4) [185.9]	284 (68.4) [134.1]
Acne	4 (4.5) [7.0]	7 (8.4) [13.0]	8 (9.4) [14.8]	22 (13.3) [13.7]	24 (14.3) [13.1]	57 (13.7) [13.0]
Headache	5 (5.7) [8.9]	4 (4.8) [7.2]	7 (8.2) [13.1]	16 (9.6) [9.7]	19 (11.3) [10.2]	39 (9.4) [8.7]
Upper respiratory tract infection	6 (6.8) [10.8]	7 (8.4) [13.1]	7 (8.2) [13.0]	23 (13.9) [14.2]	18 (10.7) [9.5]	46 (11.1) [10.3]
Rhinitis	3 (3.4) [5.3]	1 (1.2) [1.8]	6 (7.1) [11.1]	1 (0.6) [0.6]	8 (4.8) [4.1]	9 (2.2) [1.9]
Nasopharyngitis	9 (10.2) [16.3]	7 (8.4) [12.9]	6 (7.1) [10.8]	26 (15.7) [16.3]	21 (12.5) [11.0]	52 (12.5) [11.7]
Blood creatine phosphokinase increased	Redacted	Redacted	Redacted	4 (2.4) [2.3]	14 (8.3) [7.2]	18 (4.3) [3.8]
Influenza	3 (3.4) [5.2]	10 (12.0) [19.2]	5 (5.9) [9.0]	12 (7.2) [7.2]	12 (7.1) [6.1]	29 (7.0) [6.3]
Eosinophilia	1 (1.1) [1.7]	1 (1.2) [1.8]	4 (4.7) [7.2]	2 (1.2) [1.1]	6 (3.6) [3.0]	8 (1.9) [1.7]
Nausea	Redacted	Redacted	Redacted	1 (0.6) [0.6]	5 (3.0) [2.5]	7 (1.7) [1.5]
Abdominal pain	Redacted	Redacted	Redacted	5 (3.0) [2.9]	8 (4.8) [4.1]	14 (3.4) [3.0]
COVID-19	Redacted	Redacted	Redacted	7 (4.2) [4.1]	6 (3.6) [3.0]	16 (3.9) [3.4]
Vomiting	Redacted	Redacted	Redacted	10 (6.0) [5.9]	4 (2.4) [2.0]	16 (3.9) [3.4]
Gastroenteritis	Redacted	Redacted	Redacted	3 (1.8) [1.7]	6 (3.6) [3.0]	12 (2.9) [2.5]
Ligament sprain	Redacted	Redacted	Redacted	Redacted	Redacted	4 (1.0) [0.8]
Neutropenia	Redacted	Redacted	Redacted	3 (1.8) [1.7]	8 (4.8) [4.0]	12 (2.9) [2.5]
Alanine aminotransferase increased	Redacted	Redacted	Redacted	2 (1.2) [1.1]	4 (2.4) [2.0]	7 (1.7) [1.5]
Anxiety	Redacted	Redacted	Redacted	Redacted	Redacted	3 (0.7) [0.6]
Blood cholesterol increased	Redacted	Redacted	Redacted	Redacted	Redacted	2 (0.5) [0.4]
Influenza like illness	1 (1.1) [1.7]	1 (1.2) [1.8]	2 (2.4) [3.5]	2 (1.2) [1.1]	3 (1.8) [1.5]	6 (1.4) [1.3]
Pharyngitis	Redacted	Redacted	Redacted	3 (1.8) [1.7]	3 (1.8) [1.5]	7 (1.7) [1.5]
Tinea versicolour	Redacted	Redacted	Redacted	1 (0.6) [0.6]	3 (1.8)[1.5]	4 (1.0) [0.8]
Asthenia	1 (1.1) [1.7]	2 (2.4) [3.6]	1 (1.2) [1.8]	5 (3.0) [2.9]	1 (0.6) [0.5]	8 (1.9) [1.7]
Contusion	1 (1.1) [1.7]	2 (2.4) [3.5]	1 (1.2) [1.8]	3 (1.8) [1.7]	3 (1.8) [1.5]	6 (1.4) [1.3]
Cough	2 (2.3) [3.5]	1 (1.2) [1.8]	1 (1.2) [1.8]	5 (3.0) [2.9]	7 (4.2) [3.5]	13 (3.1) [2.8]
Diarrhoea	1 (1.1) [1.7]	2 (2.4) [3.6]	1 (1.2) [1.8]	4 (2.4) [2.3]	3 (1.8) [1.5]	7 (1.7) [1.5]
Epistaxis	1 (1.1) [1.7]	1 (1.2) [1.8]	1 (1.2) [1.8]	4 (2.4) [2.3]	3 (1.8) [1.5]	7 (1.7) [1.5]
Pneumonia	Redacted	Redacted	Redacted	4 (2.4) [2.3]	2 (1.2) [1.0]	7 (1.7) [1.5]
Dysmenorrhoea[a]	Redacted	Redacted	Redacted	Redacted	Redacted	5 (2.4) [2.1]
Folliculitis	Redacted	Redacted	Redacted	4 (2.4) [2.3]	6 (3.6) [3.0]	10 (2.4) [2.1]

	PC BARI AA Adolescents			Extended BARI AA Adolescents		All BARI AA Adolescents
n (%) [IR]	**PBO N =88 PYE = 58.3 n (%) [IR]**	**BARI 2 mg N = 83 PYE = 57.0 n (%) [IR]**	**BARI 4 mg N = 85 PYE = 57.1 n (%) [IR]**	**BARI 2 mg N = 166 PYE = 175.1 n (%) [IR]**	**BARI 4 mg N = 68 PYE = 204.4 n (%) [IR]**	**All Doses N = 415 PYE = 478.9 n (%) [IR]**
Seborrhoeic dermatitis	Redacted	Redacted	Redacted	2 (1.2) [1.1]	5 (3.0) [2.5]	7 (1.7) [1.5]
Leukopenia	Redacted	Redacted	Redacted	1 (0.6) [0.6]	4 (2.4) [2.0]	6 (1.4) [1.3]
Platelet count increased	Redacted	Redacted	Redacted	Redacted	Redacted	6 (1.4) [1.3]
Depression	Redacted	Redacted	Redacted	1 (0.6) [0.6]	4 (2.4) [2.0]	5 (1.2) [1.0]
Sinusitis	2 (2.3) [3.5]	3 (3.6) [5.4]	1 (1.2) [1.8]	6 (3.6) [3.5]	3 (1.8) [1.5]	9 (2.2) [1.9]
Urinary tract infection	1 (1.1) [1.7]	3 (3.6) [5.4]	1 (1.2) [1.8]	5 (3.0) [2.9]	3 (1.8) [1.5]	9 (2.2) [1.9]
Abdominal pain upper	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted
Arthralgia	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted
Back pain	Redacted	Redacted	Redacted	3 (1.8) [1.7]	1 (0.6) [0.5]	4 (1.0) [0.8]

Abbreviations: All BARI AA Adolescents = All baricitinib alopecia areata adolescents; COVID-19 = coronavirus disease 2019; Ext BARI AA Adolescents = Extended baricitinib alopecia areata adolescents; IR = incidence rate; n = number of participants in the specified category;
N = number of participants in the analysis population;
PC BARI AA Adolescents = Placebo-controlled baricitinib alopecia areata adolescents; PBO = Placebo; PYE = participant-years of exposure.
a Denominator adjusted because of sex-specific event for females: N =47 (PBO), N =38 (BARI 2 mg), N = 41 (BARI 4 mg). Percentage is based on the female population count.
Note: IRs are calculated based on participant-years at risk.

Comparison of TEAE's in the adult and adolescent safety data sets

Common TEAE's in the **PC BARI AA Adolescent safety data set** that are not yet identified as ADR were compared with the **PC BARI AA Adult safety data set**. These concerned (≥2% and n > 1):

- COVID-19
- Ligament sprain
- Anxiety
- Influenza
- Tinea versicolour
- Eosinophilia

Table 28: Summary of Common (≥2% in Study JAIO) TEAEs from the Week 36 PC BARI AA Adult, and PC BARI AA Adolescents Analysis Set

	PC BARI AA Adult			PC BARI AA Adolescents		
	PBO N = 371 PYE = 243.2 n (%) [IR]	BARI 2 mg N = 365 PYE = 240.6 n (%) [IR]	BARI 4 mg N = 540 PYE = 363.4 n (%) [IR]	PBO N = 88 PYE = 58.3 n (%) [IR]	BARI 2 mg N = 83 PYE = 57.0 n (%) [IR]	BARI 4 mg N = 85 PYE = 57.1 n (%) [IR]
Upper respiratory tract infection	26 (7.0) [11.2]	24 (6.6) [10.3]	41 (7.6) [11.8]	6 (6.8) [10.8]	7 (8.4) [13.1]	7 (8.2) [13.0]
Nasopharyngitis	19 (5.1) [8.0]	16 (4.4) [6.8]	37 (6.9) [10.7]	9 (10.2) [16.3]	7 (8.4) [12.9]	6 (7.1) [10.8]
Headache	20 (5.4) [8.4]	20 (5.5) [8.5]	36 (6.7) [10.4]	5 (5.7) [8.9]	4 (4.8) [7.2]	7 (8.2) [13.1]
Acne	4 (1.1) [1.6]	21 (5.8) [9.0]	30 (5.6) [8.5]	4 (4.5) [7.0]	7 (8.4) [13.0]	8 (9.4) [14.8]
Blood CPK increased	5 (1.3) [2.0]	3 (0.8) [1.2]	23 (4.3) [6.4]	Redacted	Redacted	Redacted
Urinary tract infection	6 (1.6) [2.5]	14 (3.8) [5.9]	18 (3.3) [5.0]	1 (1.1) [1.7]	3 (3.6) [5.4]	1 (1.2) [1.8]
Influenza	7 (1.9) [2.9]	6 (1.6) [2.5]	14 (2.6) [3.9]	3 (3.4) [5.2]	10 (12.0) [19.2]	5 (5.9) [9.0]
Cough	7 (1.9) [2.9]	5 (1.4) [2.1]	12 (2.2) [3.3]	2 (2.3) [3.5]	1 (1.2) [1.8]	1 (1.2) [1.8]
Fatigue	4 (1.1) [1.6]	3 (0.8) [1.2]	12 (2.2) [3.3]	Redacted	Redacted	Redacted
Nausea	6 (1.6) [2.5]	10 (2.7) [4.2]	11 (2.0) [3.1]	Redacted	Redacted	Redacted
Back pain	12 (3.2) [5.0]	6 (1.6) [2.5]	10 (1.9) [2.8]	Redacted	Redacted	Redacted
Arthralgia	8 (2.2) [3.3]	7 (1.9) [2.9]	9 (1.7) [2.5]	Redacted	Redacted	Redacted
Diarrhoea	8 (2.2) [3.3]	2 (0.5) [0.8]	9 (1.7) [2.5]	1 (1.1) [1.7]	2 (2.4) [3.6]	1 (1.2) [1.8]
COVID-19	2 (0.5) [0.8]	1 (0.3) [0.4]	1 (0.2) [0.3]	Redacted	Redacted	Redacted
Gastroenteritis	6 (1.6) [2.5]	6 (1.6) [2.5]	4 (0.7) [1.1]	Redacted	Redacted	Redacted
Rhinitis	Redacted	Redacted	Redacted	3 (3.4) [5.3]	1 (1.2) [1.8]	6 (7.1) [11.1]
Eosinophilia	-	-	-	1 (1.1) [1.7]	1 (1.2) [1.8]	4 (4.7) [7.2]
Abdominal pain	3 (0.8) [1.2]	4 (1.1) [1.7]	4 (0.7) [1.1]	3 (3.4) [5.3]	1 (1.2) [1.8]	3 (3.5) [5.3]
Abdominal pain upper	2 (0.5) [0.8]	5 (1.4) [2.1]-	2 (0.4) [0.5]	Redacted	Redacted	Redacted
Ligament sprain	2 (0.5) [0.8]	1 (0.3) [0.4]	3 (0.6) [0.8]	Redacted	Redacted	Redacted
Neutropenia	3 (0.8) [1.2]	2 (0.5) [0.8]	6 (1.1) [1.7]	Redacted	Redacted	Redacted
Alanine aminotransferase	3 (0.8) [1.2]	2 (0.5) [0.8]	6 (1.1) [1.6]	Redacted	Redacted	Redacted

	PC BARI AA Adult			PC BARI AA Adolescents		
	PBO N = 371 PYE = 243.2 n (%) [IR]	**BARI 2 mg N = 365 PYE = 240.6 n (%) [IR]**	**BARI 4 mg N = 540 PYE = 363.4 n (%) [IR]**	**PBO N = 88 PYE = 58.3 n (%) [IR]**	**BARI 2 mg N = 83 PYE = 57.0 n (%) [IR]**	**BARI 4 mg N = 85 PYE = 57.1 n (%) [IR]**
increased						
Anxiety	0	0	Redacted	Redacted	Redacted	Redacted
Blood cholesterol increased	2 (0.5) [0.8]	4 (1.1) [1.7]	7 (1.3) [1.9]	Redacted	Redacted	Redacted
Influenza like illness	1 (0.3) [0.4]	0	2 (0.4) [0.5]	1 (1.1) [1.7]	1 (1.2) [1.8]	2 (2.4) [3.5]
Pharyngitis	2 (0.5) [0.8]	3 (0.8) [1.2]	5 (0.9) [1.4]	Redacted	Redacted	Redacted
Tinea versicolour	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted
Asthenia	Redacted	Redacted	Redacted	1 (1.1) [1.7]	2 (2.4) [3.6]	1 (1.2) [1.8]
Contusion	Redacted	Redacted	Redacted	1 (1.1) [1.7]	2 (2.4) [3.5]	1 (1.2) [1.8]
Dysmenorrhoea[b]	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted
Sinusitis	6 (1.6) [2.5]	4 (1.1) [1.7]	5 (0.9) [1.4]	2 (2.3) [3.5]	3 (3.6) [5.4]	1 (1.2) [1.8]
Eczema	5 (1.3) [2.1]	[1.2]	4 (0.7) [1.1]	Redacted	Redacted	Redacted
Hand dermatitis	-	-	-	Redacted	Redacted	Redacted
Menstruation irregular[b]	-	-	-	Redacted	Redacted	Redacted
Oropharyngeal pain	3 (0.8) [1.2]	5 (1.4) [2.1]	8 (1.5) [2.2]	Redacted	Redacted	Redacted
Pyrexia	2 (0.5) [0.8]	4 (1.1) [1.7]	4 (0.7) [1.1]	Redacted	Redacted	Redacted
Skin papilloma	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted

Common TEAE's in the **Ext** and **All BARI AA Adolescent safety data sets** that are not yet identified as ADR were compared with the **Ext** and **All BARI AA Adult safety data sets**. Focus was on frequency category as well as the IR rate (> factor 1.5). These concerned:

- Influenza
- Cough
- Vomiting
- Ligament sprain
- Asthenia
- Epistaxis
- Dysmenorrhea
- Seborrhoeic dermatitis
- Depression
- Pyrexia
- Eosinophilia
- Leukopenia

Table 29: Summary of Common (≥2% in JAIO) TEAEs from the Week 52 Data Cuts in AA Adult and AA Adolescents Analysis Sets

	AA Adult			AA Adolescents		
	Ext BARI AA		All BARI AA	Ext BARI AA Adolescents		All BARI AA Adolescents
n (%) [IR]	BARI 2 mg N = 365 PYE = 402.1	BARI 4 mg N = 540 PYE = 720.7	All Doses N = 1244 PYE = 1668.4	BARI 2 mg N = 166 PYE = 175.1	BARI 4 mg N = 168 PYE = 204.4	All Doses N = 415 PYE = 478.9
Upper respiratory tract infection	37 (10.1) [9.4]	52 (9.6) [7.6]	113 (9.1) [7.1]	23 (13.9) [14.2]	18 (10.7) [9.5]	46 (11.1) [10.3]
Headache	27 (7.4) [6.7]	48 (8.9) [6.9]	95 (7.6) [5.9]	16 (9.6) [9.7]	19 (11.3) [10.2]	39 (9.4) [8.7]
Nasopharyngitis	22 (6.0) [5.4]	45 (8.3) [6.5]	79 (6.4) [4.9]	26 (15.7) [16.3]	21 (12.5) [11.0]	52 (12.5) [11.7]
Acne	24 (6.6) [5.9]	35 (6.5) [5.0]	77 (6.2) [4.8]	22 (13.3) [13.7]	24 (14.3) [13.1]	57 (13.7) [13.0]
Urinary tract infection	21 (5.8) [5.1]	27 (5.0) [3.7]	69 (5.5) [4.2]	5 (3.0) [2.9]	3 (1.8) [1.5]	9 (2.2) [1.9]
COVID-19	7 (1.9) [1.7]	20 (3.7) [2.7]	57 (4.6) [3.4]	7 (4.2) [4.1]	6 (3.6) [3.0]	16 (3.9) [3.4]
Blood CPK increased	3 (0.8) [0.7]	34 (6.3) [4.7]	53 (4.3) [3.2]	4 (2.4) [2.3]	14 (8.3) [7.2]	18 (4.3) [3.8]
Nausea	12 (3.3) [2.9]	13 (2.4) [1.8]	39 (3.1) [2.3]	1 (0.6) [0.6]	5 (3.0) [2.5]	7 (1.7) [1.5]
Arthralgia	14 (3.8) [3.4]	15 (2.8) [2.0]	38 (3.1) [2.3]	5 (3.0) [2.9]	2 (1.2) [1.0]	7 (1.7) [1.5]
Folliculitis	6 (1.6) [1.4]	16 (3.0) [2.2]	32 (2.6) [1.9]	4 (2.4) [2.3]	6 (3.6) [3.0]	10 (2.4) [2.1]
Influenza	7 (1.9) [1.7]	18 (3.3) [2.5]	29 (2.3) [1.7]	12 (7.2) [7.2]	12 (7.1) [6.1]	29 (7.0) [6.3]
Cough	7 (1.9) [1.7]	13 (2.4) [1.8]	26 (2.1) [1.5]	5 (3.0) [2.9]	7 (4.2) [3.5]	13 (3.1) [2.8]
Sinusitis	7 (1.9) [1.7]	11 (2.0) [1.5]	21 (1.7) [1.2]	6 (3.6) [3.5]	3 (1.8) [1.5]	9 (2.2) [1.9]
Gastroenteritis	8 (2.2) [1.9]	6 (1.1) [0.8]	19 (1.5) [1.1]	3 (1.8) [1.7]	6 (3.6) [3.0]	12 (2.9) [2.5]
Diarrhoea	4 (1.1) [0.9]	12 (2.2) [1.6]	18 (1.4) [1.1]	4 (2.4) [2.3]	3 (1.8) [1.5]	7 (1.7) [1.5]
Rhinitis	0	0	2 (0.2) [0.1]	1 (0.6) [0.6]	8 (4.8) [4.1]	9 (2.2) [1.9]
Eosinophilia	–	–	–	2 (1.2) [1.1]	6 (3.6) [3.0]	8 (1.9) [1.7]
Abdominal pain	5 (1.4) [1.2]	4 (0.7) [0.5]	12 (1.0) [0.7]	5 (3.0) [2.9]	8 (4.8) [4.1]	14 (3.4) [3.0]
Vomiting	4 (1.1) [0.9]	5 (0.9) [0.7]	13 (1.0) [0.8]	10 (6.0) [5.9]	4 (2.4) [2.0]	16 (3.9) [3.4]
Ligament sprain	1 (0.3) [0.2]	3 (0.6) [0.4]	9 (0.7) [0.5]	Redacted	Redacted	4 (1.0) [0.8]

	AA Adult			AA Adolescents		
	Ext BARI AA		All BARI AA	Ext BARI AA Adolescents		All BARI AA Adolescents
n (%) [IR]	BARI 2 mg N = 365 PYE = 402.1	BARI 4 mg N = 540 PYE = 720.7	All Doses N = 1244 PYE = 1668.4	BARI 2 mg N = 166 PYE = 175.1	BARI 4 mg N = 168 PYE = 204.4	All Doses N = 415 PYE = 478.9
Neutropenia	3 (0.8) [0.7]	10 (1.9) [1.4]	19 (1.5) [1.1]	3 (1.8) [1.7]	8 (4.8) [4.0]	12 (2.9) [2.5]
Alanine aminotransferase increased	2 (0.5) [0.5]	7 (1.3) [0.9]	15 (1.2) [0.9]	2 (1.2) [1.1]	4 (2.4) [2.0]	7 (1.7) [1.5]
Asthenia	1 (0.3) [0.2]	1 (0.2) [0.1]	3 (0.2) [0.2]	5 (3.0) [2.9]	1 (0.6) [0.5]	8 (1.9) [1.7]
Epistaxis	3 (0.8) [0.7]	1 (0.2) [0.1]	4 (0.3) [0.2]	4 (2.4) [2.3]	3 (1.8) [1.5]	7 (1.7) [1.5]
Pneumonia	3 (0.8) [0.7]	2 (0.4) [0.3]	5 (0.4) [0.3]	4 (2.4) [2.3]	2 (1.2) [1.0]	7 (1.7) [1.5]
Dysmenorrhoea	1 (0.4) [0.4]	4 (1.2) [0.9]	7 (0.9) [0.7]	Redacted	Redacted	5 (2.4) [2.1]
Seborrhoeic dermatitis	2 (0.5) [0.5]	8 (1.5) [1.1]	16 (1.3) [0.9]	2 (1.2) [1.1]	5 (3.0) [2.5]	7 (1.7) [1.5]
Leukopenia	Redacted	Redacted	5 (0.4) [0.3]	1 (0.6) [0.6]	4 (2.4) [2.0]	6 (1.4) [1.3]
Platelet count increased	-	-	-	Redacted	Redacted	6 (1.4) [1.3]
Depression	6 (1.6) [1.4]	3 (0.6) [0.4]	12 (1.0) [0.7]	1 (0.6) [0.6]	4 (2.4) [2.0]	5 (1.2) [1.0]
Abdominal pain upper	7 (1.9) [1.7]	2 (0.4) [0.3]	12 (1.0) [0.7]	5 (3.0) [2.9]	2 (1.2) [1.0]	8 (1.9) [1.7]
Oropharyngeal pain	7 (1.9) [1.7]	10 (1.9) [1.4]	23 (1.8) [1.4]	4 (2.4) [2.3]	5 (3.0) [2.5]	9 (2.2) [1.9]
Pyrexia	4 (1.1) [0.9]	9 (1.7) [1.2]	22 (1.8) [1.3]	4 (2.4) [2.3]	4 (2.4) [2.0]	8 (1.9) [1.7]

Serious adverse events and deaths

No deaths have been reported among adolescents through the data cutoff date 15 April 2025.

Few participants reported ≥1 SAEs across the treatment groups during the placebo-controlled period. A similar proportion of participants in the baricitinib group reported SAEs compared to the placebo group (Table 30). The SAEs in the baricitinib group were ligament sprain and depression. Both the SAEs of ligament sprain and of depression were not considered to be related to the study medication by the investigator.

The participant with depression had previous depression in the medical history but had normal HADS and CSSRS scores in the study, up to the event where the CSSRS score was normal but HADS was 21. The immediate cause of depression was attributed to personal matters related to school activities.

The IRs for SAEs increased from 0 and 3.5 (in the PC BARI AA Adolescent safety data asset) to 1.1 and 4.0 in the **EXT BARI AA Adolescent** safety data set for 2 mg and 4 mg baricitinib resp. Three SAEs in the 2 mg dose group were observed in 2 patients, reporting peritonsillar abscess, sarcoma, and

dermatitis allergic (n = 1, IR 0.6). In the 4 mg dose group, 9 SAEs in 8 patients reported were ligament sprain, lower limb fracture, toxicity due to various agents, upper limb fracture, somatic symptom disorder, pneumonia, and tonsillitis (n = 1, IR 0.5), and depression (n = 2, IR 1.01). Overall, most of the total of 17 SAEs in the **All BARI AA Adolescents** safety data set were clustered in the SOCs Psychiatric disorders (n = 5, including suicide attempt). The patient with a (non-fatal) suicide attempt had a history of depression, anxiety, and self-injurious behaviour prior to study enrolment, thus unlikely related to treatment. The other main cluster was for the SOC Injury, poisoning, and procedural complaints (n = 4, including upper and lower limb fracture and ligament sprain).

Table 30: The Incidence Rates for SAEs (PC BARI AA, Extended BARI, all BARI AA Adolescents)

	PC BARI AA Adolescents			**Extended BARI AA Adolescents**		**All BARI AA Adolescents**
	PBO N = 88 PYE = 58.3 n (%) [IR]	**BARI2 mg N = 83 PYE = 57.0 n (%) [IR]**	**BARI 4 mg N = 85 PYE = 57.1 n (%) [IR]**	**BARI 2 mg N = 166 PYE = 175.1 n (%) [IR]**	**BARI 4 mg N = 168 PYE = 204.4 n (%) [IR]**	**All Doses N = 415 PYE = 478.9 n (%) [IR]**
Participants with ≥1 SAE	Redacted	Redacted	Redacted	2 (1.2) [1.1]	8 (4.8) [4.0]	15 (3.6) [3.2]
Injury, poisoning, and procedural complications			Redacted	Redacted	Redacted	4 (1.0) [0.8]
Ligament sprain	Redacted	Redacted	Redacted	Redacted	Redacted	1 (0.2) [0.2]
Lower limb fracture	0	0	0	Redacted	Redacted	1 (0.2) [0.2]
Toxicity to various agents	0	0	0	Redacted	Redacted	1 (0.2) [0.2]
Upper limb fracture	0	0	0	Redacted	Redacted	1 (0.2) [0.2]
Psychiatric disorders	Redacted	Redacted	Redacted	Redacted	Redacted	5 (1.2) [1.0]
Depression	Redacted	Redacted	Redacted	Redacted	Redacted	2 (0.5) [0.4]
Major depression	0	0	0	0	0	1 (0.2) [0.2]
Somatic symptom disorder	0	0	0	Redacted	Redacted	1 (0.2) [0.2]
Suicide attempt	0	0	0	0	0	1 (0.2) [0.2]
Infections and infestations	Redacted	Redacted	Redacted	1 (0.6) [0.6]	2 (1.2) [1.0]	3 (0.7) [0.6]
Appendicitis	Redacted	Redacted	Redacted	0	0	0
Peritonsillar abscess	0	0	0	1 (0.6) [0.6]	0	1 (0.2) [0.2]
Pneumonia	0	0	0	0	1 (0.6) [0.5]	1 (0.2) [0.2]
Tonsillitis	0	0	0	0	1 (0.6) [0.5]	1 (0.2) [0.2]
Nervous system disorders	Redacted			0	0	2 (0.5) [0.4]
Epilepsy	Redacted			0	0	1 (0.2) [0.2]
Headache	0	0	0	0	0	1 (0.2) [0.2]
Gastrointestinal disorders	0	0	0	0	0	1 (0.2) [0.2]
Abdominal pain upper	0	0	0	0	0	1 (0.2) [0.2]

	PC BARI AA Adolescents			Extended BARI AA Adolescents		All BARI AA Adolescents
	PBO N = 88 PYE = 58.3 n (%) [IR]	**BARI2 mg N = 83 PYE = 57.0 n (%) [IR]**	**BARI 4 mg N = 85 PYE = 57.1 n (%) [IR]**	**BARI 2 mg N = 166 PYE = 175.1 n (%) [IR]**	**BARI 4 mg N = 168 PYE = 204.4 n (%) [IR]**	**All Doses N = 415 PYE = 478.9 n (%) [IR]**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	Redacted	Redacted	1 (0.2) [0.2]
Sarcoma	0	0	0	Redacted	Redacted	1 (0.2) [0.2]
Skin and subcutaneous tissue disorders	0	0	0	Redacted	Redacted	1 (0.2) [0.2]
Dermatitis allergic	0	0	0	Redacted	Redacted	1 (0.2) [0.2]
Respiratory, thoracic, and mediastinal disorders	Redacted	Redacted	Redacted	0	0	0
Pneumothorax spontaneous	Redacted	Redacted	Redacted	0	0	0

Adverse events of Special Interest

The Applicant evaluated an extensive list of safety topics of special interest. For this report it is mainly focussed on those AESI that are listed in the Safety Concerns of the RMP.

Serious and opportunistic infections

In the placebo-controlled period, there was 1 serious infection in the placebo group and none in the baricitinib groups. No participants discontinued study drug due to a serious infection. There was a similar number (4 – 2) of study drug interruptions in the placebo group compared to the baricitinib groups due to infections. There was a case of herpes zoster group and a case of herpes simplex in the main study. The case with herpes zoster was mild and recovered. There were no reports of treatment-emergent opportunistic infections or tuberculosis.

In the **All BARI AA Adolescent** safety data set, there were 3 serious infections (IR 0.6); none led to study discontinuation. There were no opportunistic infections or tuberculosis infections. Herpes Zoster and Herpes Simplex infections were seen in 3 resp. 2 patients (IRs 0.6 and 0.4); all were mild.

Haematologic changes

The haematologic growth promoters, erythropoietin, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, and thrombopoietin, are modulated via JAK2 signalling. JAK2 inhibition could impair the production of erythrocytes, leukocytes, or platelets.

In the placebo-controlled period (the **PC BARI AA Adolescent** safety data set):

Regarding **neutrophils**, the percentage of participants with any CTCAE grade increase (reflecting a decrease in neutrophil counts) was similar for baricitinib 2 mg (27%) compared with placebo (25%) and was higher (36%) with baricitinib 4 mg compared with placebo. Most increases were to Grade 1 or 2. There were few increases to Grade ≥3, most in the baricitinib group.

Regarding **lymphocytes**, the percentage of participants with any CTCAE grade increase (reflecting a decrease in lymphocyte counts) was similar (2.4% to 4.6%) across baricitinib 2-mg, 4-mg, and placebo groups. All increases were to Grade 1 or 2. No participants had increases to Grade ≥3.

Regarding **haemoglobin** levels, the percentage of participants with any CTCAE grade increase (reflecting a decrease in haemoglobin) was higher with baricitinib 4-mg (21%) compared with the baricitinib 2-mg (16%) and placebo (15%) groups. All increases were to Grade 1 or 2. No participants had increases to Grade ≥3 (<8 g/dL).

Regarding **platelets**, the percentage of participants who developed thrombocytosis >400 x 10^9/L for all groups was 7.5% for placebo, 9.5% in baricitinib 2 mg, and 25% for baricitinib 4 mg. The participant with a platelet increase >600 x 10^9/L did not report a thromboembolic event.

In the **Ext** and **All BARI AA Adolescent** safety data sets, comparable patterns were seen. For **neutropaenia**, there was one grade Grade 4 observation, in a patient without infections and a high count at baseline. After discontinuation normalisation of neutrophils was seen 1 month later. **Lymphopenia** was rare and Grade 3 was seen in 3 patients, no Grade 4 was observed. **Haemoglobin** decreases Grade 3 or more were not observed. For **thrombocytosis**, three patients had > 600 x 10^9/L; all had high baseline levels and there were no TEs.

Table 31: Haematologic changes in study JAIO

	PC BARI AA Adolescents			Extended BARI AA Adolescents		All BARI AA Adolescents
	PBO n/NAR (%)	**BARI 2 mg n/NAR (%)**	**BARI 4 mg n/NAR (%)**	**BARI 2 mg n/NAR (%) [IR]**	**BARI 4 mg n/NAR (%) [IR]**	**All Doses n/NAR (%) [IR]**
Neutrophil count decreased						
Any CTCAE Grade increase	22/87 (25.3)	22/83 (26.5)	30/84 (35.7)	42/166 (25.3) [24.0]	56/167 (33.5) [27.4]	113/414 (27.3) [23.6]
Increase to CTCAEGrade ≥3(<1000/µL	1/87 (1.1)	2/83 (2.4)	3/84 (3.6)	4/165 (2.4) [2.3]	7/167 (4.2) [3.4]	12/412 (2.9) [2.5]
Lymphocyte count decreased						
Any CTCAE Grade increase	4/87 (4.6)	2/83 (2.4)	3/84 (3.6)	13/166 (7.8) [7.4]	22/167 (13.2) [10.8]	38/414 (9.2) [7.9]
Increase to CTCAE Grade ≥3 (<500µ/L)	0	0	0	1/166 (0.6) [0.6]	2/167 (1.2) [1.0]	3/414 (0.7) [0.6]
Haemoglobin decreased						
Any CTCAE Grade increase	13/87 (14.9)	13/83 (15.7)	18/84 (21.4)	20/166 (12.0) [11.4]	38/167 (22.8) [18.6]	63/414 (15.2) [13.2]
Increase to CTCAE Grade ≥3 (<8.0 g/dL)	0	0	0	0	0	0
Platelet count increased						
Thrombocytosis (≤400 billion cells/L to >400 billion cells/L)	6/80 (7.5)	7/74 (9.5)	19/77 (24.7)	25/152 (16.4) [14.3]	39/154 (25.3) [19.1]	75/376 (19.9) [15.7]

	PC BARI AA Adolescents			Extended BARI AA Adolescents		All BARI AA Adolescents
	PBO n/NAR (%)	BARI 2 mg n/NAR (%)	BARI 4 mg n/NAR (%)	BARI 2 mg n/NAR (%) [IR]	BARI 4 mg n/NAR (%) [IR]	All Doses n/NAR (%) [IR]
Thrombocytosis (≤600 billion cells/L to >600 billion cells/L)	Redacted	Redacted	Redacted	1/166 (0.6) [0.6]	1/167 (0.6) [0.5]	3/414 (0.7) [0.6]

Abbreviations: AA = alopecia areata; BARI = baricitinib; CTCAE = Common Terminology Criteria for Adverse Events; IR = incidence rate; N = number of participants in the safety analysis set; n = number of participants in the specified category; PC BARI AA Adolescents = Placebo-controlled

baricitinib alopecia areata adolescents; PBO = placebo; PYE = patient-years of exposure; PYR = patient-years at risk.

Notes: Percentages for CTCAE increases are based on number of participants at risk for specified abnormality. IRs are calculated based on PYE.

Lipid increases

The proportion of participants who had a categorical increase (according to National Cholesterol Education Program criteria) for total cholesterol and LDL-C was higher in the baricitinib 2-mg and 4-mg groups compared to the placebo group (Table 32). Categorical increases of total cholesterol and LDL-C were numerically more frequent for the baricitinib 4 mg dose than for the 2 mg dose. The proportion of participants who had a categorical decrease for HDL-C tend to be lower in the baricitinib 2-mg and 4-mg groups compared to the placebo group (Table 32). A numerically higher proportion of participants had categorical increases (according to National Cholesterol Education Program criteria) for triglycerides in the baricitinib groups than in the placebo treatment group.

In the baricitinib 2-mg and 4-mg groups, the mean values slightly increased or remained stable from baseline up to Week 12 for total cholesterol (+0.10 and +0.20 mmol/L, respectively), LDL C (+0.02 and + 0.03 mmol/L, respectively), and HDL-C (+0.08 and +0.14 mmol/L, respectively). After Week 12 up to Week 24, the mean values remained stable.

In the **Ext BARI AA Adolescent** safety data sets, the IR of increases in total cholesterol, HDL-C and LDL-C were higher in the 4-mg group compared to the 2-mg group, IRs could not be compared. No new signals were observed from the **All BARI AA Adolescent** safety data set.

Table 32: Lipid changes in study JAIO.

	PC BARI AA Adolescents			Extended BARI AA Adolescents		All BARI AA Adolescents
	PBO n/NAR (%)	BARI 2 mg n/NAR (%)	BARI 4 mg n/NAR (%)	BARI 2 mg n/NAR (%) [IR]	BARI 4 mg n/NAR (%) [IR]	All Doses n/NAR (%) [IR]
Total Cholesterol NCEP Criteria Increase to 'High'	3/81 (3.7)	9/73 (12.3)	16/75 (21.3)	24/147 (16.3) [13.7]	43/152 (28.3) [21.0]	75/367 (20.4) [15.7]
LDL-C NCEP Criteria Increase to 'High'	1/83 (1.2)	6/77 (7.8)	13/78 (16.7)	20/155 (12.9) [11.4]	32/153 (20.9) [15.7]	58/379 (15.3) [12.1]
LDL-C NCEP Criteria Increase to 'Borderline High' or 'High'	4/71 (5.6)	9/65 (13.8)	13/59 (22.0)	27/131 (20.6) [15.4]	40/122 (32.8) [19.6]	78/313 (24.9) [16.3]
HDL-C NCEP Criteria Decrease to 'Low'	6/81 (7.4)	4/76 (5.3)	2/73 (2.7)	15/150 (10.0) [8.6]	4/139 (2.9) [2.0]	20/354 (5.6) [4.2]
HDL-C NCEP Criteria Increase to 'Acceptable'	8/15 (53.3)	11/16 (68.8)	15/21 (71.4)	23/33 (69.7) [13.1]	33/43 (76.7) [16.1]	58/81 (71.6) [12.1]
Triglycerides NCEP Criteria Increase to 'High'	6/84 (7.1)	9/73 (12.3)	10/76 (13.2)	22/149 (14.8) [12.6]	23/150 (15.3) [11.3]	49/369 (13.3) [10.2]

Abbreviations: AA = alopecia areata; BARI = baricitinib; C = cholesterol; HDL = high-density lipoprotein; IR = incidence rate; LDL = low-density lipoprotein;
n = number of participants in the specified category; PC BARI AA Adolescents = Placebo-controlled baricitinib alopecia areata adolescents; PBO = placebo; N = number of participants in the safety analysis set; NCEP = National Cholesterol Education Program; PYE = patient-years exposure.
Notes: Percentages are based on number of participants at risk for specified abnormality. IRs are calculated based on PYE.

Major Adverse Cardiovascular Events

MACE and other cardiac events included any potential MACE (cardiovascular death, myocardial infarction, and stroke) and other cardiovascular events (transient ischaemic attack, hospitalisation for unstable angina, hospitalisation for heart failure, serious arrhythmia, resuscitated sudden death, cardiogenic shock, and coronary revascularisations), VTEs, ATEs, and non-cardiovascular deaths.

No cases of MACE or cardiovascular events were reported in the entire JAIO study.

Venous Thromboembolic Events

Possible VTEs were identified by the study site or through medical review and were sent to a blinded, external Clinical Event Committee for adjudication.

No cases of VTEs were reported in the entire JAIO study.

Increases in Creatine phosphokinase

Increases in CPK were assessed using CTCAE criteria. Treatment-emergent AEs related to increased CPK were reviewed to identify any additional elevations in CPK that were not captured by laboratory values. Treatment-emergent AEs identified by the Rhabdomyolysis/myopathy SMQ were reviewed to determine whether the participant had an increased CPK at or near the time of the event onset.

The percentage of participants with any CTCAE grade increase (reflecting an increase in CPK) was higher in baricitinib 2 mg and baricitinib 4 mg compared with placebo. There was a higher frequency seen in the 2 mg dose compared to the 4 mg dose. Most increases were to CTCAE Grade 1 or 2. Increases to Grades 3 and 4 were reported more frequently with baricitinib 2 mg and 4 mg compared to placebo (Table 33).

No rhabdomyolysis events were reported. The frequencies and numbers of participants who reported 1 or more TEAE potentially related to muscle symptoms were: n=1 (1.2%), placebo (myalgia); baricitinib (myalgia), n=2 (2.4%). Participants in the baricitinib groups who reported a myalgia PT also reported a Grade 1 CPK increase during the study; however, these were transient, not reported at the same time as the PT and for 1 participant, a high CPK value was seen at baseline.

In the **Ext** and **All BARI AA Adolescent safety data sets**, frequencies were slightly increased for 2 and 4 mg baricitinib compared to the placebo-controlled period. There were no cases of rhabdomyolysis. A dose response was seen for the Grade 3 or higher CPK increases; all events of Grade 3 or more increases were transient, and most were attributed to exercise.

Table 33: Increases in CPK - CTCAE criteria

	PC BARI AA Adolescents			Extended BARI AA Adolescents		All BARI AA Adolescents
	PBO n/NAR (%)	**BARI 2 mg n/NAR (%)**	**BARI 4 mg n/NAR (%)**	**BARI 2 mg** n/NAR (%) [IR]	**BARI 4 mg** n/NAR (%) [IR]	**All Doses** n/NAR (%) [IR]
Any CTCAE increase	20/86 (23.3)	37/83 (44.6)	27/83 (32.5)	76/166 (45.8) [43.4]	79/165 (47.9) [38.6]	179/410 (43.7) [37.4]
Increase to CTCAE Grade ≥3 (>5 ×ULN)	3/86 (3.5)	4/80 (5.0)	4/83 (4.8)	7/163 (4.3) [4.0]	12/164 (7.3) [5.9]	24/404 (5.9) [5.0]

Abbreviations: AA = alopecia areata; BARI = baricitinib; CPK = creatine phosphokinase; CTCAE = Common Terminology Criteria for Adverse Events; IR = incidence rate; n = number of participants in the specified category; PC BARI AA Adolescents = placebo-controlled
baricitinib alopecia areata adolescents; PBO = placebo; N = number of participants in the safety analysis set; PYE = patient-years of exposure.
Notes: Percentages for CTCAE increases are based on number of participants at risk for specified abnormality. IRs are calculated based on PYE.

Malignancies

Malignancies were identified using terms from the Malignant tumours SMQ. Malignancies excluding NMSCs and NMSCs were handled separately.

A malignancy event was reported after the data cutoff date, in a patient in the baricitinib group. A diagnosis of sarcoma was made and the participant was discontinued from the study. Surgery took place and the event was resolved (follow-up ongoing).

No malignancies of Nonmelanoma skin cancer were reported.

In the **All BARI AA Adolescent safety data set**, no additional cases of malignancy nor NMSC were reported.

Abnormal Hepatic Tests and Liver injury

Mean and median AST and ALT in the baricitinib 2- and 4-mg groups remained stable and similar to the placebo group. The frequency of an increase of ALT or AST to ≥3 x ULN was low in the baricitinib groups (n=2 and n=1, respectively) and similar compared with the placebo group (Table 34). All 3 cases of ALT or AST increase on baricitinib were transient while baricitinib treatment continued. No participant had an increase ≥5 x ULN and no participant had both an increase of transaminases ≥3 x ULN and TBL ≥2 x ULN (potential Hy's law criterion).

None of these events were serious and there were no temporary interruptions or discontinuations for hepatobiliary events other than the event in the placebo group. Events in the baricitinib groups were transient while baricitinib was continued and/or occurred in participants with increased baseline levels.

In the **Ext** and **All BARI AA Adolescent** safety data sets, the IRs for ALT, AST, TBL, and ALP increases were slightly higher compared to the placebo-controlled period, but overall low and without dose dependency. For those with ALT and AST increases ≥5 x ULN, drug interruptions were sufficient for normalisation and reintroduction was successful. The patient with ALT ≥10 x ULN recovered after drug interruption; a potential cause was a rapid weight gain combined with clotting of the blood sample. Of the seven patients with increased TBL, three met criteria for possible Hy's law, of whom 1 appeared to have Gilbert syndrome and another steatohepatitis. Only two patients had ALP ≥2 x ULN, which returned to normal in one patient without interruption and remained high in the other.

Table 34: Increase of ALT, AST, ALP

	PC BARI AA Adolescents			Extended BARI AA Adolescents		All BARI AA Adolescents
	PBO n/NAR (%)	BARI 2 mg n/NAR (%)	BARI 4 mg n/NAR (%)	BARI 2 mg n/ N-obs (%) [IR]	BARI 4 mg n/ N-obs (%) [IR]	All Doses n/ N-obs (%) [IR]
ALT ≥3×ULN	2/88 (2.3)	1/83 (1.2)	1/84 (1.2)	3/166 (2.4) [2.3][a]	4/167 (2.4) [2.0]	9/414 (2.2) [1.9]
ALT ≥5×ULN	0	0	0	Redacted	Redacted	2/414 (0.5) [0.4]
ALT ≥10×ULN	0	0	0	0	0	1/414 (0.2) [0.2]
AST ≥3×ULN	Redacted	Redacted	Redacted	3/166 (1.8) [1.7]	3/167 (1.8) [1.5]	6/414 (1.4) [1.3]
AST ≥5×ULN	0	0	0	Redacted	Redacted	1/414 (0.2) [0.2]
AST ≥10×ULN	0	0	0	0	0	0
TBL ≥2×ULN	Redacted	Redacted	Redacted	3/166 (2.4) [2.3][c]	4/167 (2.4) [2.0]	7/414 (2.4) [2.1][d]
ALP ≥2×ULN	0	0[c]	0	Redacted	Redacted	2/414 (1.0) [0.8][g]

Abbreviations: AA = alopecia areata; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BARI = baricitinib; n = number of participants in the specified category; PC BARI AA Adolescents = Placebo-controlled baricitinib alopecia areata adolescents; PBO = placebo; N = number of participants in the treatment group; TBL = total bilirubin; ULN = upper limit of normal.

[a] One other participant with elevation of ALT ≥3 ×ULN was included in the source table but had an elevation at baseline. The percentage and IR in this table reflect the n in the source table.

[b] One participant with elevation of TBL ≥2 ×ULN was included in the source table.

[c] One participant with elevation of TBL ≥2 ×ULN was included in the source table. The percentage and IR in this table reflect the n in the source table.

[d] Three participants with elevation of TBL ≥2 ×ULN were included in the source table but had an elevation of TBL ≥2 ×ULN at baseline. The percentage and IR in this table reflect the n in the source table.

[e] One participant with elevation of ALP ≥2 ×ULN was included in the source table.

[f] One other participant with elevation of ALP ≥2 ×ULN was included in the source table. The percentage and IR in this table reflect the n in the source table.

[g] Two other participants with elevation of ALP ≥2 ×ULN was included in the source table but had an elevation of ALP ≥2 ×ULN at baseline. The percentage and IR in this table reflect the n in the source table.

Gastrointestinal perforation

No GI perforations were reported in the entire JAIO study.

Depression and suicidality

Two participants with no suicidal ideation or behaviour at baseline reported suicidal ideation during treatment.

- 1.1% participants in the placebo group reported suicidal ideation. The study drug was interrupted and restarted.
- 1.2% participants in the baricitinib group eventually performed suicidal behaviour and were hospitalised. Study drug was permanently discontinued.
- 1.2% participants in the baricitinib group reported suicidal ideation and an SAE of "exacerbation of depression" prior to this. The study drug was not interrupted.

A similar frequency of participants in the placebo, baricitinib 2- and 4-mg groups reported suicidal ideation based on the C-SSRS (Table 35). The most serious category was "Non-specific active suicidal thoughts" (Category 2) in the 2-mg group.

In the **Ext** and the **All BARI AA Adolescent** safety sets, the IR for PT depression and suicide/self-injury, based on MedDRA SMQ was slightly higher when compared to the placebo-controlled period for the 4 mg baricitinib dose (IR 2.5 versus 1.8). Of the 6 patients who reported depression or major depression in the updated All BARI AA Adolescents data set, all events, except 1, were deemed unrelated by the investigator.

Table 35: Suicidal ideation or behaviour, depression and self-injury (C-SSRS, MedRA SMQ)

	PC BARI AA Adolescents			Extended BARI AA Adolescents		All BARI AA Adolescents
	PBO N = 88 PYE = 58.3 n (%) [IR]	BARI 2 mg N = 83 PYE = 57.0 n (%) [IR]	BARI 4 mg N = 85 PYE = 57.1 n (%) [IR]	BARI 2 mg N = 166 PYE = 175.1 n (%) [IR]	BARI 4 mg N = 168 PYE = 204.4 n (%) [IR]	All Doses N = 415 PYE = 478.9 n (%) [IR]
Suicidal ideation, based on C-SSRS	2 (2.3)	1 (1.2)	1 (1.2)	3 (1.8)	3 (1.8)	8 (1.9)
Suicidal behaviour, based on C-SSRS	Redacted	Redacted	Redacted	Redacted	Redacted	3 (0.7)
Self-injurious behaviour without suicidal intent, based on C-SSRS	1 (1.1)	2 (2.4)	1 (1.2)	2 (1.2)	1 (0.6)	4 (1.0)
TE depression and suicide/self-injury, based on MedDRA SMQ	Redacted	Redacted	Redacted	3 (1.8) [1.7]	5 (3.0) [2.5]	11 (2.7) [2.3]

Abbreviations: All BARI AA Adolescents = All baricitinib alopecia areata adolescents; C-SSRS = Columbia Suicide Severity Rating Scale;
Ext BARI AA Adolescents = Extended baricitinib alopecia areata adolescents; IR = incidence rate; MedDRA = Medical Dictionary of Regulatory Activities; n = number of participants in the specified category; N = number of participants in the safety analysis set; PC BARI AA Adolescents = Placebo-controlled baricitinib alopecia areata adolescents; PBO = placebo; PT = preferred term; PYE = participant-years of exposure; SMQ = standardised MedDRA Query;
TE = treatment-emergent.

a N = 84 for the C-SSRS data.
b N = 235 for the C-SSRS data.
c The PTs included depression (BARI), disturbance in attention (BARI).

Growth and maturation

Growth (height, weight, and BMI) was assessed longitudinally throughout the study. Wrist/hand and knee MRI or X-rays were collected to assess radiographic bone age and the difference between chronological age and radiographic bone age over time using standard imaging methods for X-rays or MRI. Wrist/hand and knee MRIs or X-rays are to be collected at visit 2 (0 weeks from initiation of study drug), weeks 24 and 52, and every 24 weeks thereafter to week 136 or until skeletal maturity is confirmed. Growth plate closure was assessed at 4 locations (distal ulna, distal radius, distal femur, and proximal tibia). Age of menarche was recorded.

Mean changes in **height, weight, and BMI** from baseline to Week 36 for Z-scores were near zero (less than ±0.14) for all 3 growth parameters across all treatment groups (Table 36). Mean changes in height, weight, and BMI percentiles show that endpoint (36 week) percentiles were similar to baseline percentiles (less than ±3.74 percentile change) across all treatment groups for height, weight, and BMI.

Mean changes from baseline to Week 52 for Z-scores continued to be near zero (less than ± 0.14) for all growth parameters (height, weight, and BMI) across all datasets.

Table 36: Change in percentiles and z-score for height, weight and BMI in study JAIO

	PC BARI AA Adolescents			Extended BARI AA Adolescents		All BARI AA Adolescents
	Week 36 Mean Change*			Week 52 Mean Change		
	PBO (N = 88)	BARI 2 mg (N = 83)	BARI 4 mg (N = 85)	BARI 2 mg N = 83	BARI 4 mg N = 85	All Doses N = 245
Height						
Percentile change, mean (SD)	-1.17 (10.60)	-0.21 (9.48)	-0.11 (8.17)	-2.02 (8.744)	1.27 (9.994)	-1.58 (9.567)
Z-score change, mean (SD)	-0.04 (0.31)	0.01 (0.30)	-0.02 (0.27)	-0.06 (0.280)	0.05 (0.337)	-0.05 (0.314)
Weight						
Percentile change, mean (SD)	-1.09 (11.38)	1.82 (8.38)	3.22 (9.12)	0.85 (10.730)	2.83 (9.162)	1.96 (10.019)
Z-score change, mean (SD)	-0.05 (0.35)	0.04 (0.27)	0.12 (0.33)	0.02 (0.338)	0.10 (0.347)	0.06 (0.345)
BMI						
Percentile change, mean (SD)	-1.86 (12.72)	2.28 (10.66)	3.74 (11.40)	1.21 (12.775)	3.43 (10.233)	2.48 (11.570)
Z-score change, mean (SD)	-0.05 (0.42)	0.04 (0.33)	0.14 (0.40)	0.02 (0.395)	0.13 (0.371)	0.08 (0.384)

Abbreviations: All BARI AA Adolescents = All baricitinib alopecia areata adolescents; BARI = baricitinib; BMI = body mass index; Ext BARI AA Adolescents = Extended baricitinib alopecia areata adolescents; N = number of participants in the safety population; PC BARI AA Adolescents = Placebo-controlled baricitinib alopecia areata adolescents; PBO = placebo; SD = standard deviation.

Z-scores are standard scores that indicate how far and in what direction an item deviates from its distribution's mean, expressed in units of its distribution's standard deviation.

BMI is calculated as weight (kg)/ ([height (m) ^{2}]).

*Extended BARI AA and All BARI AA from the initial submission is not included in this table as change from BL data were collected at Week 36 (therefore the data is the same as PC BARI AA).

At Week 24, the mean difference between **chronological age and bone age** (that is, chronological age minus bone age) remained similar to the baseline difference and was less than 1 year on average (Table 37). There were no participants receiving baricitinib who had a difference of 2 years or less at baseline who shifted into the 2 years or more category. At Week 52, the mean difference between chronological age and radiographic bone age remained similar to the baseline difference and on average was less than 1 year in each treatment group.

Table 37: Mean difference between chronological age and bone age (W24, W52)

	PC BARI AA Adolescents			Extended BARI AA Adolescents		All BARI AA Adolescents
	Week 24 Mean Change*			Week 52 Mean Change		
Observed Mean Difference in Chronological Age vs. Bone Age	PBO (N = 88)	BARI 2 mg (N = 83)	BARI 4 mg (N = 85)	BARI 2 mg N = 166	BARI 4 mg N = 168	All Doses N = 415
Baseline, Mean (SD)	-0.33 (1.71)	-0.53 (1.57)	-0.28 (1.57)	-0.55 (1.524)	-0.47 (1.521)	-0.51 (1.506)
Mean change (SD)	-0.10 (1.56)	-0.36 (1.58)	-0.12 (1.64)	-0.08 (1.481)	-0.23 (1.520)	-0.19 (1.477)

Abbreviations: All BARI AA Adolescents = All baricitinib alopecia areata adolescents; BARI = baricitinib; Ext BARI AA Adolescents = Extended baricitinib alopecia areata adolescents; N = number of participants in the safety population; PC BARI AA Adolescents = Placebo-controlled baricitinib alopecia areata adolescents; PBO = placebo; SD = standard deviation; vs. = versus.

Note: Data in source data are available to Week 88. However, a meaningful interpretation of the data was not possible due to low numbers.

One participant was enrolled in the <30 kg weight category prior to protocol amendment(d) and was randomized to Placebo, and re-randomized to BARI 1 mg at Week 36. At Week 52, the participant was up-titrated to BARI 4 mg (high dose based on weight category ≥30 kg at Week 52).

*Extended BARI AA and All BARI AA from the initial submission is not included in this table as the change from BL data were collected at Week 24 (therefore the data is the same as PC BARI AA).

From the classification of the state of growth-plate closure at the knee: open, narrowed, partially closed, closed, there did not appear to be a different pattern regarding (early) growth plate closure for females and males treated with baricitinib 4 mg or placebo, from baseline to week 24 and week 52.

Across all treatment groups, most participants had achieved **menarche** at study baseline (mean age of menarche 12.01 to 12.44 years). Ten out of the 14 participants without menarche at baseline achieved menarche during the study with a mean age of 14.51 years in the placebo group, 13.70 years in 2-mg and 13.32 years in 4-mg groups. The mean age of participants who had not reached menarche postbaseline remained comparable between the placebo (12.92 years) and the baricitinib-treated groups (13.07 and 13.02 years). The age of onset of menarche in the All BARI AA Adolescents data remained consistent with the expected age of puberty in females (12 to 13 years old); the number of patients without menarche post baseline was low (n = 6), with a mean age of 13.34 years.

Laboratory findings

The number and percentage of participants with TE high and low laboratory results at any time were summarised by group. Central laboratory reference ranges were used to define the high and low limits.

Chemistry

Except for the lipids, hepatic enzymes, and CPK values presented as AESI, there were no chemistry analytes with changes on group level over the 36-week placebo-controlled period.

Safety in special populations

Not applicable. In study JAIO, also children <12 years of age are/will be included in a staggered approach. These data are not yet available.

Safety related to drug-drug interactions and other interactions

The known drug-drug interaction information and potential effects on other drugs were part of the original RA submission and are reflected in the current and proposed labelling for baricitinib. No additional drug-drug interaction studies were completed as part of the adolescent PC cohort.

Discontinuation due to adverse events

Permanent discontinuation

During the **placebo-controlled study period,** a total of 3 participants (2 in the placebo group and 1 in the baricitinib group) permanently discontinued from the study drug (Table 38) due to the AEs of: Flat affect (baseline age <15 years), resolved prior to discontinuation; Hypertransaminasaemia (baseline age <15 years), ongoing at discontinuation; Myalgia (baseline age <15 years), ongoing at discontinuation.

Four patients discontinued due to an AE in the **Ext BARI AA Adolescent** safety data set; altogether, 5 patients permanently discontinued the study drug (**All BARI AA Adolescent** safety data set). The IR was 1.0; more patients in the 4 mg compared to the 2 mg baricitinib groups discontinued (IR 1.5 *versus* 0.6). In baricitinib groups besides flat affect (baseline age <15 years, recovered), suicide attempt (baseline age ≥15 years, recovered), neutropenia (baseline age ≥15 years, recovered), asthenia (baseline age ≥15 years, recovered), and sarcoma (baseline age <15 years, recovered) were the AEs that led to permanent discontinuation.

Table 38: Adverse Events leading to permanent discontinuation in study JAIO

	PC BARI AA Adolescents			Ext BARI AA Adolescents		All BARI AA Adolescents
System Organ Class Preferred Terms	**PBO N = 88 PYE = 58.3 n (%) [IR]**	**BARI 2 mg N = 83 PYE = 57.0 n (%) [IR]**	**BARI 4 mg N = 85 PYE = 57.1 n (%) [IR]**	**BARI 2 mg N = 166 PYE = 175.1 n (%) [IR]**	**BARI4 mg N = 168 PYE = 204.4 n (%) [IR]**	**All Doses N = 415 PYE = 478.9 n (%) [IR]**
Participants with ≥1 AE	Redacted	Redacted	Redacted	1 (0.6) [0.6]	3 (1.8) [1.5]	5 (1.2) [1.0]
Psychiatric disorders	Redacted	Redacted	Redacted	Redacted	Redacted	2 (0.5) [0.4]
Flat effect	Redacted	Redacted	Redacted	Redacted	Redacted	1 (0.2) [0.2]
Suicide attempt	0	0	0	0	0	1 (0.2) [0.2]
Blood and lymphatic system disorders	0	0	0	Redacted	Redacted	1 (0.2) [0.2]
Neutropenia	0	0	0	Redacted	Redacted	1 (0.2) [0.2]
General disorders and administration site conditions	0	0	0	Redacted	Redacted	1 (0.2) [0.2]
Asthenia	0	0	0	Redacted	Redacted	1 (0.2) [0.2]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	Redacted	Redacted	1 (0.2) [0.2]
Sarcoma	0	0	0	Redacted	Redacted	1 (0.2) [0.2]
Hepatobiliary disorders	Redacted	Redacted	Redacted	0	0	0
Hypertransaminasaemia	Redacted	Redacted	Redacted	0	0	0

	PC BARI AA Adolescents			Ext BARI AA Adolescents		All BARI AA Adolescents
System Organ Class Preferred Terms	**PBO N = 88 PYE = 58.3 n (%) [IR]**	**BARI 2 mg N = 83 PYE = 57.0 n (%) [IR]**	**BARI 4 mg N = 85 PYE = 57.1 n (%) [IR]**	**BARI 2 mg N = 166 PYE = 175.1 n (%) [IR]**	**BARI4 mg N = 168 PYE = 204.4 n (%) [IR]**	**All Doses N = 415 PYE = 478.9 n (%) [IR]**
Musculoskeletal and connective tissue disorders	Redacted	Redacted	Redacted	0	0	0
Myalgia	Redacted	Redacted	Redacted	0	0	0

Abbreviations: AA = alopecia areata; AE = Adverse Events; BARI = baricitinib; Ext BARI AA= extended baricitinib alopecia areata; IR = incidence rate; N = number of participants in the analysis population; n = number of participants in the specified category; PC BARI AA Adolescents = Placebo-controlled baricitinib alopecia areata adolescents; PBO = Placebo; PYE = patient-years exposure; PT = preferred term; SOC = system organ class.
Note: IRs are calculated based on participant-years at risk.

Temporary interruptions

In the **PC BARI AA Adolescent** safety data set, the number of drug interruptions due to an Adverse Event and the proportions of patients with at least 1 drug interruption, were similar for the placebo and baricitinib 4 mg groups (Table 39). The duration of drug interruption was shorter in the baricitinib 4 mg group, as compared to the 2 mg and placebo groups (Table 39).

Events in the Infections and infestations SOC were responsible for most of the temporary interruptions across treatment groups. Influenza (n=2 on 2 mg and n=1 on 4 mg) and Neutropenia (n=2 on 4 mg) were the only AEs in the baricitinib groups that led to treatment interruption for more than 1 participant.

Table 39: Temporary interruptions of study drug in study JAIO *(cut-off date 10 September 2024)*

	PC BARI AA Adolescents			Ext BARI AA Adolescents	
	PBO N=88	**BARI 2 mg N=83**	**BARI 4 mg N=85**	**BARI 2 mg N=83**	**BARI 4 mg N=85**
Total number study drug interruptions (n)	13	7	12	8	12
With resumption of study drug (n)	12	7	12	8	12
Without resumption of study drug (n)	1	0	0	0	0
Number of participants with study drug interruption, n (%)					
≥1	11 (12.5)	7 (8.4)	12 (14.1)	8 (9.6)	12 (14.1)
≥2	2 (2.3)	0	0	0	0
≥3	0	0	0	0	0
Duration of dose interruption (days), mean (SD)	31.0 (51.4)	22.3 (21.8)	8.5 (5.6)	21.1 (20.49)	8.5 (5.55)
Reason for study drug interruption, n (%)					
AE[a]	8 (9.1)	3 (3.6)	8 (9.4)	4 (4.8)	8 (9.4)
Abnormal laboratory results	3 (3.4)	3 (3.6)	1 (1.2)	3 (3.6)	1 (1.2)
Protocol	0	1 (1.2)	1 (1.2)	1 (1.2)	1 (1.2)
Investigator decision	0	0	2 (2.4)	0	2 (2.4)

Abbreviations: All BARI AA Adolescents = All baricitinib alopecia areata adolescents; eCRF = electronic case report form; Ext BARI AA Adolescents = Extended baricitinib alopecia areata adolescents; n = number of participants in the specified category; N = number of participants in the analysis population; PC BARI AA Adolescents = Placebo-controlled baricitinib alopecia areata adolescents.

[a] One participant in the Placebo arm and 2 participants in the baricitinib 2 mg arm had laboratory abnormalities leading to treatment interruption that were reported as AEs by the respective sites. Based on sites' records in eCRF, these participants are presented under "abnormal laboratory result" in this table while they appear under "AE leading to treatment interruption"

In the **Ext BARI AA Adolescents** safety data set, the IRs of AEs leading to temporary interruption from the study drug were similar in the 2 mg (n = 21/166) and 4 mg (n = 24/168) groups (IR: 12.9 and 12.8, resp). Infections and infestations was the most common SOC with AEs that led to temporary interruption (2 mg [IR 7.7] and 4 mg [IR 5.6]); second most common was the SOC Investigations. In the baricitinib 4 mg group, the most frequently reported event leading to temporary interruption was Neutropenia (IR 2.0). In the **All BARI AA Adolescents** safety data set, the IR of AEs leading to temporary interruption was 11.9 (n = 53/415), and the most frequently reported event leading to temporary interruption was Influenza (IR 1.0).

Post marketing experience

Baricitinib was granted marketing authorisation in the EU for the treatment of JIA on 15 September 2023 and since then, it has been authorised in 41 countries. Also, on 18 October 2023, baricitinib was granted marketing authorisation in the EU for the treatment of paediatric AD and since then, it has been authorised in 40 countries.

Overdose

There have been 132 reports of overdose, including the terms overdose, accidental overdose, and intentional overdose. Most patients took higher baricitinib doses intentionally for pain relief. Three of the 132 reports were serious including 1 fatal case of unspecified overdose for which minimal information was provided for assessment.

Four (2.19%) child overdose cases were identified, all involving the administration of incorrect baricitinib doses. Five (2.73%) adolescent cases were identified, with 4 cases involving adolescents administered incorrect baricitinib doses, and 1 case where the adolescent accidentally took 4 mg twice daily.

All child and adolescent overdose events, except one, were non-serious. Event outcomes were not reported.

Serious infections

Serious infections were uncommonly reported (n=3269 events; reporting rate: 0.6 per 100 PYE and 0.17% of total participants exposed). The most common serious infections reported were: Pneumonia, Herpes zoster, COVID-19, and Sepsis. Of all infections, 1.5% (n=245 events) were fatal, none of which in the paediatric population.

There was a total of 61 infections reported in the paediatric population. Also in the paediatric population, the most commonly reported infections were Herpes zoster (n=8) and Nasopharyngitis (n=7). There were 23 events of serious infections reported among the paediatric population. The PT with more than 1 event were Herpes zoster (n=4), Pneumonia (n=3), and Pneumocystis jirovecii pneumonia (n=2). A total of 16 of the 23 events had missing medical history or concomitant medications. Of the 23 events, 17 had a seriousness criteria of new or prolongation of a current hospitalisation.

Haematological events

Haematological events reported in paediatric cases include: 4 events of Anaemia, 1 of these patients also reported an event of Thrombocytopenia; 1 event of Thrombocytopenia; 1 event of Neutropenia; 1 event of Lymphopenia; 1 event of Neutrophil count decreased; 1 event of Lymphocyte count decreased; 1 event of Platelet count decreased. There were no paediatric cases of Agranulocytosis reported.

Lipids

One event of Dyslipidaemia was reported in a patient treated for JIA. Three events were reported in adolescents: 2 cases of Blood triglycerides increased and 1 case of Blood cholesterol increased.

ATE and VTE

No ATE was reported in the paediatric population.

A (0.14%) paediatric case was reported as a fatal event of PE in a patient treated for COVID 19, medical history was not provided but the patient was exposed to concomitant medications including azithromycin, ceftriaxone, dexamethasone, enoxaparin, famotidine, and remdesivir.

GI perforations

One (1.20%) case of large intestine perforation was reported which coincided with COVID-19 treatment.

Myopathy

In the paediatric population, 1 case (0.24%) of CPK increase was reported in the literature. Six (1.22%) cases of CPK increase were reported in adolescents treated for AA (n=3), AD (n=2), and unknown indication (n=1).

Malignancy

One case of Fibrosarcoma was reported.

Hepatotoxicity

Eight events were reported in paediatric cases, including: 1 event of Hepatitis, 2 events of Transaminases increased, 2 events of Hepatic enzymes increased, 1 event of Portal hypertension, and 2 events of Alanine aminotransferase increased.

2.5.1. Discussion on clinical safety

Based on the placebo-controlled phase of the pivotal study, the safety profile of baricitinib in adolescents with AA is in line with the known safety profile in adolescents with JIA and AD and adults. The occurrence of (mild) treatment-emergent AEs was higher in the baricitinib 4 mg group, as compared to the 2 mg and placebo groups, primarily by mild AEs with a clear dose-response pattern. SAEs, severe AEs and discontinuations due to an AE were infrequent. Prolonged exposure up to 52 weeks did not markedly change the picture; a comparable pattern was seen as in the placebo-controlled period although the incidence rate was lower for patients with at least one treatment-emergent AE, while the IR for moderate TEAE's was somewhat higher.

Over the 36 weeks of the placebo-controlled period of the pivotal study, proportions of patients with at least 1 treatment-emergent AE were 71% in the baricitinib 4 mg group, 60% in 2 mg group and 53% in the placebo group. While the occurrence of severe and moderate AEs was numerically similar across the 3 treatment groups, the higher frequency of AEs in baricitinib treated patients was due to an increase in the occurrence of mild AEs in the placebo-controlled period. The occurrence of mild AEs has a dose-response relationship.

With prolonged follow-up up to 52 weeks, a comparable pattern of higher proportions of patients with at least 1 TEAE in the baricitinib 4 mg group compared to the 2 mg group was seen (81% versus 70%), but the IRs were lower compared to the placebo-controlled period for both doses, mainly due to

considerably lower IRs for the mild TEAE's in both dose groups, while the IRs for moderate TEAEs were somewhat increased in both dose groups compared to the IRs in the placebo-controlled period.

In the placebo-controlled period, few **SAEs** occurred and the two events in the baricitinib 4 mg group (IR 3.5) were not considered to be treatment related based on the case descriptions. In the baricitinib 2 mg group, no SAEs were reported. With prolonged follow-up up to 52 weeks, 12 SAEs were reported; 3 in baricitinib 2 mg (IR 1.1) and 9 in baricitinib 4 mg group (IR 4.0). This means that there seems to be no increased risk for SAEs with prolonged use, which is essential given the anticipated chronic use of the product. Considering all exposed patients to baricitinib, 17 SAEs in 15 patients (IR 3.2) were reported. Most were single events; (major) depression was reported three times. Five SAEs were clustered in the SOC Psychiatric disorders ((major) depression (3 cases), somatic symptom disorder, suicide attempt), and four SAEs were clustered in the SOC Injury, poisoning, and procedural complaints (upper and lower limb fracture, ligament sprain, toxicity to various agents). The vast majority of SAEs was considered not related to baricitinib. For example, the SOC Injury, poisoning, and procedural complaints contained PTs ligament sprain, fractures, and toxicity of diverse agents, which were all not related to the study drug but are more often seen in adolescents due to their lifestyle.

There were **no deaths** in the JAIO study.

During the placebo-controlled period, **severe AEs** and **permanent discontinuations due to an AE** were infrequent and the occurrence was similar for placebo and baricitinib 4 mg. Temporary interruptions due to an AE were more common but also with a similar frequency for placebo and baricitinib 4 mg groups. With prolonged exposure up to 52 weeks, severe AEs and permanent discontinuations due to AEs were still infrequent but more common in baricitinib 4 mg dose compared to the 2 mg dose. These observations remained consistent when considering all patients exposed to any dose of baricitinib.

There was an overall higher frequency of **treatment-emergent AEs** (TEAEs) in the baricitinib 4 mg group compared with placebo. Overall, the AEs that were more frequent in the baricitinib treated groups were in line with the known ADRs, including acne, headache, upper respiratory tract infections, blood CPK increased, neutropenia, ALT increased and blood cholesterol increased.

With prolonged exposure up to 52 weeks, the most common treatment emergent AEs in the 4 mg baricitinib group were comparable to the placebo-controlled period, i.e. acne, nasopharyngitis, headache, and upper respiratory tract infections. Although IRs in the 4 mg baricitinib group generally appeared similar to more favourable with prolonged exposure compared to the placebo-controlled period, higher IRs compared to the placebo-controlled period were seen in the 4 mg baricitinib group for vomiting, cough, pneumonia, and folliculitis. Except for cough and vomiting, these were already included as ADR in section 4.8 of the SmPC and were thus no new safety signals. For the baricitinib 4 mg group, the IRs for cough were similar to placebo (IR 3.5 for 4 mg baricitinib and placebo) and for vomiting no dose response was observed and it concerned 4 cases only. Both were thus not considered an ADR. No new treatment-emergent AEs were identified when considering all exposed patients to any dose baricitinib. Altogether, TEAEs were most common in the baricitinib 4 mg group and generally did not increase in frequency with prolonged exposure.

Comparison of TEAEs in the adult AA population application for baricitinib 4 mg, occurring with a frequency of ≥ 2% during the placebo-controlled period, were (next to already existing ADRs) COVID-19, ligament sprain, anxiety, Influenza-like illness, tinea versicolor, and eosinophilia. These were not considered ADRs because absolute numbers in the adolescents were very low (3 or less), a dose response relation was absent, events were mild to moderate at most, and / or the condition was acceptably more common in the general adolescent population compared to the adult population (e.g. ligament sprain). Comparison of TEAEs in the adult AA population observed during prolonged exposure up to 52 weeks for baricitinib 4 mg based on frequency category and / or an IR no factor greater than

1.5, revealed that (next to already existing ADRs) influenza, cough, vomiting, ligament sprain, asthenia, epistaxis, dysmenorrhea, seborrhoeic dermatitis, depression, pyrexia, leukopenia, and eosinophilia were more common with prolonged follow-up in adolescents compared to adults. For most TEAEs, however, the data suggested that inclusion as ADR was not warranted due to the absence of a (consistent) dose response relationship across data sets and the adult and adolescent populations, a lower IR in the Ext and / or All BARI AA Adolescent safety data set compared to the PC BARI AA Adolescent dataset, and / or a close-to-similar IR for adolescents and adults in the All BARI AA safety data sets. Further, some TEAEs (like ligament sprain, epistaxis, and dysmenorrhea) are by nature generally more common in adolescents compared to adults, irrespective of baricitinib use. Treatment-emergent AEs eosinophilia, seborrhoeic dermatitis, and leukopenia are discussed in more detail below.

Eosinophilia was more frequent (IR 1.8 and 2.7 for 2 and 4 mg baricitinib groups) compared to placebo (IR 1.7) and it was considered that this might be an ADR. However, with prolonged exposure the IRs were considerably lower (1.1 and 3.0 for baricitinib 2 mg and 4 mg resp.) compared to the placebo-controlled period, with 1.7 when considering all to baricitinib exposed patients. Further, no cases were reported in adults, and there is no clear mechanistic plausibility for a JAKi causing eosinophilia. Half of the patients with eosinophilia appeared to have a medical history of atopic dermatitis and / or allergies which might be a reasonable explanation, and all but 1 had pre-existing eosinophilia at study entry. Therefore, eosinophilia was not considered an ADR.

For **seborrhoeic dermatitis**, IRs during 52 weeks follow-up and among all exposed patients in both the Ext and the All BARI AA safety data sets in adolescents were higher compared to adults (2.5 versus 1.1 and 1.5 versus 0.9 resp.) while in the general population the other way around would have been expected (*Polaskey, JAMA Dermatol, 2024*). As the data suggest a dose response in both adults and adolescents during prolonged exposure, further evaluation was needed to determine whether this could be an ADR. Compared to the adult AA population, indeed IRs were slightly higher for the adolescents with AA, with higher IRs in the 4 versus the 2 mg dose in the All BARI AA safety data set. However, lower IRs were seen in the safety data sets supporting the paediatric AD and JIA indications (IRs of 0.4 and 0.3 resp.), compared to the paediatric AA population, and dose response could not be observed. The AD and JIA study populations comprised patients 2-18 years of age in contrast to the adolescent AA population (12 – 18 years). As seborrhoeic production increases especially during adolescence, this may be an explanation for increased rates compared to the other paediatric indications, rather than that the occurrence of seborrhoeic dermatitis is drug-induced. Further, as events were predominantly mild and mostly resolved / resolving, without a clear dose dependency, it was concluded that seborrhoeic dermatitis is unlikely an ADR of baricitinib.

For **leukopenia**, higher IRs were seen in adolescents compared to adults when exposure to baricitinib 4 mg is prolonged up to 52 weeks (IRs 2.0 for adolescents and 0.5 for adults), and when considering all exposed patients to baricitinib (IRs 1.3 for adolescents and 0.3 in adults); a dose response could not be excluded. No cases were seen in the placebo group Events appeared to coincide mainly with reported neutropenia and were all Grade 2 or lower. The IRs in the All BARI groups in paediatric AD and JIA were lower than in AA adolescents, and in paediatric AD no dose response was observed. Thus, additional inclusion of leukopenia as ADR was considered not warranted.

Psychiatric disorders appeared to cluster in the baricitinib group. The 5 instances of psychiatric disorders were cases of: anxiety, depression, flat affect, nervousness. There was a case of post-traumatic stress disorder in the placebo group. Up to now, psychiatric disorders have not been regarded as ADR of baricitinib and the current data do not point to an increased risk of depression or suicidal ideation/behaviour among those treated with baricitinib, as assessed by the C-SSRS or occurrences of suicidal behaviour. Therefore, the clustering of diverse psychiatric disorders is considered as a chance finding.

The Applicant evaluated an extensive list of safety topics of special interest. For this report it is mainly focussed on those **AESI** that are listed in the Safety Concerns of the RMP; these are discussed below. No new safety issues arose.

There was no notable increase in **serious or opportunistic infections**, MACE, VTE/ATE, or hepatotoxicity in the adolescent dataset, although these remain important potential risks and require ongoing surveillance. The main haematological changes were neutropenia and thrombocytosis that were clearly more frequent in the baricitinib 4 mg group. Both are already included as ADR in the SmPC.

CPK increases more than 5 x ULN are known ADRs for baricitinib. The occurrence of increased CPK was higher for baricitinib 2 mg and baricitinib 4 mg compared to placebo, but no dose-effect was apparent. Elevations in CPK were mostly asymptomatic and were not associated with muscle related symptoms in the same period of time; most were observed after exercise. Rhabdomyolysis was not observed.

A single **malignancy** was reported in a patient on baricitinib. Malignancies are included as important potential risk in the RMP. No further discussion in the context of adolescent AA is currently needed.

ALT and AST increases of 3 or more times the ULN are known ADRs for baricitinib. ALT and AST increases to ≥3 x ULN were infrequent in the adolescent AA data, and the present data do not otherwise show a hepatotoxic effect of baricitinib in adolescents with AA, neither during the placebo-controlled period (PC BARI AA Adolescent safety data set) nor during long-term exposure and when considering all exposed patients (Ext and All BARI AA Adolescent safety data sets).

GI perforation was evaluated as a safety topic of special interest for baricitinib. The reason was that Interleukin-6 signalling through signal transducers and activators of transcription 3 has an important role for protection of the intestinal barrier, and its inhibition may increase the risk of GI perforation. No events were reported.

The variables of **growth** (height, weight, BMI) and **maturation** (skeletal age and growth plate closure, occurrence of menarche) did not indicate a negative influence of treatment with baricitinib up to 52 weeks. Long-term safety in paediatric patients including growth and bone development, maturation and pubertal development (and response to vaccination) are followed up as missing information in the RMP.

Other than the laboratory findings discussed as AESI's, there were no analytes with clinically relevant differences between placebo and baricitinib 2 mg or 4 mg groups in routine laboratory analytes, over the first 36 weeks of treatment.

A trend towards increases in erythrocyte indices (mean corpuscular volume [MCV] and mean corpuscular haemoglobin [MCH]) was observed in baricitinib-treated patients. This is mechanistically plausible given JAK2's role in erythropoietin signalling, and similar changes have been noted in adult populations treated with JAK inhibitors. Although the magnitude of the shifts was small and not associated with anaemia or other haematological adverse events in adolescents, the finding was further discussed with updated data until week 52 (not shown in the Overview) It is agreed with the MAH that the differences seen in the erythrocyte indices in Study JAIO as well as in the adult indications are small and unlikely to be clinically relevant. In clinical practice, abnormal MCHC or MCH values are seldomly of relevance. Low Hb values (i.e. anaemia) of course is of relevance, but this was only seen in a very small patient sample (mainly girls in the age of menarche) in whom it was only marginally decreased. Indeed, baricitinib is an inhibitor of JAK1 and JAK2, and JAK2s involvement with erythropoietin signalling is well documented; hence the request to further elucidate abnormal erythrocyte indices. However, the small differences, as well as emerging scientific evidence for the mechanistic plausibility and clinical observation of elevated erythrocyte indices and alopecia, and the

modulation of erythrocyte indices by among others chronic inflammation is considered sufficient to conclude that the observed values are of no clinical importance; inclusion in section 4.8 of the SmPC is not warranted.

Urinalysis data were not updated in tables with the new data cutoff date of 15 April 2025; the issue is not pursued as there were no differences observed during the placebo-controlled period of the JAIO study, and these are also not to be expected based on knowledge of adult and adolescent data from other indications.

The post-approval spontaneous AE reports in the paediatric population were consistent with the established safety profile of baricitinib.

All ADRs are included in the updated SmPC section 4.8.

2.5.2. Conclusions on clinical safety

Based on the placebo-controlled phase of the pivotal study, the safety profile of baricitinib in adolescents with AA is in line with the known safety profile in adolescents with JIA and AD and adults. The SmPC has been adequately updated reflecting the finding of study JAIO.

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 29.1, dated 25 February 2026 with this application.

The (main) proposed RMP changes were the following:

The data for the adolescent AA population and the new proposed indication have been included in the updated RMP.

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

The PRAC considered that the Risk management plan version 29.1 is acceptable. The CHMP endorsed the Risk Management Plan version 29.1 with the following content:

Safety concerns

Table 40: Summary of safety concerns

List of Important Risks and Missing Information	
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

Pharmacovigilance plan

Table 41: Ongoing and planned additional pharmacovigilance activities

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 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);	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-induced malignancies such as cervical and many oropharyngeal cancers) • Foetal malformation following exposure in utero • Myelosuppression (agranulocytosis)	**For RA study**: Study progress reports Final study report (Objectives 1-3) **For AD Study:** Study progress reports Final report for Objective 4, AD cohort Final Report	**For RA study:** Annually in PBRER/PSUR submitted in April of each year 31 December 2027 **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

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	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.	• Myopathy including rhabdomyolysis • GI perforation Missing information: • Long-term safety • Use in very elderly (≥75 years)		31 December 2028
I4V-MC-B038: Baricitinib Drug Utilisation Study (Ongoing)	This study aims to describe changes in the utilisation of baricitinib in patients with RA, AA, or AD following the updated recommendations and limitations for use, in the new aRMMs as a measure of prescribers' compliance.	Important Identified Risks • VTE Important Potential Risks: • MACE • Opportunistic infection • Serious infection • Malignancy	Protocol submission Final study report	25 April 2023 31 July 2027

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
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 secondary 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: AD = atopic dermatitis; aRMMs = additional risk minimisation measures; ARTIS = Antirheumatic Therapies in Sweden; BSRBR = the British Society for Rheumatology Biologics Register; DILI = drug-induced liver injury; ERA = enthesitis-related arthritis; GI = gastrointestinal;; JIA = juvenile idiopathic arthritis; JPsA = juvenile psoriatic arthritis; MACE = major adverse cardiovascular events;; PBRER = periodic benefit-risk evaluation report; PML = progressive multifocal 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; VTE = venous thromboembolic event.

Risk minimisation measures

Table 42: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Herpes zoster	[Routine risk minimisation measures:] SmPC Sections 4.4 and 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 paediatric patients with JIA and AD, be brought up to date with all immunisations. PL 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:] • Healthcare Professional Educational Material • Patient Alert Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • Observational post-marketing safety study to monitor the incidence of herpes zoster in patients exposed to baricitinib for both RA and AD: • Nordic healthcare 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. 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	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • Observational post-marketing safety study to compare the incidence of VTE, including VTE validated based on clinical information, among patients exposed to baricitinib being treated for both moderate-to-severe RA and AD: • Nordic healthcare study

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	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. PIL 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:] • Healthcare Professional Educational Material • Patient Alert Card	• I4V-MC-B038: Baricitinib Drug Utilisation 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 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.,	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • Observational post-marketing safety study to compare the incidence of malignancy in patients exposed to baricitinib with patients exposed to other medications used for both moderate-to-severe RA and AD: • Nordic healthcare study • I4V-MC-B038: Baricitinib Drug Utilisation Study

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	current malignancy or history of malignancy) baricitinib should only be used if no suitable treatment alternatives are available. PIL 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	
Serious and opportunistic infections (including TB *Candida* infections, PML)	[Routine risk minimisation measures:] SmPC Sections 4.4 and 4.8 PIL 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 recommends that, prior to starting treatment, all patients including paediatric patients with JIA and AD, be brought up to date with all immunisations.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • Observational post-marketing safety study 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 both moderate-to-severe RA and AD: • Nordic healthcare study • I4V-MC-B038: Baricitinib Drug Utilisation Study

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	•Section 2 of the PIL 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:] • Healthcare Professional Educational Material • Patient Alert Card	
Myelosuppression (agranulocytosis)	[Routine risk minimisation measures:] SmPC Sections 4.2,4.4, 4.8, and 5.3 PIL 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. PIL 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 study to monitor the incidence of myelosuppression in patients exposed to baricitinib for both RA and AD: • Nordic healthcare study
Myopathy including rhabdomyolysis	[Routine risk minimisation measures:] SmPC Section 4.8 (increases in CPK PIL Section 4 (increases in CPK) [Additional risk minimisation measures:] None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • Observational post-marketing safety study to monitor the incidence of myopathy including rhabdomyolysis in patients exposed to baricitinib for both RA and AD: • Nordic healthcare study

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
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 PIL 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: None Additional pharmacovigilance activities: • Observational post-marketing safety study to monitor the incidence of potential drug-induced liver injury among patients exposed to baricitinib for both RA and AD: • Nordic healthcare study
GI Perforations	[Routine risk minimisation measures:] None [Additional risk minimisation measures:] None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • Observational post-marketing safety study to monitor the incidence of GI perforations in patients exposed to baricitinib for both RA and AD: • Nordic healthcare study
MACE (as an outcome of hyperlipidaemia)	[Routine risk minimisation measures:] 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.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • Observational post-marketing safety study to compare the incidence of hyperlipidaemia and MACE among patients exposed to baricitinib for both RA and AD: • Nordic healthcare study • I4V-MC-B038: Baricitinib Drug Utilisation Study

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	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 history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, baricitinib should only be used if no suitable treatment alternatives are available. PIL 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:] • Healthcare Professional Educational Material (lipid monitoring) • Patient Alert Card	
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 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. PIL Section 2 • States that patients should not take Olumiant if they are pregnant or think that they may be pregnant	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • Observational post-marketing safety study to monitor the incidence of foetal malformation following exposure in utero among patients exposed to baricitinib for both RA and AD: • Nordic healthcare study

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	• 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:] • Healthcare Professional Educational Material • Patient Alert Card	
Long-term safety	[Routine risk minimisation measures:] SmPC Sections 4.4 and 4.8 (hypercholesterolaemia and hypertriglyceridaemia) PIL Sections 2 and 4 No additional recommendations are included in the SmPC or PIL other than those already stated for malignancy and MACE. [Additional risk minimisation measures:] None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • Observational post-marketing safety study to monitor long-term safety in patients exposed to baricitinib for both RA and AD: • Nordic healthcare 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.	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) patients exposed to baricitinib for both RA and AD: • Nordic healthcare study

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	[Additional risk minimisation measures:] None.	
Use in patients with evidence of hepatitis B or hepatitis C infection	[Routine risk minimisation measures:] SmPC Section 4.4 PIL 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 PIL 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: None Additional pharmacovigilance activities: None
Use in patients with a history of or current lymphoproliferative disease	[Routine risk minimisation measures:] SmPC Section 4.4 PIL Section 2 PIL 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
Use in patients with active or recent primary or recurrent malignant disease	[Routine risk minimisation measures:] PIL Section 2 PIL 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,	[Routine risk minimisation measures:] SmPC Section 4.2 PIL Section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
maturation and pubertal development, and adverse response to vaccination	SmPC Section 4.2 states: • The safety and efficacy of baricitinib in children less than 2 years of age have not yet been established. No data are available. • The safety and efficacy of baricitinib in children less than 12 years of age or weighing less than 30 kg with AA have not yet been established. No data are available. PIL Section 2 advises that Olumiant is not for use in children younger than 2 years of age. It also advises that Olumiant is not for use in children under 12 years of age or weighing less than 30 kg with AA, because there is no information on use in this disease state. [Additional risk minimisation measures:] 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; DHPC = Direct Healthcare Professional Communication; DVT = deep vein thrombosis; GI = gastrointestinal; JIA = juvenile idiopathic arthritis; MACE = major adverse cardiovascular event; PE = pulmonary embolism; PIL = Patient Information Leaflet; PML = progressive multifocal leukoencephalopathy; RA = rheumatoid arthritis; SmPC = Summary of Product Characteristics; TB = tuberculosis; VTE = venous thromboembolic event.

2.7. Update of the Product Information

As a result of this variation, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly. In addition, the list of local representatives in the PL was revised.

2.7.1. User consultation

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

The proposed text modifications to the package leaflet resulting from the extended indication do not have a significant impact on the design and readability of the package leaflet and do not include text that is significantly different from that already user tested.

3. Benefit-Risk Balance

3.1. Therapeutic Context

This Application concerns an extension of the indication for Olumiant (baricitinib). The claimed extension of the indication is '… *for the treatment of severe alopecia areata in adult and adolescent patients 12 years of age and older (see section 5.1)'*. The claimed posology is 4 mg once daily for patients weighing ≥30 kg.

3.1.1. Disease or condition

Alopecia areata (AA) is an autoimmune disease characterised by patches of nonscarring hair loss. Severe AA is defined as scalp hair loss > 50% using the Severity of Alopecia Tool (SALT). Severe AA is recognised as a significant autoimmune condition with emotional and psychosocial distress, including high prevalence of depression and anxiety. Although up to 50% of patients with patchy alopecia areata experience spontaneous hair regrowth within one year, most will relapse months or years after remission.

Both children and adults may develop AA, and the disorder occurs at similar rates in males and females. AA has a lifetime prevalence of approximately 2%. The mean age for diagnosis of AA is predicted at 32 years in males and 36 years in females. The psychosocial and cosmetic burden is disproportionately higher in women and in adolescents, particularly given the visibility of scalp, eyebrow, and eyelash involvement.

3.1.2. Available therapies and unmet medical need

There are two centrally approved treatment options for AA, both JAK inhibitors. Ritlecitinib (Litfulo; JAK3, TEC inhibitor) was recently approved by the EMA for the treatment of severe AA in adults and adolescents 12 years of age and older. Baricitinib has been approved for severe AA in adults. Thus, except for ritlecitinib, there are no centrally approved therapeutic options for AA in adolescents.

Off-label treatments for AA in adults are used empirically for (paediatric and) adolescent patients. Current treatments for children <10 years of age include topical corticosteroid (Class I–III) monotherapy or in combination with topical retinoids, topical anthralin, and rarely systemic steroids (pulse therapy). Treatment in children >10 years of age may also include topical sensitisers and intralesional corticosteroids if tolerated (the latter treatment is locally approved in several European countries). According to European expert consensus statement on the systemic treatment of AA, methotrexate, hydroxychloroquine, azathioprine and other immunomodulators are used, despite limited efficacy data in this population. Use of minoxidil is controversial both due to lack of efficacy and tolerability concerns (light-headedness, adherence issues) in children.

The limited authorised treatment options for (paediatric and) adolescent patients with severe AA, and the substantial psychosocial burden, present a significant unmet need in this population.

3.1.3. Main clinical study

The single pivotal trial supporting this application is the I4V-MC-JAIO study [JAIO], to evaluate the efficacy, safety, and PK of baricitinib in paediatric patients aged 6 to <18 years with AA affecting ≥50% of the scalp. Study JAIO is a phase 3, placebo-controlled, randomised, double-blind study. The primary endpoint was the SALT score ≤20 at week 36, which corresponds to a scalp hair loss of ≤20% or at

least 80% scalp hair coverage. Two doses of baricitinib, 2 mg (low dose) and 4 mg (high dose) both once daily, were compared to placebo.

The study is ongoing; placebo-controlled 36 weeks treatment data, as well as uncontrolled, preliminary data at week 52 of the LTE part in adolescent patients has been completed and was supplied for this application. Data of another 166 patients assigned to either baricitinib 2 mg or 4 mg after completed enrolment of the placebo-controlled period, were included for safety analyses only as efficacy data were preliminary. At time of the data cut-off, a total of 80 patients in 4 mg dose, 82 in 2 mg dose, and 81 in the placebo group completed the 36 weeks placebo-controlled period. Of these, 64 patients (76%) on baricitinib 2 mg switched to 4 mg and 18 (21%) continued 2 mg at week 36; 77 patients (93%) in the 2 mg group and 79 patients (95%) in the 4 mg group completed the week 52 visits.

Data from children 6-12 years are *not* included in this application, as patient enrolment was planned to be staggered, starting after data of the adolescent group had been collected, analysed, and the B/R for the adolescent age group has been determined, as agreed by the PDCO (*EMA/PDCO Summary Report EMA/13938/2021*).

3.2. Favourable effects

The primary outcome SALT ≤20 at Week 36 was met ($p<0.001$) in both baricitinib treatment groups (4 mg and 2 mg) compared to placebo; response rates were 27% and 42% in the low and high dose groups versus 4.5% in the placebo group. Sensitivity analysis confirmed robustness of the data. Notably, the observed baricitinib response rates in the JAIO study were higher than the pooled response rates found in the adult AA studies (JAHO and JAIR), which were 16% for the low dose and 30% for the high dose baricitinib group, with a comparable 5% response rate in placebo.

The SALT-derived key secondary endpoints (SALT≤20 at weeks 16 and 24, SALT50 at week 12, SALT90 at week 36, and SALT≤10 at weeks 24 and 36), hierarchically tested, were all significant and in favour of baricitinib treatment. Other secondary endpoints, including ClinROs on scalp, eyebrow and eyelash hair loss, and the SKINDEX-16 AA-Y were numerically aligned with these findings.

Across endpoints, high dose baricitinib (4 mg) was (numerically) superior to low dose baricitinib (2 mg) and placebo, and also low dose baricitinib (2 mg) generally resulted in higher response rates than placebo.

Treatment responses were observed to start as early as 8 weeks after treatment initiation and percentages responders continued to increase up to 36 weeks. This supports that 36 weeks is an appropriate time point to stop treatment in case of non-response, as included in section 4.2 of the SmPC. No data on down-titration and / or stopping in case of maintained good response is gathered, but a rule is included based on the adult AA and the paediatric AD posology texts. This is acceptable, also for safety reasons as a mean to reduce lengthy exposure.

Subgroup analyses generally indicated higher odds for a treatment response at the primary endpoint in the 4 mg baricitinib group compared to placebo, and to lesser extent for the 2 mg group compared to placebo.

3.3. Uncertainties and limitations about favourable effects

Data from the 36 weeks placebo-controlled period were included in the current application, complemented with preliminary 52 weeks data from the LTE study finished by all patients. Data from those assigned to placebo but re-randomised to baricitinib were not included, nor were data from patients who were kept on placebo (n = 4) at week 36. It is anticipated that all available patient data

will be included in the final reporting of the LTE study. Despite that the data presented could be regarded as preliminary, the treatment effect of baricitinib once daily after 36 weeks was statistically significant, robust and of clinical relevance compared to placebo. The long-term efficacy of baricitinib in AA will be further characterised upon receipt of the final results of the LTE study (100-week data).

3.4. Unfavourable effects

The proportions of patients with at least 1 treatment-emergent AE was highest (71%) in the baricitinib 4 mg group and lowest (53%) in the placebo group; the frequency in the 2 mg group (60%) fell in between. The higher frequency of AEs in the baricitinib 4 mg group, as compared to placebo, was mostly due to mild AEs. SAEs and severe AEs and permanent discontinuations due to an AE were infrequent and the occurrence was similar for placebo and baricitinib 4 mg. Temporary interruptions due to an EA also were similar for placebo and baricitinib 4 mg groups. With prolonged exposure up to 52 weeks, incidence rates (IRs) for TEAEs in both baricitinib doses were lower compared to the placebo-controlled period, but the IR for moderate TEAEs was higher. A dose response was seen for SAEs, TEAEs, and discontinuation rates.

On level of SOC, differences between the baricitinib 4 mg group as compared to the placebo group were seen with: infections and infestations (40% *versus* 32%), skin and subcutaneous tissue disorders (19% *versus* 11%), investigations (12% *versus* 4.5%), blood and lymphatic system disorders (11% *versus* 1.1%), psychiatric disorders (5.9% *versus* 1.1%). Neoplasms (skin papilloma) occurred in the baricitinib group (n=2, 2.4%) but not in the placebo group. The 5 instances of psychiatric disorders in the baricitinib group were cases of: anxiety, depression, flat affect, nervousness.

On the PT level, the largest differences between the baricitinib 4 mg group as compared to the placebo group were seen with: acne (9.4% *versus* 4.5%), headache (8.2% *versus* 5.7%), upper respiratory tract infections (8.2% *versus* 6.8%) and rhinitis (7.1% versus 3.4%) but not nasopharyngitis, blood CPK increased (5.9% versus 2.3%), influenza (5.9% *versus* 3.4% and Covid19 (redacted), eosinophilia (4.7% *versus* 1.1%), neutropenia (redacted), ALT increased (redacted), blood cholesterol increased (redacted).

With prolonged exposure up to 52 weeks, IRs for TEAEs in baricitinib were generally more favourable compared to the placebo-controlled period, except for vomiting, cough, pneumonia, and folliculitis, for which the IR increased in the baricitinib 4 mg group.

Comparison of TEAEs observed in adults and adolescents during the placebo-controlled period in the baricitinib 4 mg group occurring with a frequency of ≥ 2%, were (next to existing ADRs) COVID-19, ligament sprain, anxiety, Influenza-like illness, tinea versicolor, and eosinophilia. With prolonged exposure, these were influenza, cough, vomiting, ligament sprain, asthenia, epistaxis, dysmenorrhea, seborrhoeic dermatitis, depression, pyrexia, leukopenia, and eosinophilia. AESI's were analysed in line with the safety concerns in the RMP, including serious and opportunistic infections, lipids, PE and VTE, liver toxicity, growth and maturation.

3.5. Uncertainties and limitations about unfavourable effects

Eosinophilia was more frequent (IR 1.8 and 7.2 for 2 and 4 mg baricitinib groups) compared to placebo (IR 1.7) and it was considered that this might be an ADR. However, with prolonged exposure the IRs were considerably lower (1.1 and 3.0 for baricitinib 2 mg and 4 mg resp.) compared to the placebo-controlled period, with 1.7 when considering all to baricitinib exposed patients. Further, no cases were reported in adults, and there is no clear mechanistic plausibility for a JAKi causing eosinophilia. Half of

the patients with eosinophilia appeared to have a medical history of atopic dermatitis and / or allergies which might be a reasonable explanation, and all but 1 had pre-existing eosinophilia at study entry.

Psychiatric disorders appeared to cluster in the baricitinib group during the placebo-controlled period. With prolonged exposure, IRs for depression (2.0) and anxiety (1.5) in the baricitinib group were identical / more favourable to the placebo-controlled period (2.0 *versus* 1.8, and 1.5 *versus* 3.5) and absolute numbers remained low (≤ 3). Suicidal ideation, suicidal behaviour, and self-injurious behaviour, as well as the TE depression and suicide/self-injury based on MedDRA SMQ were reported in only few patients up to 52 weeks, without a dose response. The 5 SAEs observed in the SOC Psychiatric disorders generally occurred in patients with a history of mental health issues. As AA has a substantial psychological impact on patients, especially in adolescents, it is concluded that the current data do not clearly indicate an increased risk of depression or suicidal ideation/behaviour among those treated with baricitinib.

Frequent confounding factors and limited long-term follow-up mean that very rare or delayed adverse events occurring > 52 weeks exposure cannot be excluded.

The baricitinib safety concerns are being monitored through the routine pharmacovigilance activities.

Additional safety data in paediatric population is being gathered in the ongoing post-approval studies in JIA, AD and AA.

3.6. Effects Table

Table 43: Effects Table for Olumiant, alopecia areata in adolescents > 12 years

Effect	Short description	Unit	Baricitinib 4 mg QD	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
SALT ≤20 at week 36 (*primary endpoint*)	Severity of ALopecia Tool	% (n/N)	42.4 (36/85)	4.5 4/88)	**SoE**: p < 0.001, data in line with more stringent SALT endpoints (key secondary endpoints including SALT≤10, a.o.)	Study JAIO
SALT ≤20 at week 24 (key secondary endpoint)	Severity of ALopecia Tool	% (n/N)	31.8 (27/85)	3.4 (3/88)	**SoE**: p < 0.001, multiplicity controlled. See also above.	Study JAIO
Unfavourable Effects						
Infections	Infections and infestations (SOC)	%	40	32	**SoE**: numerically higher in the baricitinib 4 mg group. **Unc**: comparative data up to week 36	Study JAIO
Acne		%	9.4	4.5		
Headache		%	8.2	5.7		
Blood abnormalities	Blood and lymphatic disorders (SOC)	%	11	1.1		

Abbreviations: SoE = strength of evidence, Unc. = Uncertainty

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Favourable effects

In the pivotal study, the primary outcome (SALT ≤20 at week 36) was met ($p<0.001$) in both baricitinib treatment groups (4 mg and 2 mg) compared to placebo. The response rate differences of 38% (26% – 49%) and 23% (95% CI 12% - 34%) for 4 mg and 2 mg baricitinib versus placebo are considered clinically relevant. Across all endpoints, high dose baricitinib was generally superior to low dose treatment and placebo.

The onset of treatment effect emerged as from 8 weeks after treatment initiation with continuous improvement through week 36 and no clear plateau; suggesting that treatment benefit may further increase beyond this timepoint. LTE study data will provide more evidence on this.

The relevance of treatment outcome to patients was supported by numerical changes in the ClinROs (scalp, eyebrow, eyelash) and SKINDEX-16 AA-Y.

Given the safety profile of JAK inhibitors like baricitinib, guidance about when to stop treatment with baricitinib, in case of non-response or sustained response, is provided in SmPC section 4.2, in order to reduce unnecessary exposure.

Unfavourable effects

Based on the placebo-controlled phase of the pivotal study, the safety profile of baricitinib in adolescents with AA is in line with the known safety profile in adolescents with JIA and AD and adults. This further supports the reassurance about the safety profile in adolescents with AA.

There was an overall higher frequency of treatment-emergent AEs in the baricitinib 4 mg group compared with placebo. The AEs that were more frequent in the baricitinib treated groups were in line with the known ADRs, including acne, headache, upper respiratory tract infections, blood CPK increased, neutropenia, ALT increased and blood cholesterol increased. With prolonged exposure, vomiting, cough, pneumonia, and folliculitis occurred more common; the latter two were already defined as ADRs. The treatment effects (difference between 4 mg and placebo group) were relatively small and the AEs usually mild to moderate. This points to a low impact of the most common AEs on the Benefit-Risk. Severe AEs and SAEs were infrequent and SAEs generally unrelated to baricitinib, these therefore do not impact Benefit-Risk.

Comparison of adolescent AA and adult AA safety data indicated higher rates for seborrhoeic dermatitis and leukopenia in adolescents than adults, including a possible dose response relationship. Further evaluation including data from other paediatric indications did not clearly indicate a higher risk due to use of baricitinib for seborrhoeic dermatitis; for leukopenia the increased risk was associated with the already known ADR neutropenia. The higher rates of psychiatric disorders including depression and suicidal ideation / behaviour did not clearly indicate a higher risk due to use of baricitinib.

No new safety signals emerged for AESIs pre-specified in the RMP, including serious infections, VTE, hepatic toxicity, or malignancy.

Post-marketing data in adolescents did not give rise to new safety issues, serious AEs were infrequent, also in comparison to adults. Therefore, no additional concerns or new uncertainties are raised.

The RMP and SmPC are considered adequate. The safety profile of baricitinib will be further monitored in the upcoming PSURs.

3.7.2. Balance of benefits and risks

The treatment effect of baricitinib once daily after 36 weeks was robust, statistically significant, and clinically relevant compared to placebo, and numerically larger than observed in adults. Efficacy data at 52 weeks are supportive. The safety profile of baricitinib in adolescents with AA is generally in line with the known safety profile in adolescents with JIA and AD and adults. The majority of AEs were mild to moderate, and manageable, and no new unexpected risks emerged.

3.8. Conclusions

The overall Benefit /Risk balance of baricitinib for the treatment of adolescents with AA is positive.

4. Recommendations

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 changes:

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

Extension of indication to include treatment of adolescent patients 12 years of age and older with severe alopecia areata. This is based on results from study I4V-MC-JAIO; a Phase 3, double-blind, randomised, placebo-controlled trial to evaluate the efficacy, safety, and pharmacokinetics of baricitinib in children from 6 years to less than 18 years of age with alopecia areata. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 29.1 of the RMP is also approved. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the PI and to update the list of local representatives in the Package Leaflet.

Amendments to the marketing authorisation

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

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

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency.

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

- **Additional risk minimisation measures**

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

The main objectives of the programme are to make the prescribers aware of the risks associated with the product's use, and to highlight specific risk minimisation measures to be performed before and during the treatment with baricitinib.

The MAH shall ensure that, in each Member State where baricitinib is marketed, all healthcare professionals who are expected to prescribe baricitinib are provided with the physician educational material, which should contain:

- The Summary of Product Characteristics
- The Package Leaflet including the Patient Alert Card
- The guide for healthcare professionals to support counselling of the patient
- Additional Patient Alert Cards

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

- Indication and posology statements provided to reinforce in whom baricitinib should be used
- That baricitinib increases the potential risk of infections. Patients should be instructed to seek immediate medical attention, if signs or symptoms suggesting infection appear. As there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes. Baricitinib should only be used in patients 65 years of age and older if no suitable treatment alternatives are available.
- That baricitinib use should be stopped in case of herpes zoster or any other infection that doesn't respond to standard treatment until the event resolves. Patients should not be immunised using live attenuated vaccines shortly before or during treatment with baricitinib.
- Prior to initiating treatment, it is recommended that all patients, particularly paediatric patients, be brought up to date with all immunisations in agreement with local current immunisation guidelines
- Prescribers should screen the patients for viral hepatitis before commencing baricitinib treatment. Active tuberculosis should also be ruled out.
- That baricitinib use is associated with hyperlipidaemia; prescribers should monitor the patient's lipid parameters and manage the hyperlipidaemia, if detected.
- Baricitinib increases the risk of venous thrombosis and pulmonary embolism. Baricitinib should be used with caution in patients with known risk factors for DVT/PE other than cardiovascular or malignancy risk factors. Patients should be instructed to seek immediate medical attention if signs or

symptoms of DVT/PE appear.

- That there is a potentially increased risk of MACE in patients with certain risk factors using JAK inhibitor treatment, including baricitinib. In patients 65 years of age and older, patients who are current or past long term smokers, and patients with other cardiovascular risk factors, baricitinib should only be used if no suitable treatment alternatives are available.

- That Lymphoma and other malignancies have been reported in patients receiving JAK inhibitors, including baricitinib. In patients over 65 years of age, patients who are current or past long term 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.

- That baricitinib is contraindicated in pregnancy as pre-clinical data showed reduced foetal growth and malformations. Physicians should advise women of childbearing potential to use contraception during treatment and for a week after its ending. If a planned pregnancy is considered, baricitinib treatment should be stopped.

- The purpose and use of the Patient Alert Card.

The patient alert card shall contain the following key messages:

- That treatment with baricitinib may increase the risk of infections, and viral reactivation which can become serious if not treated.

- Signs or symptoms of infections including general symptoms, and specifically tuberculosis and herpes zoster signs and symptoms; and a warning for the patients to seek immediate medical attention if signs or symptoms suggesting infection appear.

- Patients should seek immediate medical attention if signs and symptoms of myocardial infarction or stroke occur.

- That baricitinib should not be taken while pregnant and that women should inform their doctor should they become (or wish to become) pregnant.

- That baricitinib may cause a blood clot in the leg that may travel to the lungs; a description of signs and symptoms is provided, along with a warning for the patients to seek immediate medical attention if signs or symptoms suggesting a blood clot appear.

- That baricitinib may cause non melanoma skin cancer and that the patients should talk to their doctor if new skin lesions appear during or after therapy or if existing lesions change appearance, tell your doctor.

- Contact details of the prescriber.

- That the Patient Alert Card should be carried by the patient at any time and to share it with other healthcare professionals involved in their treatment.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the "EPAR-Procedural steps taken and scientific information after authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion Olumiant-II-EMAVR0000288098-AR-en.