19 May 2022
EMA/572597/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Olumiant

International non-proprietary name: baricitinib

Procedure No. EMEA/H/C/004085/II/0029/G

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

AA	Alopecia areata
AA-IGA	Alopecia Areata Investigator Global Assessment
AD	Atopic dermatitis
ADR	adverse drug reaction
AE	adverse event
All BARI AA	Safety analysis set that includes all patients with AA exposed to any dose of baricitinib at any time during the studies
All BARI 2-mg AA	Safety analysis set that includes all patients with AA exposed to baricitinib 2-mg at any time during the studies
All BARI 4-mg AA	Safety analysis set that includes all patients with AA exposed to baricitinib 4-mg at any time during the studies
ALT	alanine aminotransferase
ANCOVA	Analysis of covariance
AST	aspartate aminotransferase
AT	Alopecia totalis
ATE	arterial thromboembolism
AU	Alopecia universalis
AUC	area under the plasma concentration–time curve
BARI AA PC	Safety analysis set comparing baricitinib 2-mg and 4-mg with placebo following 36 weeks of treatment
BMI	body mass index
CL/F	apparent total clearance of the drug from plasma after oral administration
ClinRO	Clinician-reported outcomes
Cmax	maximum serum concentration
CPK	creatinine phosphokinase
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DVT	deep vein thrombosis
EB	eyebrow
EL	eyelash
EMA	European Medicines Agency
Ext BARI AA	Safety analysis set that includes all patients with AA exposed to baricitinib 2-mg or 4-mg at from dose randomization to dose or treatment change
FAS	Full analysis set
FDA	Food and Drug Administration
GFR	glomerular filtration rate

GI	gastrointestinal
HADS	Hospital Anxiety and Depression Scale
HDL-C	high-density lipoprotein cholesterol
IL	interleukin
IR	incidence rate
JAHO	Study I4V-MC-JAHO
JAIR	Study I4V-MC-JAIR
JAK	Janus kinase
LDL-C	low-density lipoprotein cholesterol
MACE	major adverse cardiovascular event
mFAS	Modified full analysis set
mLOCF	Modified last observation carried forward
NMSC	non-melanoma skin cancer
NRI	Non responder imputation
PE	pulmonary embolism
PK	pharmacokinetic(s)
PPS	Per protocol set
PRO	patient-reported outcome
PSUR	Periodic safety update report
PT	preferred term
QoL	quality of life
RA	rheumatoid arthritis
SAE	serious adverse event
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
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SmPC	Summary of Product Characteristics
SOC	system organ class
STAT	signal transducer and activator of transcription
t1/2	elimination half-life
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 group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Eli Lilly Nederland B.V. submitted to the European Medicines Agency on 31 August 2021 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
C.I.11.z	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	Type IB	None

Grouping of the following variations:
C.I.6 - Extension of indication to include treatment of severe alopecia areata in adult patients for Olumiant; as a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 12.1 of the RMP has also been submitted.
C.I.11.z - Update of RMP (version 12.1) to change the category 3 study PASS I4V-MC-B011 end of data collection for the Atopic Dermatitis cohort from 'December 2026' to 'December 2027' and the subsequent final study report milestone from 'December 2027' to 'December 2028'.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0339/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0339/2021 was 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.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC)

726/2004 - one year of market protection for a new indication bringing a significant clinical benefit in comparison with existing therapies. During the assessment of the procedure, the MAH withdraw their request for one additional year of market protection.

Scientific advice

The MAH didn't seek scientific advice to the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Johann Lodewijk Hillege

Timetable	Actual dates
Submission date	31 August 2021
Start of procedure:	18 September 2021
CHMP Rapporteur Assessment Report	15 November 2021
PRAC Rapporteur Assessment Report	18 November 2021
PRAC members comments	24 November 2021
Updated PRAC Rapporteur Assessment Report	26 November 2021
PRAC Outcome	02 December 2021
CHMP members comments	06 December 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	09 December 2021
Request for supplementary information (RSI)	16 December 2021
CHMP Rapporteur Assessment Report	21 March 2022
PRAC Rapporteur Assessment Report	25 March 2022
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	07 April 2022
CHMP members comments	11 April 2022
Updated CHMP Rapporteur Assessment Report	14 April 2022
2ND Request for supplementary information (RSI)	22 April 2022
CHMP Rapporteur Assessment Report	04 May 2022
PRAC Rapporteur Assessment Report	05 May 2022
PRAC members comments	10 May 2022
CHMP members comments	10 May 2022
Updated CHMP Rapporteur Assessment Report	12 May 2022
Updated PRAC Rapporteur Assessment Report	12 May 2022
CHMP opinion:	19 May 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The claimed therapeutic indication was as follows:

Alopecia Areata

Olumiant is indicated for the treatment of severe alopecia areata in adult patients.

Epidemiology and risk factors

Both children and adults may develop alopecia areata (AA), and the disorder occurs at similar rates in males and females (Strazzulla LC et al., 2018). AA has a lifetime prevalence of approximately 2% (Wasserman et al. 2007; Islam et al. 2015; Korta et al. 2018). The mean age for diagnosis of AA is predicted to be of 32 years in males and 36 years in females (Mirzoyev SA et al. 2013).

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 utilizes JAK1 and JAK2.

Clinical presentation

Alopecia areata is an autoimmune disease characterized by patches of nonscarring hair loss. The diagnosis of AA is based upon the appearance of the 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. Biopsy (the removal of a sample of tissue for study) is usually not necessary. AA is associated with atopic diseases such as atopic dermatitis and asthma. Severe AA is recognized as a significant autoimmune condition with emotional and psychosocial distress, including high prevalence of depression and anxiety. Although 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.

Management

There are no centrally approved products for AA. However, some authorized medications are available in individual member states (e.g. in NL, methylprednisolone and triamcinolone intra-lesion injections are approved for an AA indication). The response to treatment varies widely; few well-designed clinical trials have evaluated these therapies. Current guidelines advise on topical (corticosteroids and minoxidil) or systemic therapies (corticosteroids, corticosteroid-sparing agents such as cyclosporin and methotrexate, and biological such as ustekinumab/Stelara) (European Dermatology Forum (EDF): Evidence-based (S3) guideline for the treatment of androgenetic alopecia in women and in men, 2017; British Association of Dermatologists (BAD): Guidelines for the management of alopecia areata, 2012). However, some of those treatments are used off-label.

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 (Fridman et al. 2010).

Baricitinib was approved in the EU for the treatment of RA on 15 February 2017 (EMEA/H/C/4085) and for AD on 21 October 2020 (EMEA/H/C/004085/II/0016).

Olumiant (baricitinib) is indicated for: the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to/are intolerant to disease-modifying anti-rheumatic drugs; and for the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy. For both approved indications, the recommended dose is 4-mg once daily. A dose of 2-mg is appropriate for patients aged ≥75 or with a history of infections. If disease control is reached, patients may be tapered from 4-mg to 2-mg.

As cytokines involved in the development of AA are dependent on JAK/STAT signalling, baricitinib (a JAK inhibitor) shows 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 (Xing et al. 2014).

EMA's safety committee, PRAC, has started a review of the safety of Janus kinase (JAK) inhibitors used to treat several chronic inflammatory disorders (rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, ulcerative colitis and atopic dermatitis).

The review was prompted by the final results from a clinical trial (study A3921133) of the JAK inhibitor Xeljanz (tofacitinib). The results showed that patients taking Xeljanz for rheumatoid arthritis and who were at risk of heart disease were more likely to experience a major cardiovascular problem (such as heart attack, stroke or death due to cardiovascular disease) and had a higher risk of developing cancer than those treated with medicines belonging to the class of TNF-alpha inhibitors. The study also showed that compared with TNF-alpha inhibitors, Xeljanz was associated with a higher risk of death due to any cause, serious infections, and blood clots in the lungs and in deep veins (venous thromboembolism, VTE).

In addition, preliminary findings from an observational study involving Olumiant (baricitinib), also suggest an increased risk of major cardiovascular problems and VTE in patients with rheumatoid arthritis treated with Olumiant compared with those treated with TNF-alpha inhibitors.

In the treatment of inflammatory disorders, Olumiant and other JAK inhibitors work in a similar way to Xeljanz. PRAC will therefore carry out a review to determine whether these risks are associated with all JAK inhibitors authorised in the EU for the treatment of inflammatory disorders and whether the marketing authorisations for these medicines should be amended.

The review of JAK inhibitors in the treatment of inflammatory disorders has been initiated at the request of the European Commission (EC) under Article 20 of Regulation (EC) No 726/2004 and is currently on-going.

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

The baricitinib clinical development programme for AA includes 2 pivotal global clinical studies (Study I4V-MC-JAHO [JAHO] and Study I4V-MC-JAIR [JAIR]) to evaluate the safety and efficacy of baricitinib in adult patients with severe AA defined as ≥50% scalp hair loss. Both studies were outpatient, multicentre, randomized, double-blind, placebo-controlled, parallel-group trials.

Study JAHO was a Phase 2/3, adaptive, and operationally seamless study. The Phase 2 portion was designed to identify up to 2 doses of baricitinib to be evaluated in the Phase 3 portion of the study.

In the Phase 3 portion of JAHO and Study JAIR, the efficacy and safety of 2-mg/day and 4-mg/day of baricitinib were compared to placebo in adult patients with severe AA. This submission includes efficacy data for 855 patients enrolled in the Phase 3 AA studies through Week 36 (placebo-controlled period), and for 629 patients (approximately 74%) randomised to baricitinib through Week 52.

No EMA scientific guideline is available for the development of treatments for AA, and no EU scientific advice for AA has been sought.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The ERA was complete at time of initial MAA, and the MAH has updated the Predicted Environmental Concentrations (PEC) values to include the new indication, resulting in the following PEC, predicted no-effect concentrations (PNEC) values and ratios:

Table 1 Baricitinib updated ERA

Environmental compartment	Maximum PEC	PNEC	PEC/PNEC
Surface water	0.06 µg/L	60 µg/L	0.001
Sediment	230 µg/kg	27150 µg/kg	0.008
Surface water (microorganism)	0.06 µg/L	100000 µg/L	0.0000006
Ground water	0.015 µg/L	210 µg/L	0.00007
Sewage Treatment Plant (microorganism)	0.6 µg/L	100000 µg/L	0.000006

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

2.2.2. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

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

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Study Identifier; Location of Report; Report Type; Study Status; Participating Countries	Objective	Design; Control Type	Treatment and Regimen: Dose/Route/Frequency	Number of Subjects Who Were Randomized	Diagnosis or Inclusion Criteria	Treatment Duration
Controlled Clinical Studies for the Treatment of Alopecia Areata						
I4V-MC-JAHO; 5.3.5.1; Full; Ongoing; **Phase 2** United States and Japan **Phase 3** Unites States, South Korea, and Mexico	To test the hypothesis that the 4-mg dose or 2-mg dose of baricitinib is superior to placebo in the treatment of patients with severe or very severe AA.	Phase 2/3, multicenter, randomized, double-blind, placebo-controlled, operationally seamless, adaptive, parallel-group, outpatient study.	Patients were randomized to receive the following treatment orally, once daily from Weeks 0 to 36 **Phase 2** • Placebo • Baricitinib 1 mg, • Baricitinib 2 mg, or • Baricitinib 4 mg **Phase 3** • Placebo • Baricitinib 2 mg, or • Baricitinib 4 mg	**Double-blind placebo-controlled treatment period (Weeks 0 to 36)[a]** **Phase 2** Randomized (N=110) (1:1:1:1) • Placebo (N=28) • Baricitinib 1 mg (N=28) • Baricitinib 2 mg (N=27) • Baricitinib 4 mg (N=27) **Phase 3** Randomized (N=654) (2:2:3) • Placebo (N=189) • Baricitinib 2 mg (N=184) • Baricitinib 4 mg (N=281)	• ≥18 to ≤60 years for males and ≥18 to ≤70 years for females; • Severe (SALT 50-94) or very severe (SALT 95-100) AA • Current AA episode lasting >6 months and <8 years • No spontaneous improvement over the past 6 months	**Phase 2 and Phase 3** Up to 200 weeks

Study Identifier; Location of Report; Report Type; Study Status; Participating Countries	Objective	Design; Control Type	Treatment and Regimen: Dose/Route/Frequency	Number of Subjects Who Were Randomized	Diagnosis or Inclusion Criteria	Treatment Duration
Controlled Clinical Studies for the Treatment of Alopecia Areata						
I4V-MC-JAIR; 5.3.5.1; Full; Ongoing; United States, Japan, China, Taiwan, South Korea, Australia, Brazil, Argentina, and Israel	To test the hypothesis that the 4-mg dose or 2-mg dose of baricitinib is superior to placebo in the treatment of patients with severe or very severe AA.	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study	Patients were randomized to receive the following treatment orally, once daily, from Weeks 0 to 36 • Placebo • Baricitinib 2 mg, or • Baricitinib 4 mg	**Double-blind placebo-controlled treatment period (Weeks 0 to 36)[a]** Randomized (N=546) (2:2:3) • Placebo (N=156) • Baricitinib 2 mg (N=156) • Baricitinib 4 mg (N=234)	• ≥18 to ≤60 years for males and ≥18 to ≤70 years for females; • Severe (SALT 50-94) or very severe (SALT 95-100) AA • Current AA episode lasting >6 months and <8 years • No spontaneous improvement over the past 6 months	Up to 200 weeks

[a] Values shown are for the numbers of patients in the FAS population for the JAIR and JAHO Phase 3 studies and IAS population for the JAHO Phase 2 portion. The numbers of patients included in safety analyses were slightly smaller and are reported with safety results.

Abbreviations: AA = alopecia areata; FAS = full analysis set; IAS = interim analysis set; N = number of patients in group; SALT = Severity of Alopecia Tool.

2.3.2. Pharmacokinetics

Phase 2/3 Study I4V-MC-JAHO (JAHO), evaluated the clinical pharmacology of baricitinib in patients with severe AA (that is, scalp hair loss of ≥50%). This study evaluated baricitinib at doses of 1-, 2-, and 4-mg once daily (QD) in the Phase 2 portion and 2- and 4-mg QD in the Phase 3 portion of the study with a primary endpoint of proportion of patients achieving Severity of Alopecia Tool (SALT) score ≤20 at 36 weeks. A total of 2685 plasma concentration data from 546 patients treated with baricitinib and 725 SALT scores from 725 patients enrolled in Study JAHO were included in the PK and PK/PD analyses, respectively.

Methods

Bioanalytical method

Baricitinib plasma samples obtained during the studies were analysed using a validated liquid-liquid extraction followed by a liquid chromatography with tandem mass spectrometry detection method (validation report: 8232103). Covance Bioanalytical Services, LLC located in Indianapolis, Indiana, USA, performed the bioanalytical methods. The lower limit of quantification was 0.20 ng/mL, and the upper limit of quantification was 200.00 ng/mL. Samples above the limit of quantification were diluted to yield results within the calibrated range (dilution integrity: 10x). The interassay accuracy (% relative error) during validation ranged from 0.7% to 3.3%. The interassay precision (% relative standard deviation) during validation ranged from 2.0% to 6.3%. Baricitinib was stable for up to 1290 days when stored at approximately -60 to -80°C.

A total of 2977 samples (incl. 19 placebo samples) were analysed within 593 days of collection. 32 samples were reanalysed due to high internal standard (n = 29), interference peak in blank samples (n = 1), poor chromatography (n = 1) or missing internal standard (n = 1). During bioanalysis of study samples, interassay accuracy (%relative error) and interassay precision (%relative standard deviation) ranged from 99.7 to 100.6% and 2.2% to 3.3%, respectively. A total of 204 samples were reanalysed

to assess incurred sample reproducibility. A 100% of repeat and original results were within 20% of each other.

Population pharmacokinetic model

The objective of the population pharmacokinetic analysis for baricitinib in patients with alopecia areata is to support dose selection. Specifically, the analyses aimed to:

- Characterise the population pharmacokinetics of baricitinib and estimate the magnitude of interpatient variability in baricitinib exposure.
- Identify intrinsic and extrinsic factors that may impact baricitinib exposure.

The analysis dataset contained data from the phase 2/3 study JAHO in patients with alopecia areata. In short, this study was a multicentre, randomised, double-blind, placebo-controlled adaptive phase 2/3 study to evaluate the efficacy and safety of baricitinib in adult patients with severe or very severe alopecia areata. In phase 2 of the trial, patients were randomised to placebo or baricitinib 1 mg, 2-mg or 4-mg once daily. Pharmacokinetic samples were collected at week 0 (0.25 and 1.0h post-dose), week 4 (2-4 hours post-dose), week 8 (4-6 hours post-dose) and weeks 12 and 16 (pre-dose).

A total of 2915 observations from 546 patients from study JAHO were obtained for analysis. However, 230 observations were excluded due to: below the quantification limit (n = 200, 6.9% of the total samples), concentrations prior to first drug administration or within lag time (n = 10), biologically implausible concentrations with time from dose greater than 60 hours (n = 14), samples collected after PK collection period (n = 4). This resulted in 2685 baricitinib concentrations from 546 in the final dataset.

The structural model consisted of a 2-compartment model with zero-order absorption (including lag time) and linear elimination (**Figure 1**). The pharmacokinetic analysis in patients with alopecia areata applied the same model characterizing the PK of baricitinib in healthy volunteers, patients with rheumatoid arthritis and atopic dermatitis, and adopted as priors the estimates for parameters and covariates from the final PK model for atopic dermatitis. Potentially significant covariates (body weight, gender, race and ethnicity and eGFR) were tested individually for their effect on each of the relevant model parameters using NONMEM 7.4.2. The criterion for forward inclusion was a p-value no greater than 0.01 (Δ6.635 minimum objective function [MOF] for inclusion of one parameter). The variance estimate for BSV on the relevant parameter had to decrease by 5% or more for the covariate to be retained in the full model. The significance of the potential covariates was evaluated using backward elimination ($p<0.001$ or MOF of 10.828). Continuous covariates used linear, power, or exponential models. Categorical covariates used a categorical model.

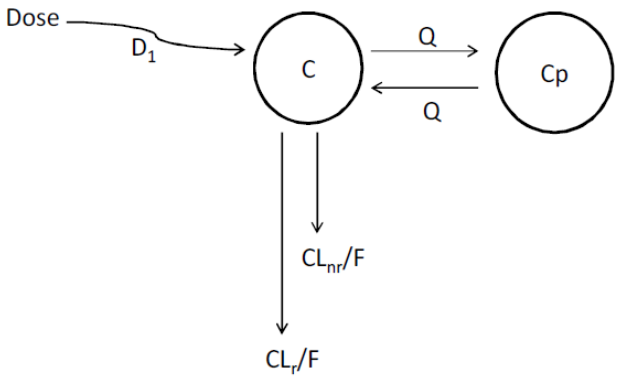


Figure 1. Schematic representation of the population pharmacokinetic model of baricitinib following oral administration

A visual predictive check (VPC) was performed to ensure that the model maintained fidelity with the data (Agoram et al. 2006; Bergstrand et al. 2011). The VPC approach entailed simulating PK data with the developed model, taking into account variability in all parameters as given by the residual error term. The distributions of simulated concentrations, conditional on the posterior distribution of model parameters, were compared to the observed distributions and ensured concordance. Ninety percent prediction intervals were computed from these simulated data and examined visually for the fraction of observations outside these bounds.

Model parameters and visual predictive check of the final model are displayed in Table 2 and Figure 2.

Table 2. Pharmacokinetic and Covariate Parameters in Final Population

Model Parameter (Unit)	Population Mean (%SEE)	BSV[a] (%SEE)	Mean (95% CI) from Bootstrap Analysis
Box-Cox transformation parameter for D_1	0.0906 (13.0)	—	0.0891 (0.0732 - 0.0993)
D_1 (hr)	0.204 (6.27)	214 (13.7)	0.201 (0.184 – 0.213)
LAG (hr)	0.119 (FIX)	—	—
CL_r/F (L/hr)	6.43 (2.30)	50.5 (10.7)	6.51 (6.33 - 6.66)
CL_{nr}/F(L/hr)	2.97 (4.07)	45.2 (9.03)	2.87 (2.75 – 3.00)
V_1/F (L)	89.3 (1.11)	15.5 (28.3)	89.3 (87.7 – 90.8)
Q (L/hr)	1.78 (4.33)	15.1 (FIX)	1.78 (1.68 – 1.86)
V_2/F (L)	29.2 (13.1)	125 (35.9)	29.7 (26.2 – 32.9)
Covariate for change in eGFR on CL_r/F[b]	0.00700 (24.9)	—	0.00662 (0.00310 - 0.0105)
Covariate for body weight on V_1/F[c]	0.0113 (7.63)	—	0.0113 (0.00958 – 0.0128)
Covariate for gender on V_1/F[c]	0.176 (22.2)	—	0.180 (0.128 – 0.243)
Covariance for CL_r/F and CL_{nr}/F[d]	—	0.174 (7.24)	—
Covariance for CL_r and V_1/F[d]	—	-0.0316 (18.9)	—
Proportional error[e]	0.321 (9.25)	—	0.322 (0.311 – 0.334)

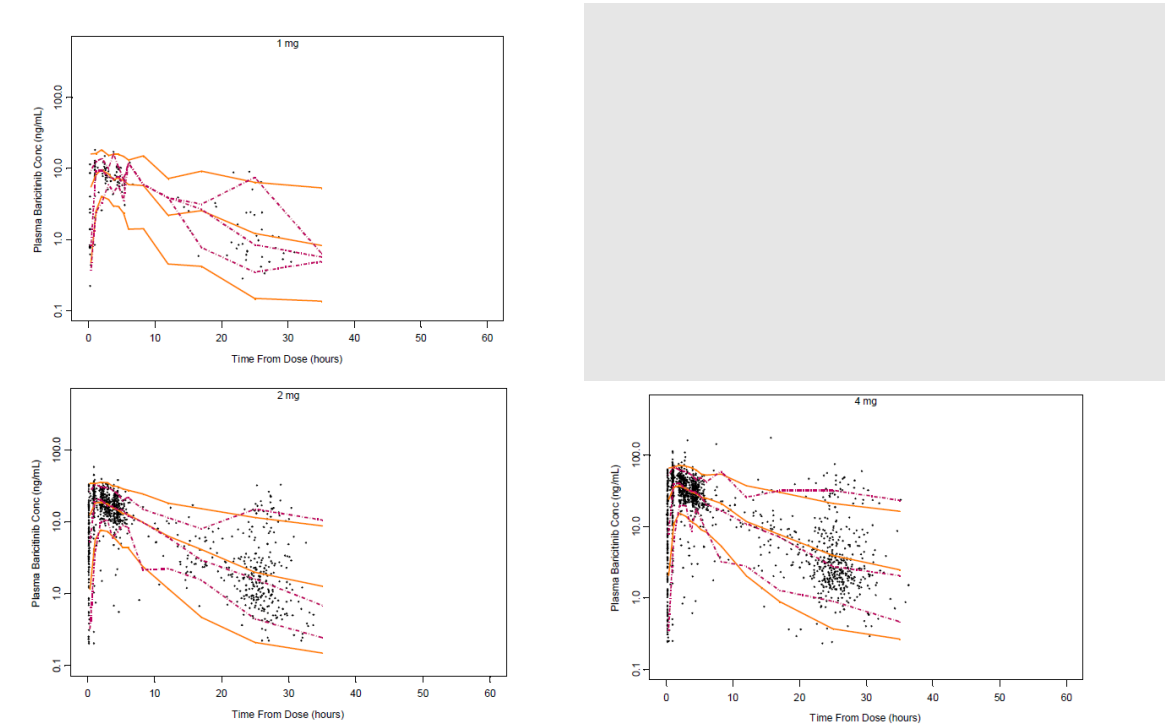


Figure 2. Visual predictive check for 1-, 2-, and 4-mg doses for the final population pharmacokinetic model.

Pharmacokinetics in the target population

Table 2 shows the key pharmacokinetic parameter estimates in patients with Alopecia Areata using individual post hoc parameter estimates from the final population pharmacokinetic model and compared with the individual post hoc estimates for the patients with Atopic Dermatitis and Rheumatoid Arthritis.

Table 3. Comparison of Mean (CV%) Population Pharmacokinetic Parameter Estimates in Patients with Alopecia Areata, Atopic Dermatitis, and Rheumatoid Arthritis

Parameter	Alopecia Areata[a]	Atopic Dermatitis[b]	Rheumatoid Arthritis[c]
CL/F (L/hr)[d]	11.0 (36)	11.2 (33)	9.42 (34)
CL_r/F (L/hr)	7.81 (40)	8.12	6.86
CL_{nr}/F (L/hr)	3.16 (32)	3.09	2.56
V/F (L)[e]	127 (19)	126 (17)	108 (19)
$t_{1/2}$ (h)	15.8 (35)	12.9 (36)	12.5 (27)
$AUC_{\tau,ss}$ at 4 mg (ng*hr/mL)[f]	435 (55)	415 (50)	483 (40)
$C_{max,ss}$ at 4 mg (ng/mL)[f]	47.5 (23)	45.9 (21)	53.3 (22)

The estimated mean CL/F of 11.0 L/h in patients with alopecia areata was similar to that in patients with AD (11.2 L/h) and approximately 17% higher than that in patients with rheumatoid arthritis (9.42 L/h). This was likely due to overall better renal function in patients with alopecia areata and atopic dermatitis compared with patients with rheumatoid arthritis. The median baseline eGFR was similar in patients with alopecia areata (eGFR=106.2 mL/min/1.73 m^2) compared with atopic dermatitis (eGFR=108 mL/min/1.73 m^2) and was higher than that in patients with rheumatoid arthritis (eGFR=90.8 mL/min/1.73 m^2).

Based on covariate testing, significant predictors of baricitinib PK included renal function (on CLr/F) and body weight and gender (on V1/F). The effect of renal function on the PK of baricitinib in patients with alopecia areata was similar to that characterized in patients with rheumatoid and atopic dermatitis. Although the covariates of body weight and gender were statistically significant on V1/F, the effect size was smaller than the between-subject variability in the $AUC_{\tau,ss}$ (55%) and $C_{max,ss}$ (23%) of baricitinib.

2.3.3. Pharmacodynamics

Mechanism of action

Baricitinib is a selective and reversible inhibitor of Janus kinase (JAK)1 and JAK2. In isolated enzyme assays, baricitinib inhibited the activities of JAK1, JAK2, Tyrosine Kinase 2 and JAK3 with IC50 values of 5.9, 5.7, 53 and > 400 nM, respectively.

JAKs are enzymes that transduce intracellular signals from cell surface receptors for a number of cytokines and growth factors involved in haematopoiesis, inflammation and immune function. Within the intracellular signalling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs), which activate gene expression within the cell. Baricitinib modulates these signalling pathways by partially inhibiting JAK1 and JAK2 enzymatic activity, thereby reducing the phosphorylation and activation of STATs..

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 (Fridman et al. 2010). 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

In the E-R analysis using data from phase 2/3 JAIHO study for AA indication, the majority of daily average concentration at steady state of dosing (Cav,ss) values in the lower 2 quartiles were from the baricitinib 2-mg doses, while values in the upper 2 quartiles were comprised mainly of values from the 4-mg dose (Figure 3). Clinically relevant higher rates of SALT ≤20 responses were observed at Week 36 in the 2 upper quartiles of exposure (mean SALT ≤20 response rate for Q3 and Q4 = 0.38) compared with the 2 lower quartiles (mean SALT ≤20 response rate for Q1 and Q2 = 0.24).

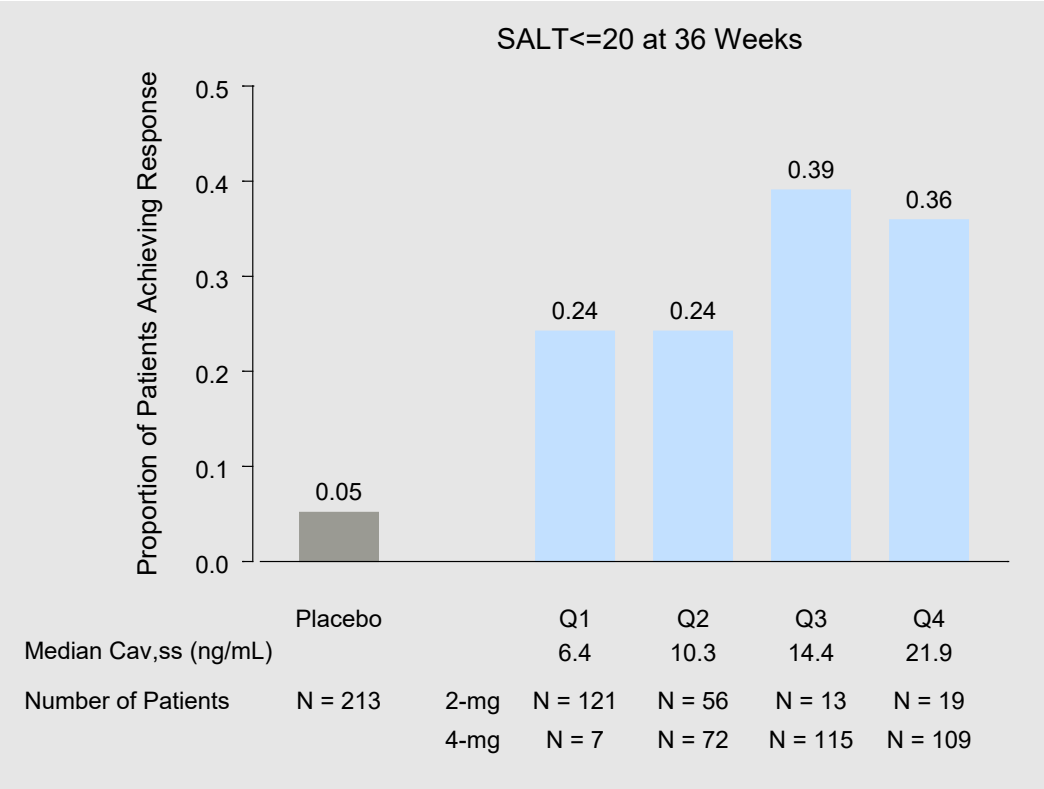


Figure 3 Exposure-response analysis: observed SALT ⩽20 response rates by concentration quartiles at Week 36 for patients receiving placebo, 2-mg, or 4-mg baricitinib once daily doses in Study JAHO.

2.3.5. Discussion on clinical pharmacology

Exposure-response analysis of phase 2/3 JAHO study supports the efficacy of the proposed 2-mg and 4-mg BD dosing regimen in the AA population. Considering that baricitinib is already approved for RA and AD indications, this approach is acceptable for the intended AA indication. Selecting 2-mg and 4-mg doses for phase 3 studies based on these results is justified.

Mean apparent clearance (CL/F) and half-life in patients with alopecia areata was 11.0 L/hr (CV = 36.0 %) and 15.8 hrs (CV = 35.0 %), respectively. C_{max} and AUC at steady state in patients with alopecia areata are 0.9-fold those seen in rheumatoid arthritis.

2.3.6. Conclusions on clinical pharmacology

The extent of data provided on the pharmacodynamics of baricitinib for AA indication is acceptable to the CHMP. Exposure-response analysis of phase 2/3 JAHO study supports the efficacy of the proposed 2-mg and 4-mg BD dosing regimen in the AA population.

2.4. Clinical efficacy

2.4.1. Dose response study

A dose of 4-mg is the recommended main dose for the AD and RA indications. In a Phase 2 study conducted in patients with moderate-to-severe AD (Study JAHG), both the 2 and 4-mg doses showed

benefit on the primary and major secondary endpoints, as compared with placebo, and both doses had an acceptable safety profile at Week 16. However, the 4-mg dose appeared to demonstrate a more rapid benefit (at 4 weeks) on more stringent endpoints, compared to the 2-mg dose. A similar trend between the baricitinib 4-mg and 2-mg doses was also observed in patients with RA. Dose-response for the AA indication was studied in the 'phase 2' part of the JAHO trial.

Phase 2 part of the Study JAHO

Based on available data, 3 doses were included in the Phase 2 part of the Study JAHO, including a 1 mg dose, to cover the range of exposures where clinical responses could be anticipated. Based on efficacy and safety data observed in the Phase 2 portion of Study JAHO, doses of 2- and 4-mg QD were selected for the Phase 3 part of the study.

To determine which dose(s) qualified for investigation in the Phase 3 portion of Study JAHO as well as Phase 3 Study JAIR, the MAH conducted an interim analysis once all patients had reached Week 12 or discontinued early (data cut-off date 29 May 2019). The MAH also analysed data from the portion of patients who had already reached Week 16 at the time of the interim analysis. After review of available data published for other JAK inhibitors, the MAH selected $SALT_{30}$ at Week 12 and $SALT_{50}$ at Week 16 (corresponding to at least 30% and 50% improvement of SALT score from baseline, respectively) as predictors for the primary endpoint (SALT ≤20 at Week 36).

Both baricitinib 4-mg and 2-mg demonstrated numerical superiority over placebo and baricitinib 1 mg for SALT30 at Week 12 and SALT50 at Week 16. Based upon these results, the MAH chose to investigate baricitinib 2-mg and 4-mg, in comparison to placebo, in the Phase 3 portion of Study JAHO and Study JAIR.

At the Week 36 (second interim) analysis, baricitinib 2-mg and 4-mg demonstrated a statistically significant improvement compared to placebo for the primary endpoint of AA-Investigator's Global Assessment of 0 or 1 with a ≥2-point improvement at Week 36 (Table 4). Results from the secondary endpoints were in line with the primary endpoint. Based upon these results, the MAH chose to continue to investigate baricitinib 2-mg and 4-mg in Phase 3.

Table 4 Efficacy Results at Week 36 in the Phase 2 Portion of Study JAHO

Week 36	PBO (N = 28)	BARI 1 mg (N = 28)	BARI 2 mg (N = 27)	BARI 4 mg (N = 27)
Response, n (%) (95% CI)[a]	1 (3.6) (0.6, 17.7)	0 (0.0) (0.0, 12.1)	9 (33.3) (18.6, 52.2)	14 (51.9) (34.0, 69.3)
Difference (95% CI) vs PBO[a]	NA	-3.6 (-17.7, 8.8)	29.8 (9.4, 48.8)	48.3 (25.5, 65.9)
Odds Ratio (95% CI) vs PBO[b]	NA	0.34 (0.01, 8.38)	9.88 (1.54, 63.38)	22.20 (3.42, >99.99)
p-Value vs. PBO[b]	NA	0.510	0.016	0.001

AA-IGA = Alopecia Areata Investigator's Global Assessment; CI = confidence interval; IGA = Investigator's Global Assessment; IP = investigational product; N = number of patients in the analysis population; n = number of patients in the specified category; NA = not applicable.

2.4.2. Main studies

The baricitinib clinical development programme for AA includes 2 pivotal global clinical studies (Study I4V-MC-JAHO [JAHO] and Study I4V-MC-JAIR [JAIR]) to evaluate the safety and efficacy of baricitinib

in adult patients with severe AA defined as ≥50% scalp hair loss. Both studies were multicentre, randomized, double-blind, placebo controlled, parallel-group, and outpatient.

Data from patients enrolled in the Phase 2 portion of Study JAHO, used for dose-finding, were not included in the efficacy analyses of the Phase 3 portion of the study.

In the Phase 3 portion of JAHO and Study JAIR, the efficacy and safety of 2-mg/day and 4-mg/day of baricitinib were compared to placebo in adult patients with severe AA. This submission includes efficacy data for 855 patients enrolled in the Phase 3 AA studies through Week 36 (placebo-controlled period), and for 629 patients (approximately 74%) randomised to baricitinib through Week 52.

Studies JAHO and JAIR are ongoing. Efficacy results have been submitted up to week 36 for 100% of patients, and week 52 for up to 80% of patients.

Objectives

Both 'phase 3' studies (Study I4V-MC-JAHO [JAHO] and Study I4V-MC-JAIR [JAIR]) had the same primary, secondary and additional objectives.

Primary objective

To test the hypothesis that the 4-mg dose or 2-mg dose of baricitinib is superior to placebo in the treatment of patients with severe or very severe AA.

Secondary objectives (Double-Blind, Placebo-Controlled Treatment Period)

To compare the efficacy of baricitinib 4-mg or 2-mg to placebo in AA during the double-blind, placebo controlled treatment period as measured by physician assessed signs and symptoms of AA

Other Secondary Objectives (Double-Blind, Placebo-Controlled Treatment Period)

To compare the efficacy of baricitinib 4-mg or 2-mg to placebo in AA during the double-blind, placebo controlled treatment period as measured by physician assessed signs and symptoms of AA

To compare the efficacy of baricitinib 4-mg or 2-mg to placebo in AA during the double-blind, placebo controlled treatment period as assessed by PRO measures and quality of life tools

Exploratory Objectives

May include evaluating the response to baricitinib treatment regimens on clinical measures and PROs. These endpoints may include dichotomous endpoints or change from Baseline for the following measures: SALT; SALT30; ClinRO Measure for Nail Appearance, Eyebrows, and/or Eyelash Hair Loss; PROs for Scalp Hair Assessment, Eyebrows, and Eyelashes; Nail Appearance and Eye Irritation; Skindex- 16 AA; SF-36; EQ-5D-5L; and HADS. Assessments of efficacy may be performed beyond Week 104 up to Week 200.

Design

Study JAHO is an adaptive, operationally seamless, Phase 2/3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient study. Phase 2 portion has been discussed previously in this report. In Phase 3, efficacy and safety of 2-mg dose QD and 4-mg QD doses of baricitinib was compared to placebo in adult patients with severe (SALT score of 50 to 94) or very severe (SALT score of 95 to 100) scalp AA.

Study JAIR is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and safety of baricitinib 2-mg once daily and baricitinib 4-mg once daily in adult patients with severe (SALT score of 50-94) or very severe (SALT score of 95-100) AA.

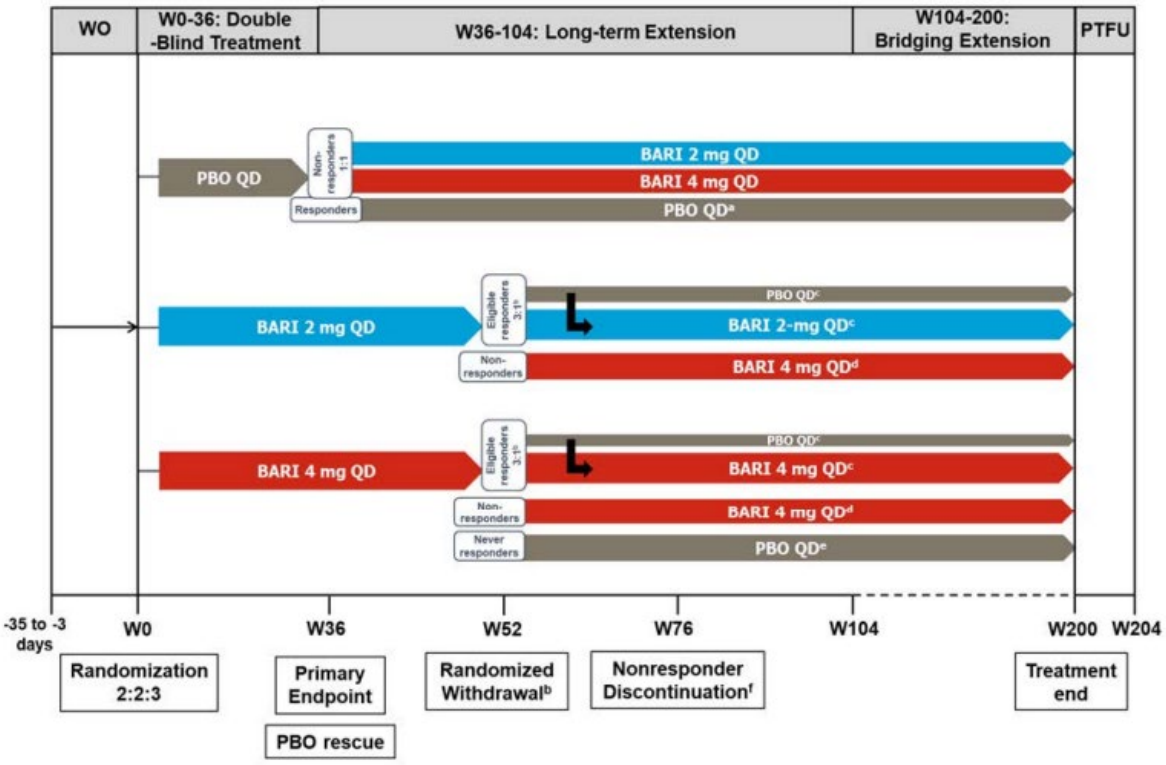


Figure 4 Illustration of JAHO (phase 3 portion) study design

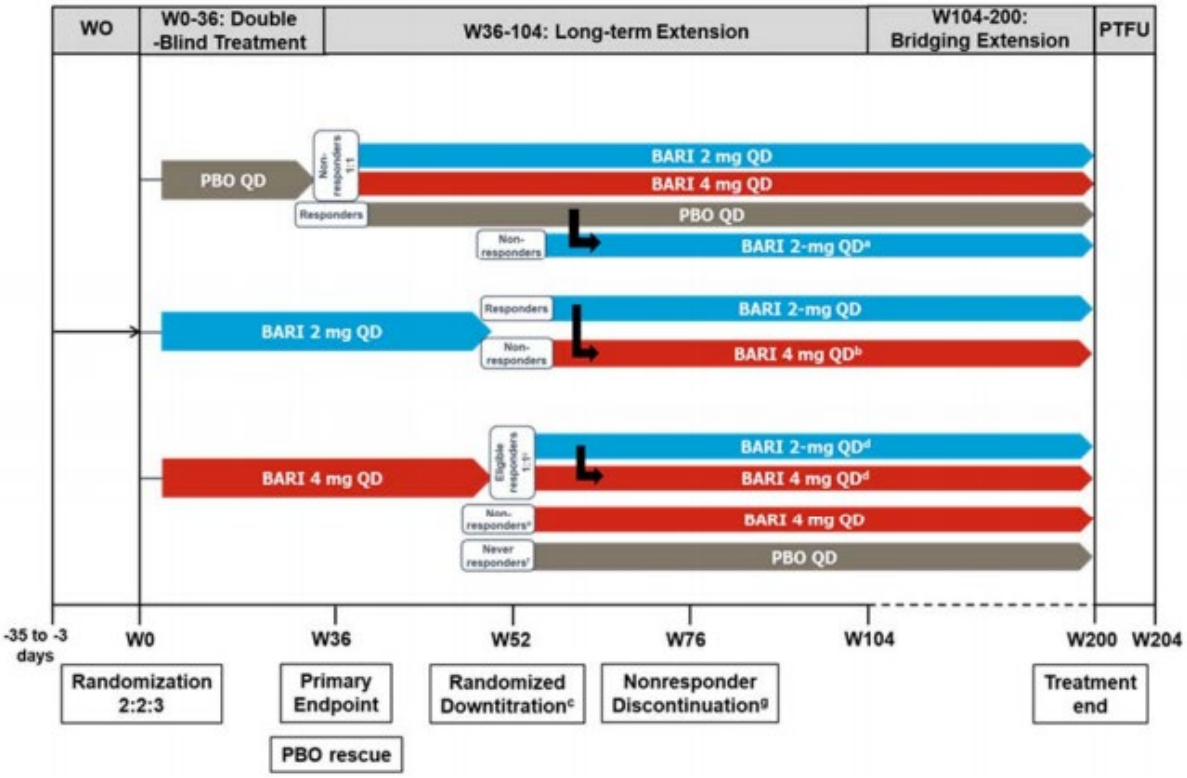


Figure 5 Illustration of JAIR study design.

Both studies were divided into 5 periods.

- **Period 1**: Screening
  - The Screening Period
    - was between 3 and 35 days prior to Visit 2 (Week 0), and
    - patients who met all of the inclusion criteria and none of the exclusion criteria continued to Visit 2.
- **Period 2**: Double-Blind Treatment Period (Weeks 0 to 36)
  Patients who met all eligibility criteria at Visit 2 (Week 0) were randomized in a 2:2:3 ratio to receive
    - placebo QD,
    - baricitinib 2-mg dose QD, or
    - baricitinib 4-mg dose QD.
- **Period 3**: Long-Term Extension
  All patients who have completed Study Period 2 (Week 36) entered the Long-Term Extension Period (up to 68 weeks of additional treatment [Study Period 3]). Patients continued their current treatment assignment unless predefined criteria were met for rescue.

  <u>At Week 36:</u>
  o Patients in the placebo treatment arm who had not achieved SALT ≤20 at Week 36, and who reach the Week 36 Visit were rescued to baricitinib and randomized in a 1:1 ratio to baricitinib 2-mg dose or baricitinib 4-mg dose.
  o Patients in the placebo arm who achieved a SALT ≤20 at Week 36 remained on placebo. These patients who experienced spontaneous regrowth remained on placebo for the remainder of the trial, even if a relapse is observed later during the study.
  o All patients in the baricitinib treatment arms continued in their current treatment group, regardless of their treatment response at Week 36.
  Studies JAHO and JAIR differed in their design from week 52 onwards, mainly: randomised treatment withdrawal was performed in JAHO, while randomised down-titration was performed in JAIR.

  <u>At Week 52 in JAHO:</u>
  <u>Responders: SALT ≤20</u>

  o Patients in baricitinib treatment arms who achieve a SALT ≤20 at Week 52 (responders) were eligible for randomized withdrawal, provided that they have stayed on the same dose of baricitinib from initial randomization (Visit 2).

  o Responders who were rescued to baricitinib at Week 36, were not eligible for randomized withdrawal and remained in their same treatment group.

  o Eligible patients were automatically randomized in a blinded manner by the IWRS in a 3:1 ratio to either stay on their current dose of baricitinib or transition to placebo (randomized withdrawal).

  o Any patients in the placebo treatment arm at Week 52 who have achieved a SALT ≤20 remained on placebo.

  o Responders who experienced a loss of treatment benefit after Week 52 (defined as >20-point absolute worsening in total SALT score), and who:

☐ were randomized to placebo at Week 52 (randomized withdrawal), will be automatically retreated with their baricitinib dose, as randomized at Baseline (Visit 2).

☐ remained on baricitinib at Week 52 (randomized withdrawal), continued to receive the same dose of baricitinib.

☐ were randomized to placebo at Baseline (Visit 2), remained on placebo.

Nonresponders: SALT >20

o Patients who have been in the baricitinib 4-mg treatment group from Baseline AND have never achieved a SALT ≤20 by Week 52 AND did not have a ≥2-point improvement from Baseline in ClinRO Measures for Eyebrow or Eyelash Hair Loss at Week 52 automatically transitioned to placebo.

o Patients who have been in the baricitinib 4-mg treatment group and have achieved a SALT ≤ 20 before Week 52 and have lost response, remained on baricitinib 4-mg dose.

o Those who have been in the baricitinib 2-mg treatment group from Baseline were rescued to baricitinib 4-mg.

o Those who were rescued to baricitinib at Week 36 continued in their current treatment arm at Week 52.

At Week 76:

o Patients who were nonresponders (SALT >20) at Weeks 52 AND 76 were automatically discontinued from the study at Week 76, unless they have a ≥2 point improvement from Baseline in ClinRO Measures for Eyebrow or Eyelash Hair Loss.

At Week 52 in JAIR:

Responders (SALT ≤20)

o Patients in the 4-mg dose baricitinib treatment arm who achieve a SALT ≤20 at Week 52 (responders) are eligible for randomized downtitration, provided that they have stayed on the same dose of baricitinib from initial randomization (Visit 2).

o Patients who were rescued to baricitinib at Week 36 and patients randomized to 2-mg dose baricitinib will not be eligible for randomized downtitration and will remain in their same treatment group.

o Eligible patients will be automatically randomized in a blinded manner by the interactive web-response system (IWRS) in a 1:1 ratio to either stay on their current 4-mg dose of baricitinib or transition to 2-mg dose of baricitinib (randomized downtitration).

o Patients in the placebo treatment arm at Week 52 who have achieved a SALT ≤20 will

remain on placebo.

o Responders who experience a loss of treatment benefit after Week 52 (defined as >20-point absolute worsening in total SALT score), and who:

☐ were randomized to 2-mg dose of baricitinib at Week 52 (randomized downtitration), will be automatically retreated with the 4-mg dose of baricitinib,as randomized at Baseline (Visit 2).

☐ remained on 4-mg dose of baricitinib at Week 52 (randomized downtitration), will continue to receive the same dose of baricitinib.

☐ were randomized to 2-mg dose at Baseline (Visit 2), will be rescued to 4-mg dose.

☐ had remained on placebo since Baseline (Visit 2), will be rescued to baricitinib 2-mg.

Nonresponders (SALT >20)

o Patients who have been in the baricitinib 4-mg dose treatment group from Baseline AND have never achieved a SALT ≤20 by Week 52 AND do not have a ≥2-point improvement from Baseline in clinician-reported outcome (ClinRO) measure for eyebrow or eyelash hair loss at Week 52 will be automatically transitioned to placebo.

o Patients who have been in the baricitinib 4-mg dose treatment group and have achieved a SALT ≤20 before Week 52 and have lost response, will remain on baricitinib 4-mg dose.

o Those who have been in the baricitinib 2-mg dose treatment group from Baseline will be rescued to baricitinib 4-mg dose.

o Those who were rescued to baricitinib at Week 36 will continue in their current treatment arm at Week 52.

o Those who were randomized to placebo at Baseline and were not eligible for rescue to baricitinib at Week 36 (spontaneous remission) will be rescued to baricitinib 2-mg.

Note: Investigators should consider discontinuing patients who do not present any improvement of AA lesions by Week 64 (Visit 14).

- **Period 4**: Bridging Extension in JAHO

  o Patients who have completed Week 104 and have not met criteria for permanent discontinuation had the possibility to remain in the trial for up to 96 additional weeks (up to Week 200).

  o During Period 4, patients continued to receive the same treatment they received during Period 3.

  o Responders who had been randomized to placebo at Week 52 (randomized withdrawal) and have remained on placebo, had the possibility to be retreated with their baricitinib dose as randomized at Baseline (Visit 2) if they experienced a loss of benefit (defined as >20-point absolute worsening in total SALT score).

  Bridging Extension in JAIR

  o Patients who were randomized to placebo at Baseline and were not eligible for rescue to baricitinib at Week 36 or during Period 3 (spontaneous remission) will continue to have the opportunity to be rescued to baricitinib 2-mg if they experience loss of treatment benefit.

  o Baricitinib 4mg responders who had been randomized to baricitinib 2-mg at Week 52 (randomized downtitration) and have remained on baricitinib 2-mg, will have the possibility to be retreated with baricitinib 4-mg if they experience a loss of benefit (defined as >20-point absolute worsening in total SALT score) during Period 4.

- **Period 5**: Post-Treatment Follow-Up

o Patients who complete the study through Visit 24 (Week 200), had a Post- Treatment Follow-Up visit (Visit 801) approximately 28 days after the last dose of IP.

o Patients who have completed Week 200 and who continued on marketed product beyond Week 200 did not need to complete Period 5 (Visit 801).

o Patients who have received at least 1 dose of study intervention and discontinued early from the study must have an Early Termination visit and return for the Post-Treatment Follow-Up visit (Visit 801) approximately 28 days after the last dose of IP.

Study participants

Inclusion/Exclusion

The in/exclusion criteria were similar for the phase 3 portion of Study I4V-MC-JAHO [JAHO] and Study I4V-MC-JAIR [JAIR]. To be eligible to participate in the phase 3 studies (JAHO and JAIR), patients must have:

☐ been at least 18 years of age and ≤60 years of age for males and ≤70 years of age for females at the time of informed consent.

☐ had severe or very severe AA, as determined by all of the following:

o current AA episode of more than 6 months' duration and hair loss encompassing ≥50% of the scalp, as measured by SALT (AA-IGA of 3 or 4, corresponding respectively to SALT = 50 to 94 and SALT = 95 to 100) at Visit 1 AND Visit 2.

o no spontaneous improvement (that is, no more than 10-point spontaneous reduction in SALT) over the past 6 months.

o current episode of severe or very severe AA of less than 8 years.

☐ Patients who have severe or very severe AA for ≥8 years may be enrolled if episodes of regrowth, spontaneous or under treatment, have been observed on the affected areas of the scalp over the past 8 years.

Patients were **excluded** from inclusion in the study if they meet the following criteria:

☐ had primarily "diffuse" type of AA (characterized by diffuse hair shedding).

☐ were currently experiencing other forms of alopecia, or any other concomitant conditions that would interfere with evaluations of the effect of study medication on AA.

☐ had inadequate washout with the following therapies including but not limited to:

o corticosteroids
o JAK inhibitors
o monoclonal antibodies
o phototherapy
o immunosuppressants

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.

Treatments

Both studies (Study I4V-MC-JAHO [JAHO] and Study I4V-MC-JAIR [JAIR]) incorporated randomization and blinding methods to minimize bias. Enrolled patients were randomized in 2:2:3 ratio for

- placebo once daily
- baricitinib 2-mg QD, or
- baricitinib 4-mg QD.

Table 5 outlines the study intervention(s).

Table 5 ***Study Intervention(s) Administered.***

Treatment Regimen	Investigational Product Supplied	Dose
Baricitinib 4 mg QD[a]	Baricitinib 4-mg tablets Placebo to match 2-mg tablets	2 tablets per day
Baricitinib 2 mg QD	Baricitinib 2-mg tablets Placebo to match 4-mg tablets	2 tablets per day
Placebo QD	Placebo to match 4-mg tablets Placebo to match 2-mg tablets	2 tablets per day

Concomitant Therapy

The following medications were permitted during the study:

☐ topical corticosteroids except on the scalp, eyebrows, and eyelashes

☐ topical calcineurin inhibitors except on the scalp, eyebrows, and eyelashes

☐ 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 are permitted

☐ non-live vaccinations such as seasonal vaccination, non-live herpes zoster (for subjects who become eligible during the trial), and/or all emergency vaccinations such as rabies or tetanus vaccinations

☐ bimatoprost ophthalmic solution (if on stable dose for 8 weeks prior to randomization)

☐ finasteride (or other 5 alpha reductase inhibitors) or oral or topical minoxidil, if on a stable dose for 12 months prior to randomization, and

☐ HMG CoA reductase inhibitors or "statins" (for example, simvastatin, simvastatin + ezetimibe) for treatment of hypercholesterolemia and the prevention of cardiovascular disease.

Treatment with concomitant therapies for other medical conditions, such as diabetes and hypertension, was permitted during the study.

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

The primary and key secondary endpoints were adjusted for multiplicity in both Phase 3 studies (Study I4V-MC-JAHO [JAHO] and Study I4V-MC-JAIR [JAIR]). Additional efficacy endpoints were prespecified in the study protocols but were not adjusted for multiplicity.

Primary Efficacy endpoint - Severity of Alopecia Tool (SALT)

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 (Olsen et al. 1999, 2004).

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%.

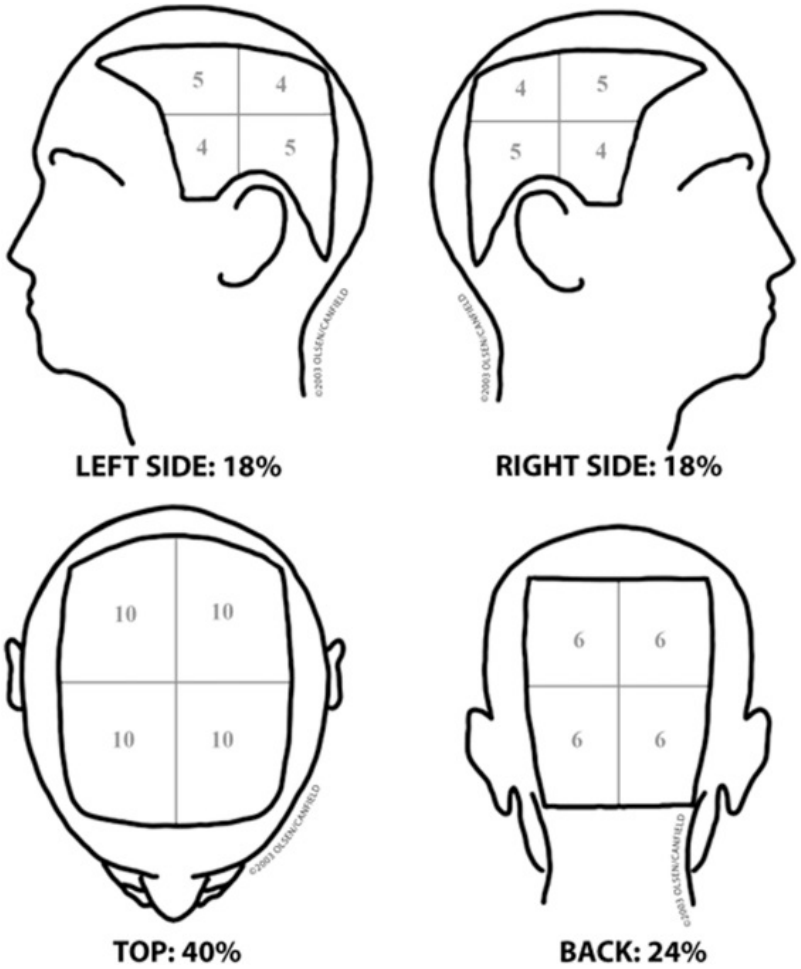


Figure 6 SALT aid for determining scalp surface area.

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 (Olsen et al. 1999, 2004).

The primary endpoint for the Phase 3 AA studies is SALT ≤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 (Wyrwich et al. 2020a).

Key Secondary Efficacy Endpoints

- *Additional Severity of Alopecia Tool Assessments*

The AA studies included more stringent SALT assessments (i.e. $SALT_{90}$ and SALT ≤10 at Week 36) as key secondary endpoints. These assessments correspond to at least 90% improvement of SALT score from baseline and ≤10% scalp hair loss, respectively. The studies also included SALT assessments at earlier timepoints, including SALT ≤20, SALT ≤10 and the less stringent endpoint of $SALT_{50}$, to investigate the onset of treatment benefit.

- *Scalp Hair Assessment Patient Reported Outcome*

The MAH developed the Scalp Hair Assessment PRO™ to assess the patient's perception of current extent of scalp involvement. The PRO is a 5-point, single-item patient assessment of scalp hair loss severity:

- 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).
- 4 - Nearly all or all (95% to 100% of my scalp is missing hair).

Because this is a newly introduced outcome measure, the MAH has submitted the evidence dossier describing the development and validation of this measure. The content validity of the Scalp Hair Assessment PRO was assessed via qualitative interviews with 10 dermatologists with clinical expertise in AA and 45 patients with ≥50% AA-related scalp hair loss (n=30 in Round 1 and n=15 in Round 2). The measurement properties of the Scalp Hair Assessment PRO were evaluated using data from JAHO and JAIR studies. The FAS from Studies JAHO (Phase 3 portion) and JAIR were used in the psychometric analyses. Data up to and including Week 36 were included.

Test-retest reliability of the Scalp Hair Assessment PRO was examined in a subset of the analysis population who had stable disease status based on their SALT score category at screening and baseline visits, with ≥7 to ≤14 days between visits. The Intraclass Correlation Coefficients (ICCs) observed ranged from 0.70 to 0.85, with higher scores indicating better reliability.

Discriminant validity of the Scalp Hair Assessment PRO was evaluated using t-tests to distinguish scores between subgroups defined on SALT score at baseline (that is, those with a SALT score of 50-94 versus 95-100). Patients with a SALT score of 95 to 100 had statistically significantly higher (worse) scores on the Scalp Hair Assessment PRO than those reporting less severe hair loss of 50%-94%. However, validity using the Skindex-16 Emotions Domain score as a reference, could only be demonstrated for one of the pivotal trials (JAHO). Furthermore, Scalp Hair Assessment PRO scores were not observed to differ significantly between patients with better or worse SF-36v2 Item 1 scores (overall health) in either Study JAHO or Study JAIR.

For **concurrent validity**, it was hypothesized that moderate to large correlations would be observed between the Scalp Hair Assessment PRO and the Skindex-16 Emotions Domain, and the Scalp Hair Assessment PRO and SF-36v2 Item 1 (overall health); however, small to moderate Pearson correlations (that is, ≥0.0 to ≤0.4) were observed at all time points in both Phase 3 studies.

Clinical relevance was evaluated in the development study (Wyrwich et al. 2020c). Most of the patients in round 1 and round 2 who were asked (34 of 35, 97%) indicated that treatment would be successful if they moved from ≥ 50% missing hair at baseline to the 'limited' category (≤ 20% missing hair) on the Scalp Hair Assessment PRO.

Sensitivity to change, was not evaluated in the pivotal trials, no further information on sensitivity was provided.

- *Clinician-Reported Outcomes for Eyebrow Hair Loss and Eyelash Hair Loss*

The MAH developed 2 novel Clinician-reported outcomes (ClinRO) to measure 2 important signs of AA:

- ClinRO Measure for EB Hair Loss™ and
- ClinRO Measure for EL Hair Loss™.

Both ClinRO Measures use a 4-point response scale (Table 6).

Table 6 ***ClinRO measures for Eyebrow and Eyelash hair loss***

Score	ClinRO Measure for Eyebrow Hair Loss™	ClinRO Measure for Eyelash Hair Loss™
0	The eyebrows have full coverage and no areas of hair loss	The eyelashes form a continuous line along the eyelids on both eyes
1	There are minimal gaps in eyebrow hair **and** distribution is even	There are minimal gaps **and** the eyelashes are evenly spaced along the eyelids on both eyes
2	There are significant gaps in eyebrow hair **or** distribution is not even	There are significant gaps along the eyelids **or** the eyelashes are not evenly spaced along the eyelids
3	No notable eyebrow hair	No notable eyelashes

Abbreviation: ClinRO = clinician-reported outcome.

Assessment of the test-retest reliability, Discriminant validity and convergent validity of the ClinRO Measure for Eyebrow/Eyelashes Hair Loss was investigated in 2 clinical studies, Study JAHO and Study JAIR, in patients with severe to very severe AA.

Test-retest reliability of the ClinRO Measure for Eyebrow/Eyelashes Hair Loss was examined in a subset of the analysis population who had stable disease status based on their SALT score category. The ICCs observed ranged from 0.89 to 0.90 in JAHO and JAIR trials for ClinRO Measure of Eyebrow Hair Loss. The ICCs observed for the ClinRO Measure for Eyelash Hair Loss were 0.90 in both studies, indicating good test-retest reliability among stable patients.

Discriminant validity of the ClinRO Measure for Eyebrow/Eyelashes Hair Loss was evaluated using t-tests to distinguish scores between subgroups defined on the PRO Measure for Eyebrow/Eyelashes score at baseline. Patients with more severe eyebrow hair loss as assessed by the PRO were hypothesized to have significantly higher (worse) scores on the ClinRO Measure for Eyebrow/Eyelashes Hair Loss. Supplemental analyses using subgroups defined by the Skindex-16 Emotions Domain score and SALT score at baseline were also performed.

In Study JAIR, patients with low (less than or equal to median) versus high (greater than median) scores on the Skindex-16 Emotions Domain Score had significantly higher (worse) scores on the ClinRO Measure for Eyebrow Hair Loss according to both primary and sensitivity analyses. However, this was not observed in Study JAHO, where there was no statistically significant difference in ClinRO Measure for Eyebrow Hair scores between these 2 groups in either the primary or sensitivity analyses.

Patients with more severe eyelash hair loss (that is, those with a PRO Measure for Eyelashes score of 2 or 3) had statistically significantly higher (worse) scores on the ClinRO Measure for Eyelash Hair Loss

than those reporting less severe eyelash hair loss (that is, a PRO Measure for Eyelashes score of 0 or 1). Therefore, in both Phase 3 studies, both primary (parametric t-tests) and sensitivity (nonparametric Kruskal-Wallis tests) analyses demonstrated that the ClinRO Measure for Eyelash Hair Loss could differentiate significantly between known groups of patients with different severity of eyelash hair loss. Additionally, patients with less scalp hair loss as assessed by the SALT (score ≥50 and ≤94) and patients with greater than median Skindex-16 Emotions Domain scores had significantly lower (better) scores on the ClinRO Measure for Eyelash Hair Loss than those with greater scalp hair loss as assessed by the SALT (score ≥95 and ≤100) or less than or equal to median Skindex-16 Emotions Domain scores in both trials according to both primary and sensitivity analyses.

Convergent validity was assessed by Pearson correlations and Spearman rank-based correlation coefficients at baseline and Week 36 between the ClinRO Measure for Eyebrow Hair Loss and the PRO Measure for Eyebrows (primary), SALT (exploratory), Skindex-16 Emotions Domain (exploratory), and SF-36v2 Item 1 (exploratory). Correlations (that is, ≥0.5) were observed between the ClinRO Measure for Eyebrow Hair Loss and the PRO Measure for Eyebrows at baseline and Week 36 in both Phase 3 studies (Pearson correlation range 0.85-0.88). In the exploratory evaluations, moderate (that is, ≥0.3 to <0.5) to large (that is, ≥0.5) correlations between the ClinRO Measure for Eyebrow Hair Loss and the SALT were observed at all time points in both studies. A correlation was observed between the ClinRO Measure for Eyelash Hair Loss and the PRO Measure for Eyelashes at baseline and Week 36 in both Phase 3 studies (Pearson correlation range 0.86-0.88). In the exploratory evaluations, moderate (that is, ≥0.3 to <0.5) to large (that is, ≥0.5) correlations between the ClinRO Measure for Eyelash Hair Loss and the SALT were observed at all time points in both studies.

Additional secondary efficacy endpoints

- *Skindex-16™ Adapted for Alopecia Areata*

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 adults with scalp AA.

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. (Reid et al. 2012).

- *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 (Zigmond and Snaith 1983; White et al. 1999). Scores for each domain (i.e. Anxiety and Depression) can range from 0 to 21, with higher scores indicating greater anxiety or depression (Zigmond and Snaith 1983; Snaith 2003). A HADS Anxiety Score or HADS Depression Score of ≥8 indicates that a patient is suffering from anxiety or depression, respectively (Bjelland et al. 2002).

- *Patient-Reported Outcome Measure for Eyebrow*

The MAH has developed a novel PRO assessment measuring the extent of EB Hair Loss: PRO Measure for EB Hair Loss. This PRO assessment is a single item that uses a 4-point response scale, ranging from 0 (full coverage and no areas of hair loss) to 3 (no notable EB hair) (Wyrwich et al. 2020b).

- *Patient-Reported Outcome Measure for Eyelash*

The MAH has developed a novel PRO assessment measuring the extent of EL Hair Loss: PRO Measure for EL Hair Loss. This PRO assessment is a single item that uses a 4-point response scale, ranging from 0 (ELs form a continuous line along the eyelids on both eyes) to 3 (no notable ELs) (Wyrwich et al. 2020b).

Table 7 ***Final versions of PRO measures for eyebrows and eyelashes***

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
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

Sample size

Phase 3 Portion of Study JAHO

It was calculated that approximately up to 625 patients needed to be eligible for the primary efficacy analysis. That sample size will provide more than 90% power to detect a difference between the highest baricitinib dose selected and placebo treatment groups in the primary endpoint based on a Chi-square test, without continuity correction, at a significance level of 0.05, and assuming a difference of response of 25% (Kennedy Crispin et al. 2016; Mackay-Wiggan et al. 2016) with a 5% placebo response rate. Sample size was computed through using EAST v.6.4. P.

Study JAIR

Because 2 doses of baricitinib were identified to continue into Phase 3 after the interim analysis in Study JAHO, approximately 678 patients should have been screened in order to enroll approximately 476 patients in Study JAIR. The enrolled patients were planned to be randomized in a 2:2:3 ratio for placebo

QD (136 subjects), baricitinib low dose QD (136 subjects), or baricitinib high dose QD (204 subjects). This sample size provides more than 90% power to test the superiority of the selected baricitinib high dose to placebo or the superiority of the selected baricitinib low dose to placebo in the primary endpoint based on a 2-sided Fisher exact test within the graphical testing scheme, at an initial significance level of 0.04 for the high dose and 0.01 for the low dose.

The assumptions used for the power calculation are as follows: 30% response rate for the selected baricitinib high dose, 20% response rate for the selected baricitinib low dose, and 5% response rate for placebo (Kennedy Crispin et al. 2016; Mackay-Wiggan et al. 2016). The initial alpha allocation may be adjusted in the SAP when newer information was obtained on the endpoints that were tested and were finalized prior to the primary database lock.

Randomisation

In both the Phase 3 Portion of Study JAHO and Study JAIR assignment to treatment groups was determined by a computer-generated random sequence using an interactive web-based response system (IWRS). The IWRS was used to assign bottles, each containing double-blind IP tablets, to each patient at each visit starting at Visit 2 (Week 0). Site personnel confirmed that they had located the correct bottles by entering a confirmation number found on the bottle into the IWRS. Both studies randomised patients 2:2:3 at baseline to placebo, baricitinib 2-mg or baricitinib 4-mg. Randomisation in both studies was stratified by geographic region (North America, Asia and Rest of World) and duration of current episode at baseline (<4 years versus ≥4 years).

Blinding

Both JAHO and JAIR are double-blind studies. To preserve the blinding of the study, a minimum number of persons was able to see the randomization table and treatment assignments before study completion. All study assessments were performed by study personnel who were blinded to the patients' treatment groups. The 4-mg and 2-mg tablets have a distinctive shape and color. A double-dummy design was used for blinding, where each strength tablet had its matching placebo. Study drugs were delivered to patients in bottles.

JAHO was a seamless phase II/III trial with a decision point and interim analysis for futility and dose selection performed after 12-week follow-up was completed for the first 100 participants randomized. A second interim analyses of the phase II data were planned when these participants were followed-up for 36 weeks. A selected group of individuals was unblinded to work on this interim analysis. At the time of the first interim analysis, approximately 200 participants were already included in the phase III part of the trial. Assignment of all participants in the phase III part of the trial remained blinded.

In both the phase III part of JAHO and the JAIR study unblinding was performed after database lock for the primary efficacy analysis.

Statistical methods

Populations and treatment groups

Unless otherwise specified, efficacy analyses in the Phase 3 studies JAHO and JAIR were conducted on the Full Analysis Set (FAS) population, which included all patients who were randomized. Sensitivity analyses were performed in the modified Full Analysis Set (mFAS) and the per protocol set (PPS).

Population	Description
Full Analysis Set (FAS)	All patients randomized in Study JAIR will be included in the FAS. Patients will be analyzed according to the IP to which they were randomized at Baseline (Visit 2). Of note, FAS is essentially the ITT population.
Modified Full Analysis Set (mFAS) Population	All patients randomized in Study JAIR and received at least 1 dose of IP, will be included in the mFAS. It excludes patients with female pattern baldness and male patients with diffuse AGA[a] (Grade IV and above) (Norwood 1975) identified at Week 36. Patients will be analyzed according to the IP to which they were randomized at Baseline (Visit 2).
Per-Protocol Set (PPS)	The PPS will include all mFAS patients who are not deemed noncompliant with treatment, who do not have any of the important protocol deviations that exclude patients from the PPS, and whose investigator site does 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.
Safety Population	The Safety Population is defined as all patients who were randomized in Study JAIR, 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. Patients will be analyzed according to the treatment group to which they were assigned.

Abbreviations: AGA = androgenetic alopecia; GCP = good clinical practice; IP = Investigational product, ITT = intent-to-treat.

[a] Some male patients with Grade IV AGA and female patients with patterned baldness may only be identified after hair regrowth.

Analyses performed

The primary analysis of discrete efficacy and health outcomes variables was a logistic regression analysis with fixed effect for treatment group and adjustment for the baseline value and stratification factors geographic region and duration of current episode at Baseline (<4 years vs ≥4 years). The p-value and 95% confidence interval (CI) for the odds ratio from the logistic regression model were used for primary statistical inference. In the case when logistic regression model did not produce statistical results due to sparse data, Fisher exact test was used. The difference in percentages and 95% CI of the difference in percentages using the Newcombe-Wilson method without continuity correction were used for descriptive purposes unless, otherwise, specified.

The primary analysis for the continuous efficacy and health outcome variables was an ANCOVA with treatment group as the main predictor and adjustment for the baseline value and stratification factors geographic region and duration of the current episode at Baseline (<4 years vs ≥4 years). Type III tests for LS means will be used for statistical comparison between treatment groups. The LS mean difference, standard error, p-value, and 95% CI are also be reported.

Time-to-event analysis were be done and analyzed using log-rank test and Kaplan-Meier curves.

Handling of dropouts and missing data

Missing discrete efficacy and health outcomes variables were imputed using NRI for logistic regression analyses. Patients were considered non-responders for the NRI-based analysis if they did not meet clinical response criteria or if they permanently discontinued study treatment or discontinued from the study at any time prior to the time point of interest for any reason.

The modified last observation carried forward (mLOCF) was used for imputation of missing continuous efficacy and health outcome variables for ANCOVA analyses. The LOCF method uses the most recent non-missing postbaseline assessment. The use of LOCF was considered reasonable as very few patients experienced waxing and waning in scalp hair coverage during treatment in the Phase 2 portion of the JAHO study. The specific modification to the LOCF is that data after permanent study treatment discontinuation will not be carried forward.

The primary censoring rule excluded data collected after permanent study drug discontinuation or data collected at remote visits due to the COVID-19 pandemic. The associated estimand for the primary objective is to measure the effect of baricitinib 4-mg or baricitinib 2-mg vs placebo on patients with severe or very severe AA as assessed by the proportion of patients achieving SALT ≤20 at Week 36, assuming that treatment response disappears at the visits conducted remotely because of the COVID-19 pandemic or after patients discontinue from study or treatment.

Sensitivity analyses

Analyses for primary and key secondary health outcomes were repeated in the modified full analysis set (mFAS). Analyses for the primary outcome were repeated in the per protocol set (PPS).

To determine the impact of the COVID-19 pandemic on the efficacy assessment of primary and key secondary endpoints, two types of supplemental analyses were performed.

First, a secondary censoring rule was considered where data collected remotely was included in the analysis. Analyses for the secondary censoring used NRI or mLOCF for imputation of missing outcomes.

Second, a hybrid imputation was implemented to handle the missing data due to the COVID-19 by multiple imputation or other missing data not due to COVID-19 by nonresponder imputation. The hybrid imputation handled missing data due to the COVID-19 pandemic by multiple imputation and other missing data not due to COVID-19 by nonresponder imputation or mLOCF. This imputation procedure addresses the hybrid estimand assuming that the effects of treatments will be the same had patients not experienced any intercurrent event related to COVID-19 (e.g., either remote visits or missed visits due to COVID-19, etc.) or the effect will disappear after any intercurrent event not related to COVID-19. The hybrid imputation was combined with the primary censoring rule.

In addition, the following sensitivity analyses were prespecified in protocols and/or statistical analyses plans. Regarding the non-responder imputation (NRI), additional analyses were to be performed on all available data, hence including data collected after permanent treatment discontinuation. The placebo multiple imputation (pMI) method was planned as an additional analysis for the analysis of the primary efficacy endpoint, as well as key secondary endpoints. In the SAP, the pMI was replaced by the hybrid imputation method. Finally, the tipping point analysis was planned as an additional sensitivity analysis for some key secondary objectives and prespecified in both protocols and statistical analysis plans.

Multiplicity adjustment

Multiplicity adjusted analyses were be performed on the primary and key secondary objectives in order to control the overall family-wise Type I error rate within each study at a 2-sided alpha level of 0.05.

The graphical multiple testing procedure described in Bretz et al. (2011) was used. The graphs used for the final analyses are given in the final versions of the Statistical Analysis Plan (version 4 for JAHO and version 3 for JAIR). A different graph was used in JAHO and JAIR studies. In both JAHO and JAIR, the primary endpoint SALT ≤20 at week 36 was first tested at a 2-sided α=0.025 for both 2-mg and 4-mg doses. If at least 1 of null hypotheses is rejected, the testing process continues with testing of secondary endpoints at week 36 followed by testing of secondary endpoints at week 24, 12 and 16. The testing process continues as long as there is at least 1 hypothesis in the scheme that can be rejected at its allocated alpha level at that point.

No adjustment was made for endpoints outside of the graphical testing procedure (these were all tested independently using an alpha of 0.05).

The following graph was used in the JAHO study:

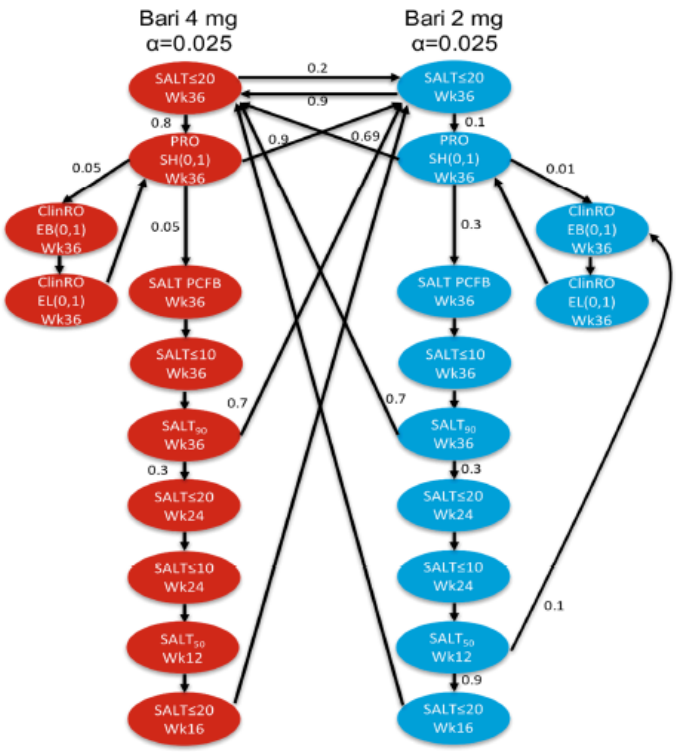


Figure 7 Graphical testing procedure for I4V-MC-JAHO

The graph for the JAIR study was the following:

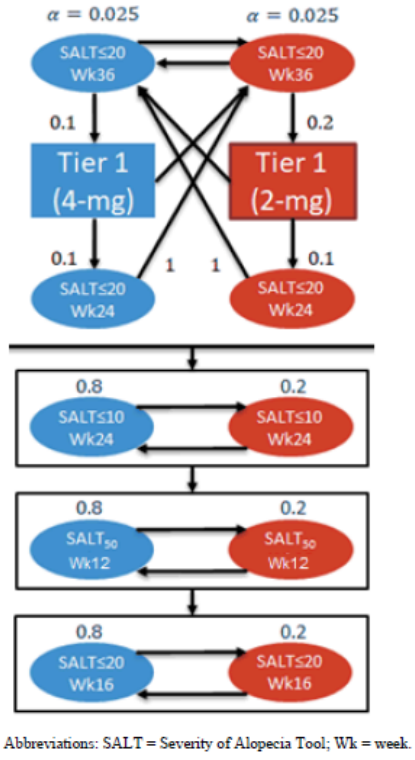


Figure 8 Overview of the graphical testing procedure for I4V-MC-JAIR

Tier 1 in the graph for JAIR refers to key secondary endpoints at 36 weeks which were tested in the following order:

Abbreviations: ClinRO = clinician-reported outcome; EB = eyebrow; EL = eyelash; PCFB = percent change from baseline; PRO = patient-reported outcome; SALT = Severity of Alopecia Tool; $SALT_{90}$ = at least 90% improvement from baseline in SALT score; Wk = week.

Figure 9 Graphical testing procedure within Tier 1 group of endpoints

Results

Participant flow

Study JAHO, Phase 3 portion

A total of 829 patients entered the Phase 3 portion of the study. A total of 654 patients were randomized to a treatment group. The rates of study treatment discontinuation before Week 36 ranged from 11.1% in placebo 8.7% in baricitinib 2-mg, and 6.8% in the baricitinib 4-mg group (Figure 10).

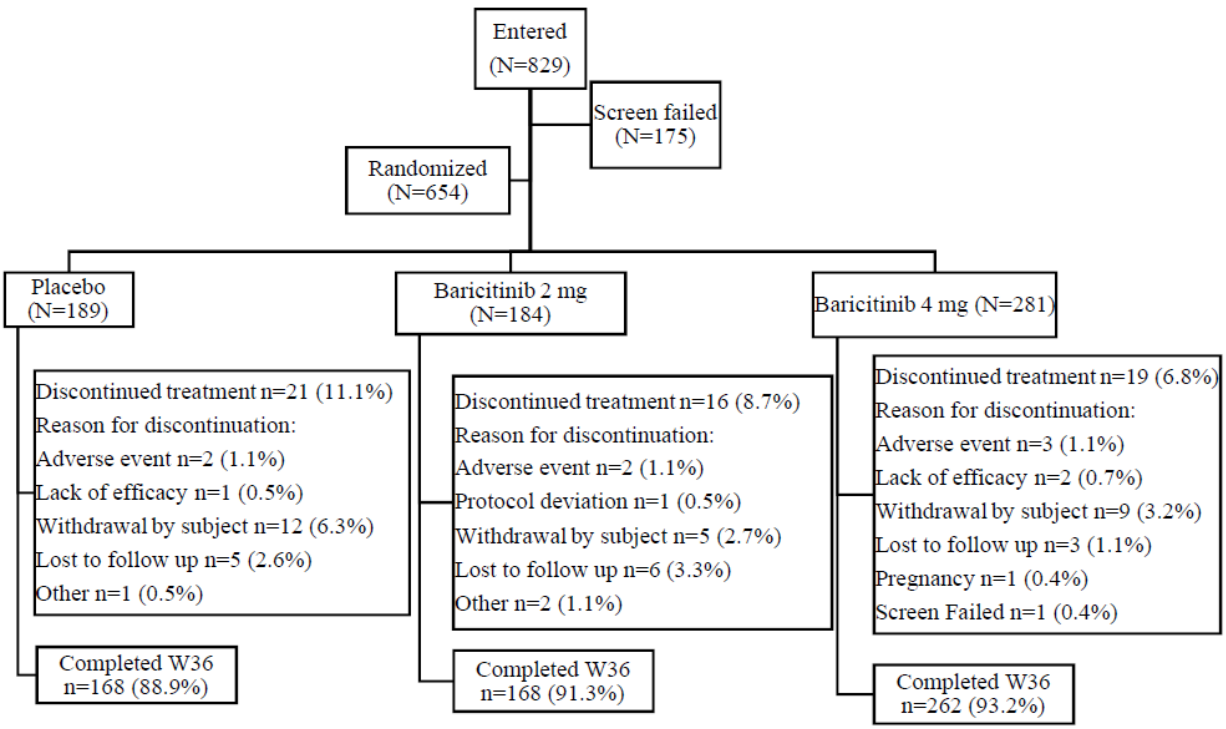


Figure 10 Study treatment disposition. JAHO phase 3 portion

Study I4V-MC-JAIR [JAIR]

A total of 727 patients were screened; 546 of these patients were randomized to a treatment group. Study discontinuation rates ranged from 13.5% in the placebo group 10.9% in the baricitinib 2-mg group, and 7.7 % in the baricitinib 4-mg group. Overall, 490 patients completed the Week 36 treatment visit and entered the JAIR long-term extension period (Figure 11).

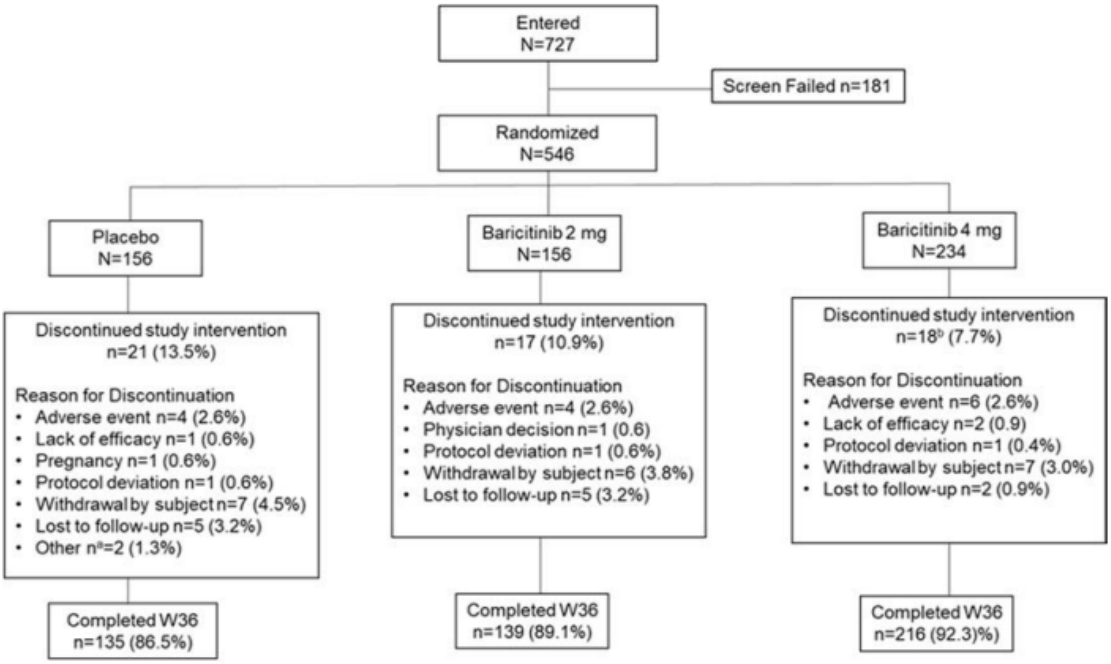


Figure 11 Study intervention disposition figure. Study JAIR.

Across the 2 studies, 91% of patients completed Week 36. The most common reasons for study discontinuation were withdrawal by patient, lost to follow-up and adverse event.

Recruitment

JAHO study initiated on 24 September 2018 (first patient first visit). JAIR study initiated at 08 July 2019 (first patient first visit). For both studies, the primary completion date (the analyses presented in this report) and database lock date were on 02 February 2021.

Conduct of the study

The clinical data package submitted in this application only includes data generated outside the EU. Participating countries in the AA Phase 3 studies are shown in Table 8.

Table 8 Participating countries

	Study JAHO		Study JAIR
Number of Patients	Phase 2: 110	Phase 3: 654	546
Participating Countries	Japan, South Korea, Mexico, USA		Argentina, Australia, Brazil, China, Israel, Japan, South Korea, Taiwan, USA

The MAH discusses the following reasons to justify registration in EU countries:

- Baricitinib is already registered in the EU for the treatment of RA and AD. The pharmacokinetic (PK) and pharmacodynamic (PD) analyses made to support these registrations demonstrated that baricitinib is not sensitive to intrinsic ethnic factors. This is consistent with the results of the analyses made to support the AA indication.
- Clinical practice for the treatment of severe AA does not differ significantly around the world.
- 52% of the patients studied in the AA clinical programme were Caucasian, versus 36% that were Asian and 8% that were Black.
- No data suggest regional differences in AA pathophysiology.

Protocol deviations

JAHO/Phase 3 portion

There were 111 patients, 16.9% of the total, identified to have at least 1 important protocol deviation. The most frequent important protocol deviations, totalling 44 patients (6.7%), were related to discrepancies between the duration of current episode entered into the IWRS at Visit 2 for stratification (<4 years versus ≥4 years) and the confirmed date of onset of current episode entered later into the electronic CRF. 28 protocol deviations were due to informed consent issues. 16 cases were due to violation of inclusion/exclusion criteria: inadequate washout of prior AA treatment (5 patients: 2 on placebo), episode less than 6 months (4 patients), inadvertent enrolment (5 patient), latent TB (1 patient) and lab abnormalities (1 patient).

Nine patients had significant noncompliance with study treatment (<80% compliance) during the 36-week double-blind treatment period:5 patients on placebo. 2 patients on baricitinib 2-mg.2 patients on baricitinib 4-mg.

JAIR

It was determined that 89 patients (16.3% of the randomized population) had at least one important protocol deviation. The most frequent important protocol deviations, totalling 38 patients (7%), were related to discrepancies between the duration of current episode entered into IWRS at Visit 2 for stratification (<4 years versus ≥4 years) and the date of onset of current episode entered later into the eCRF. A similar rate of discrepancies was observed in the other Phase 3 trial (JAHO). 18 cases were due to violation of inclusion/exclusion criteria: inadvertent enrolment (6 patient), inadequate washout of prior AA treatment (3 patients: all on baricitinib), lab abnormalities (3 patients), IWRS data entry error impacting stratification (2 patient), enrolled with active or chronic HBV infection (1 patient), spontaneous regrowth within 6 months from the enrollment (1 patient), exposed to a live vaccine during the screening period (1 patient), enrolled with hair loss less than 50% of scalp (1 patient).

Twenty-seven (27) patients were reported with significant noncompliance (4.9% of the randomized population). Eleven patients were in placebo group. Nine patients had documentation of noncompliance

(<80% compliance to the study treatment use). For the remaining 18 patients, counting of returned study treatment was not available for the complete Period 2 due to some visits being missing or performed remotely, therefore these patients were assessed as noncompliant.

Baseline data

Patient Demographics

The mean age was 37.5 years across the studies. A low proportion of patients aged 65 years or older were enrolled in the studies due to the upper age limit specified in the inclusion criteria (i.e. 60 years for males and 70 years for females). A slightly higher proportion of females enrolled in the studies compared to males (61% versus 39%, respectively). A higher proportion of patients were enrolled in North America and Asia in Study JAHO compared to Study JAIR, and only 3 countries participated in Study JAHO.

Table 9 Patient Demographics; FAS Population

	Phase 3 Portion of Study JAHO			Study JAIR			Pooled		
	PBO N=189	BARI 2-mg N=184	BARI 4-mg N=281	PBO N=156	BARI 2-mg N=156	BARI 4-mg N=234	PBO N=345	BARI 2-mg N=340	BARI 4-mg N=515
Age N-obs	**N=189**	**N=184**	**N=280**	**N=155**	**N=156**	**N=234**	**N=344**	**N=340**	**N=514**
Age (years), mean (SD)	37.4 (12.91)	38.0 (12.78)	36.3 (13.27)	37.1 (12.35)	39.0 (12.99)	38.0 (12.65)	37.2 (12.64)	38.4 (12.87)	37.1 (13.00)
Age group, n (%)									
<65 years	185 (97.9)	179 (97.3)	274 (97.9)	152 (98.1)	149 (95.5)	230 (98.3)	337 (98.0)	328 (96.5)	504 (98.1)
≥65 years	4 (2.1)	5 (2.7)	6 (2.1)	3 (1.9)	7 (4.5)	4 (1.7)	7 (2.0)	12 (3.5)	10 (1.9)
<40 years	111 (58.7)	103 (56.0)	174 (62.1)	90 (58.1)	84 (53.8)	130 (55.6)	201 (58.4)	187 (55.0)	304 (59.1)
≥40 years	78 (41.3)	81 (44.0)	106 (37.9)	65 (41.9)	72 (46.2)	104 (44.4)	143 (41.6)	153 (45.0)	210 (40.9)
Gender, n (%)									
Male	80 (42.3)	75 (40.8)	116 (41.3)	58 (37.2)	53 (34.0)	90 (38.5)	138 (40.0)	128 (37.6)	206 (40.0)
Female	109 (57.7)	109 (59.2)	165 (58.7)	98 (62.8)	103 (66.0)	144 (61.5)	207 (60.0)	212 (62.4)	309 (60.0)
Race N-obs	**N=188**	**N=183**	**N=280**	**N=156**	**N=156**	**N=234**	**N=344**	**N=339**	**N=514**
Race, n (%)									
Asian	78 (41.5)	76 (41.5)	114 (40.7)	51 (32.7)	49 (31.4)	67 (28.6)	129 (37.5)	125 (36.9)	181 (35.2)
Black or African American	17 (9.0)	7 (3.8)	28 (10.0)	16 (10.3)	12 (7.7)	18 (7.7)	33 (9.6)	19 (5.6)	46 (8.9)
White	83 (44.1)	93 (50.8)	123 (43.9)	85 (54.5)	92 (59.0)	144 (61.5)	168 (48.8)	185 (54.6)	267 (51.9)
Native Hawaiian or other Pacific Islander	1 (0.5)	1 (0.5)	1 (0.4)	0	1 (0.6)	0	1 (0.3)	2 (0.6)	1 (0.2)
American Indian or Alaska native	8 (4.3)	5 (2.7)	8 (2.9)	0	0	0	8 (2.3)	5 (1.5)	8 (1.6)
Multiracial	1 (0.5)	1 (0.5)	6 (2.1)	4 (2.6)	2 (1.3)	5 (2.1)	5 (1.5)	3 (0.9)	11 (2.1)
Geographic region, n (%)									

North America	103 (54.5)	102 (55.4)	153 (54.4)	54 (34.6)	54 (34.6)	82 (35.0)	157 (45.5)	156 (45.9)	235 (45.6)
Asia[a]	70 (37.0)	70 (38.0)	107 (38.1)	42 (26.9)	42 (26.9)	63 (26.9)	112 (32.5)	112 (32.9)	170 (33.0)
Rest of World[b]	16 (8.5)	12 (6.5)	21 (7.5)	60 (38.5)	60 (38.5)	89 (38.0)	76 (22.0)	72 (21.2)	110 (21.4)
Weight (kg), mean (SD)	75.15 (19.32)	74.30 (17.77)	74.69 (17.02)	73.74 (17.46)	72.30 (16.15)	74.00 (15.72)	74.51 (18.49)	73.38 (17.05)	74.38 (16.43)
	Phase 3 Portion of Study JAHO			**Study JAIR**			**Pooled**		
	PBO N=189	**BARI 2-mg N=184**	**BARI 4-mg N=281**	**PBO N=156**	**BARI 2-mg N=156**	**BARI 4-mg N=234**	**PBO N=345**	**BARI 2-mg N=340**	**BARI 4-mg N=515**
BMI N -obs	**N=188**	**N=184**	**N=281**	**N=156**	**N=156**	**N=234**	**N=344**	**N=340**	**N=515**
BMI group, N (%)									
<25 kg/m2	94 (50.0)	93 (50.5)	139 (49.5)	82 (52.6)	72 (46.2)	109 (46.6)	176 (51.2)	165 (48.5)	248 (48.2)
≥25 to <30 kg/m2	50 (26.6)	55 (29.9)	85 (30.2)	41 (26.3)	56 (35.9)	72 (30.8)	91 (26.5)	111 (32.6)	157 (30.5)
≥30 kg/m2	44 (23.4)	36 (19.6)	57 (20.3)	33 (21.2)	28 (17.9)	53 (22.6)	77 (22.4)	64 (18.8)	110 (21.4)
Renal function, n (%)									
Impaired (eGFR <60 mL/min/1.73 m2)	1 (0.5)	2 (1.1)	1 (0.4)	1 (0.6)	1 (0.6)	0	2 (0.6)	3 (0.9)	1 (0.2)
Not impaired (eGFR ≥60 mL/min/1.73 m2)	188 (99.5)	182 (98.9)	280 (99.6)	155 (99.4)	155 (99.4)	234 (100)	343 (99.4)	337 (99.1)	514 (99.8)

Baseline Disease Characteristics

Over half of all patients enrolled in the studies had very severe AA at baseline (SALT 95-100). The median SALT score across the studies was 96. The mean duration from the first onset of AA diagnosis was 12.1 years in Study JAHO and 12.2 years in Study JAIR. The mean duration of the current AA episode was 3.9 years and was higher in Study JAIR than Study JAHO. Across the 2 AA studies, the mean duration of current AA episode was slightly higher in the placebo and baricitinib 2-mg groups compared to baricitinib 4-mg. However, the proportion of patients with a current episode duration ≥4 years was slightly higher in the 4-mg groups compared to the other treatment groups.

Approximately 38% of patients reported an atopic background, defined as a medical history of or ongoing atopic dermatitis, allergic rhinitis, allergic conjunctivitis or allergic asthma. Investigators determined that approximately 44% of patients had AA universalis. Investigators determined that approximately 9% of patients had AA ophiasis, which presents as a band-like pattern of hair loss along the border of the temporal and occipital bones (Pratt et al. 2017).

Across the AA studies, 69% of patients had significant or complete EB Hair Loss at baseline, and 58% 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.

Table 10 Baseline Disease Characteristic; FAS Population

	Phase 3 Portion of Study JAHO			Study JAIR			Pooled		
	PBO N=189	BARI 2-mg N=184	BARI 4-mg N=281	PBO N=156[a]	BARI 2-mg N=156	BARI 4-mg N=234	PBO N=345	BARI 2-mg N=340	BARI 4-mg N=515
Duration from onset of AA (years), mean (SD)	12.64 (11.23)	12.10 (9.79)	11.81 (11.09)	11.8 (10.19)	13.1 (11.80)	11.9 (11.12)	12.26 (10.76)	12.55 (10.75)	11.85 (11.10)
Duration of current AA episode (years), mean (SD)	3.53 (3.65)	3.86 (4.69)	3.46 (3.37)	4.68 (5.49)	4.39 (6.09)	3.94 (3.35)	4.05 (4.60)	4.10 (5.38)	3.68 (3.37)
<4 years, n (%)	134 (70.9)	127 (69.0)	189 (67.3)	94 (60.3)	103 (66.0)	140 (59.8)	228 (66.1)	230 (67.6)	329 (63.9)
≥4 years, n (%)	55 (29.1)	57 (31.0)	92 (32.7)	62 (39.7)	53 (34.0)	94 (40.2)	117 (33.9)	110 (32.4)	186 (36.1)
Age of onset of AA, n (%)									
<18 years	77 (40.7)	59 (32.1)	108 (38.4)	57 (36.5)	55 (35.3)	74 (31.6)	134 (38.8)	114 (33.5)	182 (35.3)
≥18 years	112 (59.3)	125 (67.9)	173 (61.6)	99 (63.5)	101 (64.7)	160 (68.4)	211 (61.2)	226 (66.5)	333 (64.7)
SALT score, mean (SD)	84.7 (17.82)	86.8 (18.01)	85.3 (18.18)	85.0 (17.79)	85.6 (18.08)	84.8 (18.08)	84.8 (17.78)	86. 3 (18.02)	85.1 (18.12)
SALT score, median	95.0	99.0	96.0	95.0	97.0	95.0	95.0	99.0	96.0
SALT category, n (%)									
Severe (50-94)	92 (48.7)	77 (41.8)	133 (47.3)	74 (47.7)	70 (44.9)	115 (49.1)	166 (48.3)	147 (43.2)	248 (48.2)
Very severe (95-100)	97 (51.3)	107 (58.2)	148 (52.7)	81 (52.3)	86 (55.1)	119 (50.9)	178 (51.7)	193 (56.8)	267 (51.8)
Atopic background[b], n (%)									
Yes	73 (38.6)	67 (36.4)	97 (34.5)	67 (42.9)	63 (40.4)	87 (37.2)	140 (40.6)	130 (38.2)	184 (35.7)
No	116 (61.4)	117 (63.6)	184 (65.5)	89 (57.1)	93 (59.6)	147 (62.8)	205 (59.4)	210 (61.8)	331 (64.3)
Classified as universalis, n (%)	74 (39.2)	83 (45.1)	127 (45.2)	66 (42.3)	70 (44.9)	111 (47.4)	140 (40.6)	153 (45.0)	238 (46.2)
Classified as ophiasis, n (%)	13 (6.9)	17 (9.2)	27 (9.6)	12 (7.7)	16 (10.3)	24 (10.3)	25 (7.2)	33 (9.7)	51 (9.9)

PRO for Scalp Hair Assessment N-obs	**N=189**	**N=184**	**N=280**	**N=156**	**N=156**	**N=234**	**N=345**	**N=340**	**N=514**
PRO for Scalp Hair Assessment[c]									
3 (50%-94%)	72 (38.1)	57 (31.0)	102 (36.4)	60 (38.5)	56 (35.9)	78 (33.3)	132 (38.3)	113 (33.2)	180 (35.0)
4 (95%-100%)	109 (57.7)	118 (64.1)	173 (61.8)	91 (58.3)	93 (59.6)	137 (58.5)	200 (58.0)	211 (62.1)	310 (60.3)
ClinRO for EB Hair Loss N-obs	**N=187**	**N=184**	**N=278**	**N=153**	**N=156**	**N=233**	**N=340**	**N=340**	**N=511**
ClinRO for EB Hair Loss, n (%)[c]									
0	32 (17.1)	29 (15.8)	55 (19.8)	21 (13.7)	34 (21.8)	45 (19.3)	53 (15.6)	63 (18.5)	100 (19.6)
1	31 (16.6)	19 (10.3)	35 (12.6)	20 (13.1)	18 (11.5)	27 (11.6)	51 (15.0)	37 (10.9)	62 (12.1)
2	53 (28.3)	46 (25.0)	73 (26.3)	46 (30.1)	35 (22.4)	49 (21.0)	99 (29.1)	81 (23.8)	122 (23.9)
3	71 (38.0)	90 (48.9)	115 (41.4)	66 (43.1)	69 (44.2)	112 (48.1)	137 (40.3)	159 (46.8)	227 (44.4)
ClinRO for EL Hair Loss N-obs	**N=187**	**N=184**	**N=278**	**N=153**	**N=156**	**N=233**	**N=340**	**N=340**	**N=511**
ClinRO for EL Hair Loss, n (%)[c]									
0	49 (26.2)	53 (28.8)	77 (27.7)	40 (26.1)	44 (28.2)	70 (30.0)	89 (26.2)	97 (28.5)	147 (28.8)
1	42 (22.5)	20 (10.9)	34 (12.2)	23 (15.0)	23 (14.7)	23 (9.9)	65 (19.1)	43 (12.6)	57 (11.2)
2	38 (20.3)	35 (19.0)	74 (26.6)	31 (20.3)	26 (16.7)	43 (18.5)	69 (20.3)	61 (17.9)	117 (22.9)
3	58 (31.0)	76 (41.3)	93 (33.5)	59 (38.6)	63 (40.4)	97 (41.6)	117 (34.4)	139 (40.9)	190 (37.2)

Prior Alopecia Areata Therapy

Approximately 90% of patients in the AA studies reported prior AA therapy (Table 11). Over 26% of patients had used topical immunotherapy. Over 50% had used systemic immunosuppressant or immunomodulator therapy, the most common of which was corticosteroids (39%). Around 19% had used ciclosporin, and approximately 11% had used methotrexate. Approximately 5% of patients had used a JAK inhibitor. Patients with prior inadequate response to JAK inhibitors were excluded from the trials.

A washout of systemic and topical treatments for AA was incorporated before randomisation to minimise confounding effects of prior treatment. Durations of required washouts took into consideration that a delay of several weeks may be observed between treatments and regrowth of hair in patients with AA.

Table 11 Prior Alopecia Areata Therapy; FAS Population

	Phase 3 portion of Study JAHO			Study JAIR			Pooled		
	PBO N=189	BARI 2-mg N=184	BARI 4-mg N=281	PBO N=156	BARI 2-mg N=156	BARI 4-mg N=234	PBO N=345	BARI 2-mg N=340	BARI 4-mg N=515
Prior therapy, n (%)[a]	173 (91.5)		247 (87.9)	149 (95.5)	144 (92.3)	211 (90.2)	322 (93.3)	307 (90.3)	458 (88.9)
Systemic agents, n (%)									
Immunosuppressant/ Immunomodulator	101 (53.4)	84 (45.7)	138 (49.1)	97 (62.2)	89 (57.1)	124 (53.0)	198 (57.4)	173 (50.9)	262 (50.9)
Corticosteroid	68 (36.0)	51 (27.7)	103 (36.7)	77 (49.4)	77 (49.4)	102 (43.6)	145 (42.0)	128 (37.6)	205 (39.8)
JAK inhibitor	12 (6.3)	7 (3.8)	15 (5.3)	9 (5.8)	6 (3.8)	10 (4.3)	21 (6.1)	13 (3.8)	25 (4.9)
Others	57 (30.2)	55 (29.9)	88 (31.3)	54 (34.6)	32 (20.5)	52 (22.2)	111 (32.2)	87 (25.6)	140 (27.2)
Ciclosporin	46 (24.3)	45 (24.5)	69 (24.6)	27 (17.3)	17 (10.9)	27 (11.5)	73 (21.2)	62 (18.2)	96 (18.6)
Methotrexate	15 (7.9)	17 (9.2)	28 (10.0)	27 (17.3)	16 (10.3)	31 (13.2)	42 (12.2)	33 (9.7)	59 (11.5)
Other systemic (non-immunosuppressant)	17 (9.0)	20 (10.9)	28 (10.0)	15 (9.6)	16 (10.3)	18 (7.7)	32 (9.3)	36 (10.6)	46 (8.9)
Intralesional therapy, n (%)	101 (53.4)	92 (50.0)	152 (54.1)	88 (56.4)	82 (52.6)	104 (44.4)	189 (54.8)	174 (51.2)	256 (49.7)
Topical therapy excluding immunotherapy, n (%)	108 (57.1)	102 (55.4)	173 (61.6)	98 (62.8)	97 (62.2)	148 (63.2)	206 (59.7)	199 (58.5)	321 (62.3)
Topical immunotherapy, n (%)	45 (23.8)	57 (31.0)	84 (29.9)	41 (26.3)	31 (19.9)	63 (26.9)	86 (24.9)	88 (25.9)	147 (28.5)
Procedures, n (%)	30 (15.9)	41 (22.3)	65 (23.1)	35 (22.4)	31 (19.9)	47 (20.1)	65 (18.8)	72 (21.2)	112 (21.7)
Phototherapy, n (%)	23 (12.2)	34 (18.5)	54 (19.2)	28 (17.9)	24 (15.4)	37 (15.8)	51 (14.8)	58 (17.1)	91 (17.7)

Concomitant therapy

A limited number of concomitant therapies were permitted for the treatment of AA during the studies. Only 4.3% of patients used concomitant therapies for AA during the studies.

Table 12 Summary of Concomitant Medications Used for Alopecia Areata; Pooled Week 36 Efficacy Population, Primary Placebo-Controlled Integrated Analysis Set; Week 0 through 36

	PBO (N=345)		BARI 2-mg (N=340)		BARI 4-mg (N=515)	
Preferred Term	n	(%)	n	(%)	n	(%)
Subjects with >=1 Medication	11	(3.2)	12	(3.5)	28	(5.4)
ATC Level 1 DERMATOLOGICALS	7	(2.0)	4	(1.2)	16	(3.1)
MINOXIDIL	3	(0.9)	1	(0.3)	11	(2.1)
AMINOBENZOIC ACID;CYSTINE;KERATIN;PANTOTHENIC ACID;SACCHAROMYCES CEREVISIAE;THIAMINE	0		0		1	(0.2)
BIMATOPROST	1	(0.3)	0		1	(0.2)
CICLOPIROX	0		0		1	(0.2)
DESONIDE	0		1	(0.3)	1	(0.2)
FLUOCINONIDE	0		0		1	(0.2)
OTHER DERMATOLOGICALS	1	(0.3)	1	(0.3)	1	(0.2)
TACROLIMUS	0		0		1	(0.2)
TRIAMCINOLONE	0		0		1	(0.2)
FINASTERIDE	0		1	(0.3)	0	
HYDROCORTISONE	1	(0.3)	0		0	
METHYLPREDNISOLONE	1	(0.3)	0		0	
PIMECROLIMUS	1	(0.3)	0		0	

Patient compliance

Patient compliance with study medication was assessed at each scheduled visit during the treatment period (Visit 3 through Visit 18) by counting returned tablets. Descriptive statistics for percent compliance and non-compliance rate were summarized using the FAS population for Phase 3 portion by treatment group for Week 0 through 36, with data up to permanent treatment discontinuation.

The mean compliance (Table 13) is the average of individual compliance percentage (0 to 100) among the FAS population based on the calculation of the number of tablets taken by the patient versus the expected number of tablets.

At each visit, patients were dispensed bottles containing 36 tablets for each dosage of baricitinib (baricitinib 2 mg or matching placebo and baricitinib 4 mg or matching placebo). Patients received 1 bottle of each dosage when visit intervals was 4 weeks, 2 bottles when visit interval was 8 weeks and 3 bottles when visit interval was 12 weeks.

The number of tablets taken by the patient is based on the total number of tablets dispensed and returned during the specific time period. If patients were unable to return to sites (remote visit) or did not bring back used bottles to the investigative site, the returned number of tablets was imputed as 0, which could result in some patients appearing as over compliant (>100% compliance; Table 13).

The number of expected doses, tablets dispensed, tablets returned, and percentage compliance is listed by patient for Week 0 to 36, with data up to permanent treatment discontinuation.

Table 13 Summary of Patient Treatment Compliance Week 0 to 36 Studies JAHO and JAIR

	Study JAHO			**Study JAIR**		
	PBO N = 189	**BARI 2 mg N = 184**	**BARI 4 mg N = 281**	**PBO N = 156**	**BARI 2 mg N = 156**	**BARI 4 mg N = 234**
n-obs	189	184	280	155	156	234
Mean	99.4	110.6	99.9	117.5	120.1	113.9
SD	16.40	90.68	9.25	281.87	280.59	229.49
Non compliant[a] n (%)	8 (4.2)	10 (5.4)	11 (3.9)	13 (8.3)	8 (5.1)	16 (6.8)

Outcomes and estimation

Primary endpoint

In Studies JAHO and JAIR, both baricitinib 4-mg and 2-mg met the primary endpoint, demonstrating statistically significant improvements compared to placebo in SALT ≤20 at Week 36.

The proportion of patients demonstrating SALT ≤20 at Week 36 in the treatment groups were comparable across the 2 trials.

At both the individual-study level and the pooled-database level, the response rate of baricitinib 4-mg for SALT ≤20 at Week 36 was approximately 14 percentage points higher than that of baricitinib 2-mg (Table 14). In post-hoc analysis, the difference between baricitinib 4-mg and 2-mg was statistically significant.

Table 14 Proportion of Patients Achieving SALT ≤20 at Week 36; FAS Population

	Phase 3 Portion of Study JAHO			**Study JAIR**			**Pooled**		
	PBO N=189	**BARI 2-mg N=184**	**BARI 4-mg N=281**	**PBO N=156**	**BARI 2-mg N=156**	**BARI 4-mg N=234**	**PBO N=345**	**BARI 2-mg N=340**	**BARI 4-mg N=515**
Response, n (%) 95% CI	10 (5.3) (2.9, 9.5)	40 (21.7) (16.4, 28.2)	99 (35.2) (29.9, 41.0)	4 (2.6) (1.0, 6.4)	27 (17.3) (12.2, 24.0)	76 (32.5) (26.8, 38.7)	14 (4.1) (2.4, 6.7)	67 (19.7) (15.8, 24.3)	175 (34.0) (30.0, 38.2)
Difference vs placebo, % (95% CI)	NA	16.4 (9.7, 23.4)	29.9 (23.2, 36.2)	NA	14.7 (8.3, 21.6)	29.9 (23.1, 36.3)	NA	15.6 (11.0, 20.5)	29.9 (25.2, 34.4)
p-value vs placebo[a]	NA	**<0.001**	**<0.001**	NA	**<0.001**	**<0.001**	NA	<0.001	<0.001

Sensitivity analyses

The MAH has conducted sensitivity analyses to evaluate the impact of protocol deviations and differences among analysis populations. Data collected remotely due to the COVID-19 pandemic were included in secondary censoring rule analyses. Missing data due to the COVID-19 pandemic were imputed using hybrid imputation for the primary and key secondary endpoint analyses.

Table 15 Results of Sensitivity Analyses (JAHO)

Pop	**Description of Analysis**	**Censoring Rule**	**Location of Analysis**	**Indicated Dose Compared to Placebo p≤0.05**			
				Measure	Timepoint	2 mg	4 mg
	SALT						
mFAS	SALT ≤20 Response Rate at Each Post-Baseline Visit Week 0 through 36	Primary	Table JAHO.8.29	SALT ≤20	Wk 16 Wk 24 Wk 36	× ✓ ✓	✓ ✓ ✓

Table 16 Results of Sensitivity Analyses (JAIR)

Population	Description of Analysis	Censoring Rule	Location of Analysis	Indicated Dose Compared to Placebo p≤0.05			
				Measure	Time point	2 mg	4 mg
	SALT						
mFAS	SALT ≤20 Response Rate at Each Post-Baseline Visit Weeks 0 through 36	Primary	Table JAIR 8.28	SALT ≤20	Wk 16 Wk 24 Wk 36	✓ ✓ ✓	✓ ✓ ✓

Key Secondary Endpoints

Severity of Alopecia Tool ≤20 at Week 24 and Week 16

Baricitinib 4-mg demonstrated a statistically significant improvement compared to placebo in SALT ≤20 as early as Week 16 in Study JAHO and as early as Week 24 in Study JAIR, after adjustment for multiplicity (Figure 19). Baricitinib 2-mg demonstrated a statistically significant improvement compared to placebo in SALT ≤20 at Week 24 and Week 36 in Study JAHO, and only at Week 36 in Study JAIR, after adjustment for multiplicity.

For earlier timepoints not in the graphical testing procedure, baricitinib 4-mg demonstrated a statistically significant improvement compared to placebo in SALT ≤20 as early as Week 8 in Study JAHO and Week 12 in Study JAIR. Baricitinib 2-mg demonstrated a statistically significant improvement compared to placebo in SALT ≤20 starting at Week 24 in Study JAHO and Week 16 in Study JAIR.

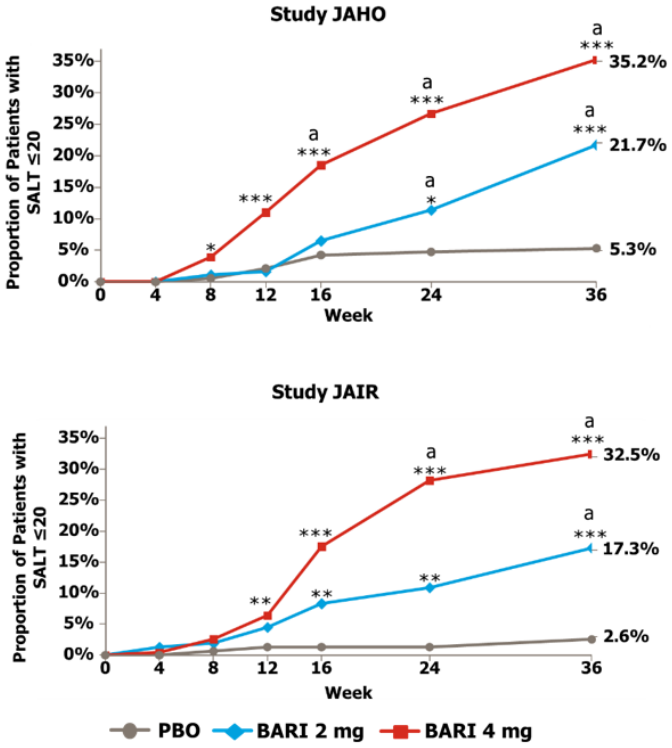


Figure 12 Proportion of patients achieving SALT ⩽20 through Week 36 FAS population, primary censoring rule (NRI).

Severity of Alopecia Tool Percent Change from Baseline

For SALT percent change from baseline, both baricitinib 4-mg and 2-mg demonstrated a statistically significant improvement compared to placebo at Week 36 in Study JAHO within the framework of the graphical testing procedure. In Study JAIR, for SALT percent change from baseline only baricitinib 4-mg demonstrated a statistically significant improvement compared to placebo.

Severity of Alopecia Tool 90 and Severity of Alopecia Tool ≤10

$SALT_{90}$ and SALT ≤10 are more stringent endpoints, representing almost complete coverage of the scalp by hair.

For $SALT_{90}$ and SALT ≤10 at Week 36, both baricitinib 4-mg and 2-mg demonstrated a statistically significant improvement compared to placebo in Study JAHO within the framework of the graphical testing procedure. In Study JAIR, only baricitinib 4-mg demonstrated a statistically significant improvement compared to placebo at the same Week-36 endpoints within the framework of the graphical testing procedure.

For SALT ≤10 at Week 24, both baricitinib 4-mg and 2-mg demonstrated a statistically significant improvement compared with placebo in Study JAHO within the framework of the graphical testing procedure. In Study JAIR, for SALT ≤10 at Week 24 both doses failed to demonstrate statistically significant improvement within the framework of the graphical testing.

Severity of Alopecia Tool 50

Baricitinib 4-mg demonstrated a statistically significant improvement compared with placebo in the proportion of patients achieving $SALT_{50}$ at Week 12 within the framework of the graphical testing procedure in Study JAHO but not in Study JAIR. Baricitinib 2-mg failed to demonstrate statistically significant improvement over placebo in the proportion of patients achieving $SALT_{50}$ at Week 12 in both trials within the framework of the graphical testing procedure.

Table 17 Results for Key Secondary SALT Endpoints through Week 36FAS Population

	Phase 3 Portion of Study JAHO			**Study JAIR**			**Pooled**		
	PBO N=189	**BARI 2-mg N=184**	**BARI 4-mg N=281**	**PBO N=156**	**BARI 2-mg N=156**	**BARI 4-mg N=234**	**PBO N=345**	**BARI 2-mg N=340**	**BARI 4-mg N=515**
SALT ≤20 at W24									
Response, n (%) 95% CI	9 (4.8) (2.5, 8.8)	21 (11.4) (7.6, 16.8)	75 (26.7) (21.9, 32.2)	2 (1.3) (0.4, 4.6)	17 (10.9) (6.9, 16.8)	66 (28.2) (22.8, 34.3)	11 (3.2) (1.8, 5.6)	38 (11.2) (8.3, 15.0)	141 (27.4) (23.7, 31.4)
Difference vs placebo, % (95% CI)	NA	6.7 (1.1, 12.5)	21.9 (15.6, 27.8)	NA	9.6 (4.5, 15.5)	26.9 (20.6, 33.1)	NA	8.0 (4.2, 12.0)	24.2 (19.8, 28.4)
p-value vs placebo[a]	NA	**0.013**	**<0.001**	NA	0.002	**<0.001**	NA	<0.001	<0.001
SALT ≤20 at W16									
Response, n (%) 95% CI	8 (4.2) (2.2, 8.1)	12 (6.5) (3.8, 11.1)	52 (18.5) (14.4, 23.5)	2 (1.3) (0.4, 4.6)	13 (8.3) (4.9, 13.7)	41 (17.5) (13.2, 22.9)	10 (2.9) (1.6, 5.3)	25 (7.4) (5.0, 10.6)	93 (18.1) (15.0, 21.6)
Difference vs placebo, % (95% CI)	NA	2.3 (-2.5, 7.3)	14.3 (8.6, 19.6)	NA	7.1 (2.3, 12.5)	16.2 (10.8, 21.7)	NA	4.5 (1.1, 8.0)	15.2 (11.3, 19.0)
p-value vs placebo[a]	NA	0.288	**<0.001**	NA	0.008	<0.001	NA	0.007	<0.001

SALT ≤10 at W36									
Response, n (%)	7 (3.7)	23 (12.5)	73 (26.0)	1 (0.6)	17 (10.9)	55 (23.5)	8 (2.3)	40 (11.8)	128 (24.9)
95% CI	(1.8, 7.4)	(8.5, 18.1)	(21.2, 31.4)	(0.1, 3.5)	(6.9, 16.8)	(18.5, 29.3)	(1.2, 4.5)	(8.8, 15.6)	(21.3, 28.8)
Difference vs placebo, % (95% CI)	NA	8.8 (3.3, 14.7)	22.3 (16.2, 28.0)	NA	10.3 (5.3, 16.1)	22.9 (17.1, 28.7)	NA	9.4 (5.7, 13.5)	22.5 (18.4, 26.6)
p-value vs placebo[a]	NA	**0.002**	**<0.001**	NA	0.002	**<.001**	NA	<0.001	<0.001
SALT ≤10 at W24									
Response, n (%) 95% CI	5 (2.6) (1.1, 6.0)	14 (7.6) (4.6, 12.4)	51 (18.1) (14.1, 23.1)	1 (0.6) (0.1, 3.5)	12 (7.7) (4.5, 13.0)	44 (18.8) (14.3, 24.3)	6 (1.7) (0.8, 3.7)	26 (7.6) (5.3, 11.0)	95 (18.4) (15.3, 22.0)
Difference vs placebo, % (95% CI)	NA	5.0 (0.4, 10.0)	15.5 (10.2, 20.7)	NA	7.1 (2.7, 12.3)	18.2 (12.8, 23.7)	NA	5.9 (2.8, 9.4)	16.7 (13.0, 20.4)
p-value vs placebo[a]	NA	**0.027**	**<0.001**	NA	0.010	<0.001	NA	<0.001	<0.001
SALT PCFB at W36									
Baseline mean	84.67	86.82	85.31	84.98	85.62	84.77	84.81	86.27	85.06
LSM change from baseline (SE)	-8.13 (3.10)	-31.23 (3.16)	-45.79 (2.66)	-2.96 (2.72)	-28.21 (2.77)	-47.45 (2.23)	-5.63 (1.96)	-29.67 (1.99)	-46.37 (1.61)
LSM difference vs placebo (95% CI)	NA	-23.10 (-30.57, -15.63)	-37.65 (-44.42, -30.89)	NA	-25.25 (-32.78, -17.72)	-44.49 (-51.33, -37.65)	NA	-24.04 (-29.34, -18.73)	-40.74 (-45.55, -35.92)
p-value vs placebo[b]	NA	**<0.001**	**<0.001**	NA	<0.001	**<0.001**	NA	<0.001	<0.001
SALT$_{90}$ at W36									
Response, n (%) 95% CI	6 (3.2) (1.5, 6.8)	21 (11.4) (7.6, 16.8)	63 (22.4) (17.9, 27.6)	1 (0.6) (0.1, 3.5)	13 (8.3) (4.9, 13.7)	50 (21.4) (16.6, 27.1)	7 (2.0) (1.0, 4.1)	34 (10.0) (7.2, 13.6)	113 (21.9) (18.6, 25.7)
Difference vs placebo, % (95% CI)	NA	8.2 (3.0, 13.9)	19.2 (13.5, 24.7)	NA	7.7 (3.2, 13.1)	20.7 (15.1, 26.4)	NA	8.0 (4.5, 11.8)	19.9 (16.0, 23.8)
p-value vs placebo[a]	NA	**0.003**	**<0.001**	NA	0.008	**<0.001**	NA	<.001	<.001
SALT$_{50}$ at W12									
Response, n (%) 95% CI	9 (4.8) (2.5, 8.8)	18 (9.8) (6.3, 14.9)	61 (21.7) (17.3, 26.9)	4 (2.6) (1.0, 6.4)	17 (10.9) (6.9, 16.8)	55 (23.5) (18.5, 29.3)	13 (3.8) (2.2, 6.3)	35 (10.3) (7.5, 14.0)	116 (22.5) (19.1, 26.3)
Difference vs placebo, % (95% CI)	NA	5.0 (-0.3, 10.6)	16.9 (11.0, 22.6)	NA	8.3 (2.8, 14.4)	20.9 (14.7, 27.0)	NA	6.5 (2.7, 10.5)	18.8 (14.5, 22.9)

p-value vs placebo[a]	NA	0.047	**<0.001**	NA	0.005	<0.001	NA	<0.001	<0.001

Abbreviations: BARI = baricitinib; CI = confidence interval; ClinRO = clinician-reported outcome; EB = eyebrow; EL = eyelash; FAS = full analysis set; N = number of patients in the analysis population; n = number of patients in the specified category; N2 = number of eligible patients for categorical assessment; PBO = placebo; PRO = patient-reported outcome; SALT = Severity of Alopecia Tool; $SALT_{50/90}$ = at least 50/90% improvement from baseline in SALT score; SE = standard error.

a Patients also achieved at least a 2-point improvement from baseline.
b Only assessed in patients with a score ≥3 at baseline.
c Only assessed in patients with a score ≥2 at baseline.
*p-value for baricitinib versus placebo ≤0.05.
**p-value for baricitinib versus placebo ≤0.01.
***p-value for baricitinib versus placebo ≤0.001.
Note: Results in bold were statistically significant after adjustment for multiplicity. Other results designated with asterisks had p≤0.05 but were not significant after adjustment for multiplicity.

PRO for Scalp Hair Assessment

In Studies JAHO and JAIR, both baricitinib 4-mg and 2-mg demonstrated a statistically significant improvement compared to placebo in PRO for Scalp Hair Assessment 0 or 1 with ≥2-point improvement from baseline at Week 36, after adjustment for multiplicity. At both the individual-study level and the pooled-database level, the response rate of baricitinib 4-mg for PRO for Scalp Hair Assessment 0 or 1 with ≥2-point improvement from baseline at Week 36 was approximately 18 percentage points higher than that of baricitinib 2-mg.

Table 18 Proportion of Patients Achieving PRO for Scalp Hair Assessment Score of 0 or 1 with ≥2-Point Improvement from Baseline at Week 36 FAS Population among Patients with Score ≥3 at Baseline

	Phase 3 Portion of Study JAHO			**Study JAIR**			**Pooled**		
	PBO N2=181	**BARI 2-mg N2=175**	**BARI 4-mg N2=275**	**PBO N2=151**	**BARI 2-mg N2=149**	**BARI 4-mg N2=215**	**PBO N2=332**	**BARI 2-mg N2=324**	**BARI 4-mg N2=490**
Response, n (%) 95% CI	9 (5.0) (2.6, 9.2)	28 (16.0) (11.3, 22.2)	91 (33.1) (27.8, 38.9)	6 (4.0) (1.8, 8.4)	24 (16.1) (11.1, 22.8)	74 (34.4) (28.4, 41.0)	15 (4.5) (2.8, 7.3)	52 (16.0) (12.5, 20.4)	165 (33.7) (29.6, 38.0)
Difference vs placebo, % (95% CI)	NA	11.0 (4.7, 17.6)	28.1 (21.4, 34.3)	NA	12.1 (5.4, 19.2)	30.4 (23.0, 37.4)	NA	11.5 (7.0, 16.3)	29.2 (24.2, 33.8)
p-value vs placebo[a]	NA	**<0.001**	**<0.001**	NA	**0.001**	**<0.001**	NA	<.001	<.001

ClinRO Measures for EB and EL Hair Loss

Baricitinib 4-mg demonstrated statistical significance for both endpoints in Studies JAIR and JAHO. Baricitinib 2-mg demonstrated statistical significance in Study JAHO only.

Analysis of the Pooled Week 36 Efficacy Population demonstrated a statistically significant improvement compared to placebo for both baricitinib 4-mg and 2-mg in ClinRO Measures for EB and EL Hair Loss 0 or 1 with ≥2-point improvement from baseline at Week 36.

At the pooled-database level, the response rates of baricitinib 4-mg for the ClinRO Measure for EB and EL Hair Loss 0 or 1 with ≥2-point improvement from baseline at Week 36 were approximately 17 and 22 percentage points higher, respectively, than those of baricitinib 2-mg.

Table 19 Proportion of Patients Achieving ClinRO Measures for Eyebrow and Eyelash Hair Loss 0 or 1 with ≥2-Point Improvement from Baseline at Week 36; FAS Population among Patients with Score ≥2 at Baseline

	Phase 3 Portion of Study JAHO			Study JAIR			Pooled		
	PBO N=189	BARI 2-mg N=184	BARI 4-mg N=281	PBO N=156	BARI 2-mg N=156	BARI 4-mg N=234	PBO N=345	BARI 2-mg N=340	BARI 4-mg N=515
ClinRO Measure for Eyebrow Hair Loss™ 0 or 1 with ≥2-Point Improvement from Baseline at W36									
Response, n/N2 (%) 95% CI	4/124 (3.2) (1.3, 8.0)	26/136 (19.1) (13.4, 26.5)	59/188 (31.4) (25.2, 38.3)	5/112 (4.5) (1.9, 10.0)	12/104 (11.5) (6.7, 19.1)	56/161 (34.8) (27.9, 42.4)	9/236 (3.8) (2.0, 7.1)	38/240 (15.8) (11.8, 21.0)	115/349 (33.0) (28.2, 38.0)
Difference vs placebo, % (95% CI)	NA	15.9 (8.4, 23.6)	28.2 (20.3, 35.4)	NA	7.1 (-0.3, 15.0)	30.3 (21.4, 38.4)	NA	12.0 (6.8, 17.5)	29.1 (23.4, 34.5)
p-value vs placebo[a]	NA	**<0.001**	**<0.001**	NA	0.076	**<0.001**	NA	<0.001	<0.001
ClinRO Measure for Eyelash Hair Loss™ 0 or 1 with ≥2-Point Improvement from Baseline at W36									
Response, n/N2 (%) 95% CI	3/96 (3.1) (1.1, 8.8)	15/111 (13.5) (8.4, 21.1)	56/167 (33.5) (26.8, 41.0)	5/90 (5.6) (2.4, 12.4)	9/89 (10.1) (5.4, 18.1)	48/140 (34.3) (26.9, 42.5)	8/186 (4.3) (2.2, 8.3)	24/200 (12.0) (8.2, 17.2)	104/307 (33.9) (28.8, 39.3)
Difference vs placebo, % (95% CI)	NA	10.4 (2.7, 18.3)	30.4 (21.6, 38.1)	NA	4.6 (-3.7, 13.2)	28.7 (18.7, 37.5)	NA	7.7 (2.2, 13.3)	29.6 (23.1, 35.4)
p-value vs placebo[a]	NA	0.012	**<0.001**	NA	0.260	**<0.001**	NA	0.007	<0.001

Additional Efficacy Endpoints

AA produces visible disfiguring patches of hair loss that are randomly distributed and of various sizes, or total hair loss, both of which can lead to a profound distortion of appearance (Pratt et al. 2017). Hair loss in visible areas, such as the scalp, eyebrows, and eyelashes, is considered by patients with AA to be the most bothersome aspect of the condition and the primary cause of their distress (FDA 2017; Davey et al. 2019; Aldhouse et al. 2020).

The SALT is widely used in clinical trials to assess the extent of scalp-hair loss in AA and has been considered sufficient to measure disease extent in clinical practice in a recent international consensus (Meah et al. 2020).

There has been very limited clinical research activity in AA over the past decades, and there is an overall lack of guidance on treatment goals in AA. Therefore, prior to initiating this clinical programme, the MAH conducted physician and patient interviews to define a clinically relevant definition of treatment success in patients with severe scalp AA (≥ 50% scalp hair loss, that is, a SALT score ≥50). This led to the proposal of an Alopecia Areata Investigator Global Assessment score of 0 or 1 (corresponding to a SALT score ≤20) as a definition of treatment success for patients with severe scalp AA (Wyrwich et al. 2020).

Multiple studies have shown that AA may have a significant negative impact on health related quality of life and result in higher levels of anxiety and a greater risk of depression (Liu et al. 2016, Okhovat et al. 2019). Quality of life impairment and psychological burden are important considerations for the therapeutic management of patients with AA (Messenger et al. 2012, Rossi et al. 2019).

Skindex-16 Adapted for Alopecia Areata

The Skindex-16 was identified as a potential measure for adaptation, as it captures the most relevant and clinically important aspects of health status for patients with chronic dermatologic conditions. The Skindex-16 was originally developed for dermatology conditions and includes the question stem 'your skin condition'. Therefore, the Skindex-16 AA was adapted by the MAH for use with adults with AA primarily through changing 'your skin condition' with 'your alopecia' or 'your scalp'. A sample version of the adapted instrument for cognitive testing was approved for use by the original author and license holders.

Qualitative research to determine the relevance of AA patients' understanding and interpretation of the Skindex-16 AA was conducted in The MAH sponsored research through 2 rounds of interviews with a total of 37 patients. Skindex-16 adapted for AA items were relevant to patients and their experience with AA. Overall, the Skindex-16 AA was well understood and considered by patients to assess relevant concepts associated with AA. The updated adapted version of the Skindex-16 AA was used in Studies JAIR and JAHO.

The Skindex-16 AA is composed of 16 items grouped under 3 domains: Symptoms (4 items), Emotions (7 items), and Functioning (5 items). Each item is scored on a 7-point Likert-type scale and transformed to a linear scale ranging from 0 (never bothered) to 100 (always bothered) for analysis. No minimal clinically important change has been defined for Skindex domain scores, but responsiveness to change in skin status was demonstrated in other dermatological conditions (Chren et al. 2001).

In Studies JAHO and JAIR, baricitinib 4-mg demonstrated a statistically significant improvement compared to placebo for mean change from baseline in Skindex-16 Emotions and Functioning domains at Week 36. Baricitinib 4-mg also demonstrated a statistically significant improvement compared to placebo for mean change from baseline in the Skindex-16 Symptoms domain at Week 36 in Study JAIR.

In Studies JAHO and JAIR, baricitinib 2-mg demonstrated a statistically significant improvement compared to placebo for mean change from baseline in the Skindex-16 Emotions domain at Week 36. Baricitinib 2-mg also demonstrated a statistically significant improvement compared to placebo in mean change from baseline in the Symptoms domain at Week 36 in Study JAHO.

Table 20 Efficacy Results for Skindex-16™ at Week 36; FAS Population (among Patients with Baseline Assessment), Primary Censoring Rule

	Phase 3 Portion of Study JAHO			Study JAIR		
	PBO N=119	BARI 2-mg N=108	BARI 4-mg N=171	PBO N=156	BARI 2-mg N=156	BARI 4-mg N=234
Emotions						
Baseline mean	67.29	66.40	66.07	69.56	70.45	68.03
LSM change from baseline (SE)	-11.96 (2.38)	-23.46 (2.48)	-22.97 (1.99)	-11.98 (2.15)	-18.73 (2.17)	-25.40 (1.73)
LSM difference vs placebo (95% CI)	NA	-11.50 (-17.71, -5.30)	-11.01 (-16.57, -5.45)	NA	-6.75 (-12.68, -0.82)	-13.42 (-18.80, -8.04)
p-value vs placebo[a]	NA	<0.001	<0.001	NA	0.026	<0.001
Functioning						
Baseline mean	48.18	49.10	53.98	52.88	48.40	49.13
LSM change from baseline (SE)	-10.12 (2.25)	-15.19 (2.34)	-17.16 (1.87)	-9.67 (1.91)	-14.05 (1.93)	-18.00 (1.54)
LSM difference vs placebo (95% CI)	NA	-5.07 (-10.94, 0.80)	-7.04 (-12.31, -1.77)	NA	-4.38 (-9.65, 0.88)	-8.33 (-13.10, -3.56)
p-value vs placebo[a]	NA	0.090	0.009	NA	0.103	<0.001
Symptoms						
Baseline mean	20.80	19.64	18.42	18.80	18.03	16.42

LSM change from baseline (SE)	0.02 (1.67)	-4.74 (1.74)	-2.73 (1.39)	1.17 (1.42)	-1.85 (1.43)	-3.04 (1.14)
LSM difference vs placebo (95% CI)	NA	-4.76 (-9.13, -0.40)	-2.75 (-6.67, 1.17)	NA	-3.02 (-6.91, 0.88)	-4.21 (-7.75, -0.68)
p-value vs placebo[a]	NA	0.033	0.168	NA	0.129	0.020

The placebo and treatment groups from both studies were pooled to assess improvement in the skindex domains at Week 36 according to the responder status (achieving SALT ≤20 versus not achieving SALT ≤20). Skindex domains were further analysed and stratified by baseline characteristics:

- gender (male, female)
- duration of current episode (<4 years versus ≥4 years), and
- SALT score (severe [SALT 50-94], very severe [SALT 95-100]).

At Week 36, patients achieving SALT ≤20 showed greater improvements in all skindex-16 domains than patients with SALT >20. For the duration of current episode ≥4 years and SALT 95-100 score at baseline subgroups the Skindex-16 Symptoms Domain worsened for those with SALT >20. All other subgroups showed improvement in all 3 domains and the patients with SALT ≤20 within each subgroup showed greater improvement than those with SALT >20 (Figure 12, Figure 13, Figure 14).

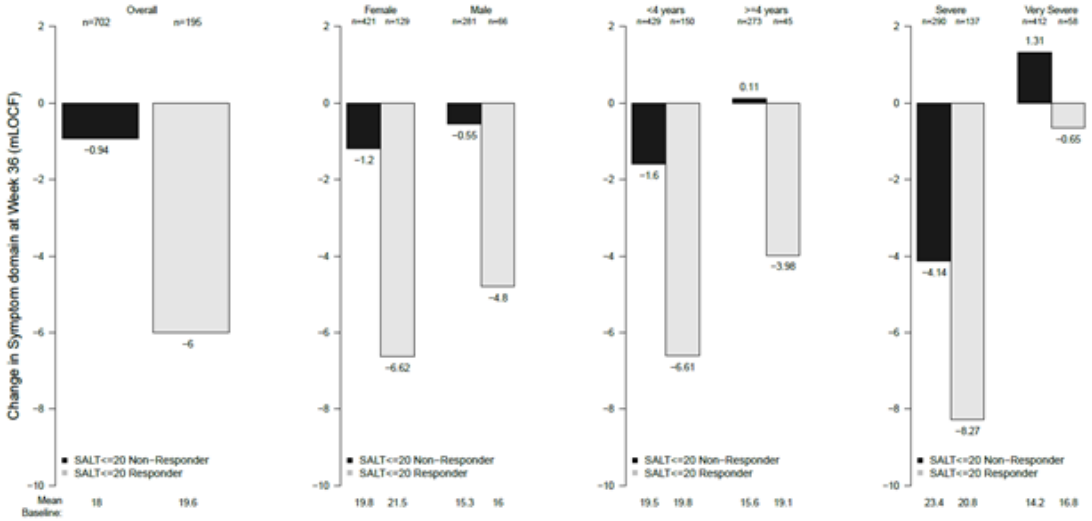


Figure 13 Change from baseline in Skindex−16 adapted for AA symptom domain by SALT status at Week 36 and baseline characteristics (mLOCF) at Week 36 by SALT ≤20 responder subgroup.

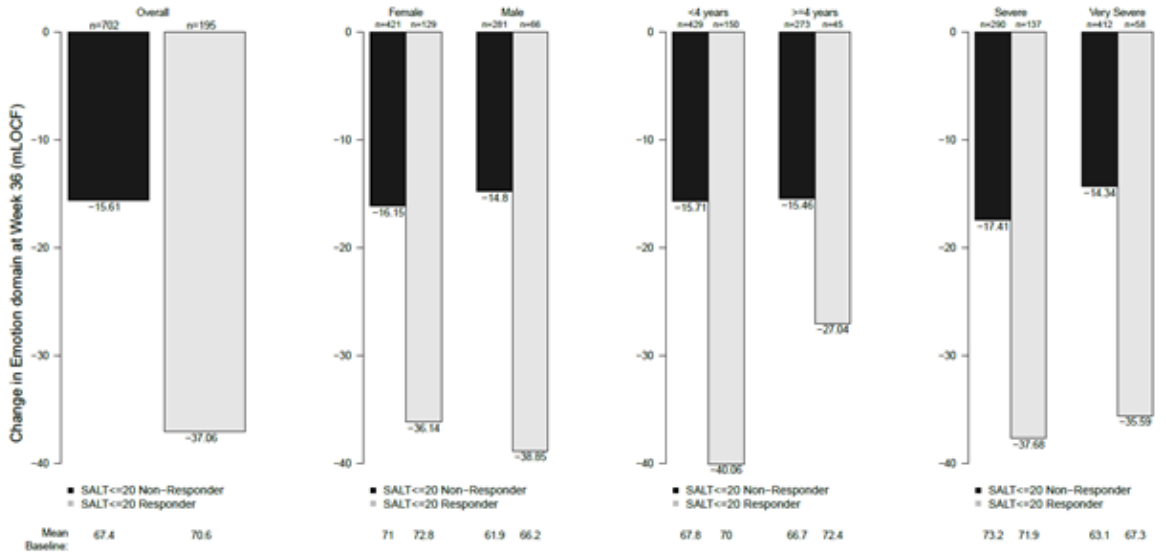


Figure 14 Change from baseline in Skindex−16 adapted for AA emotion domain by SALT status at Week 36 and baseline characteristics (mLOCF) at Week 36 by SALT ≤20 responder subgroup.

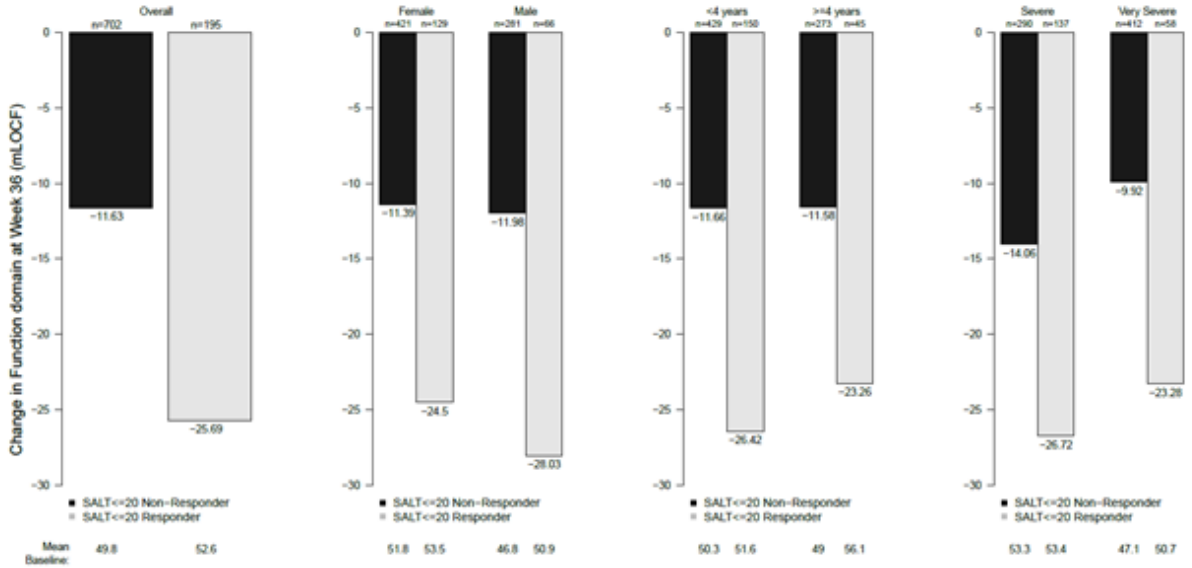


Figure 15 Change from baseline in Skindex−16 adapted for AA functioning domain by SALT status at Week 36 and baseline characteristics (mLOCF) at Week 36 by SALT ≤20 responder subgroup.

Hospital Anxiety and Depression Scale

The HADS has been adapted for use across multiple diseases to assess psychological symptoms, including many dermatological conditions (Hansson et al. 2009). Although HADS has not been specifically validated in AA, research suggests that patients with AA are potentially at a higher risk of anxiety and depression (Okhovat et al. 2019).

HADS is a 14-item self-assessment scale that determines the levels of anxiety (7 items) and depression (7 items) that a patient is experiencing over the past week. HADS utilises a 4-point Likert response scale (e.g., 0 to 3) for each item, and is intended for ages 12 to 65 years. Scores for each domain (anxiety and depression) can range from 0 to 21 where higher scores indicate greater anxiety or depression. A HADS-Anxiety or HADS-Depression score of ≥8 is indicative of notable anxiety or depression (Hansson et al. 2009).

In Studies JAHO and JAIR, baricitinib 4-mg demonstrated a statistically significant improvement compared to placebo for mean change from baseline in the HADS Anxiety total score at Week 36. Baricitinib 4-mg also demonstrated a statistically significant improvement compared to placebo for mean change from baseline in the HADS Depression total score at Week 36 in Study JAIR.

Table 21 Efficacy Results for HADS at Week 36 in FAS Population, Primary Censoring Rule

	Phase 3 portion of Study JAHO			Study JAIR		
	PBO N=189	BARI 2-mg N=184	BARI 4-mg N=281	PBO N=156	BARI 2-mg N=156	BARI 4-mg N=234
Mean Change from Baseline in HADS Anxiety Total Score						
Baseline mean	6.74	6.22	6.12	5.90	6.22	6.37
LSM change from baseline (SE)	-0.40 (0.23)	-1.22 (0.24)	-0.93 (0.20)	-0.47 (0.23)	-0.67 (0.23)	-1.19 (0.18)
LSM difference vs placebo (95% CI)	NA	-0.82 (-1.38, -0.25)	-0.54 (-1.05, -0.02)	NA	-0.20 (-0.82, 0.42)	-0.72 (-1.28, -0.16)
p-value vs placeboa	NA	0.005	0.040		0.518	0.012
Mean Change from Baseline in HADS Depression Total Score						
Baseline mean	3.96	4.21	3.95	3.69	3.78	3.83
LSM change from baseline (SE)	0.04 (0.21)	-0.38 (0.21)	-0.28 (0.18)	0.29 (0.21)	-0.22 (0.21)	-0.39 (0.17)
LSM difference vs placebo (95% CI)	NA	-0.42 (-0.93, 0.09)	-0.32 (-0.78, 0.14)	NA	-0.51 (-1.08, 0.07)	-0.68 (-1.20, -0.16)
p-value vs placeboa	NA	0.107	0.174	NA	0.083	0.010

The placebo and treatment groups from both studies were pooled to assess improvement in symptoms of anxiety and depression at Week 36 according to the responder status (achieving SALT ≤20 versus not achieving SALT ≤20).

These analyses were performed for each subpopulation of patients with baseline HADS-Anxiety ≥8 or HADS-Depression ≥8 and stratified by baseline characteristics:

- gender (male, female)
- duration of current episode (<4 years versus ≥4 years), and
- SALT score (severe [SALT 50-94], very severe [SALT 95-100]).

At Week 36, patients achieving SALT ≤20 showed greater improvements in HADS-Anxiety or HADS-Depression than those with SALT >20. All subgroups showed improvement in both domains. Within each subgroup, the patients with SALT ≤20 showed greater improvement than those with SALT >20 (Figure 15, Figure 16).

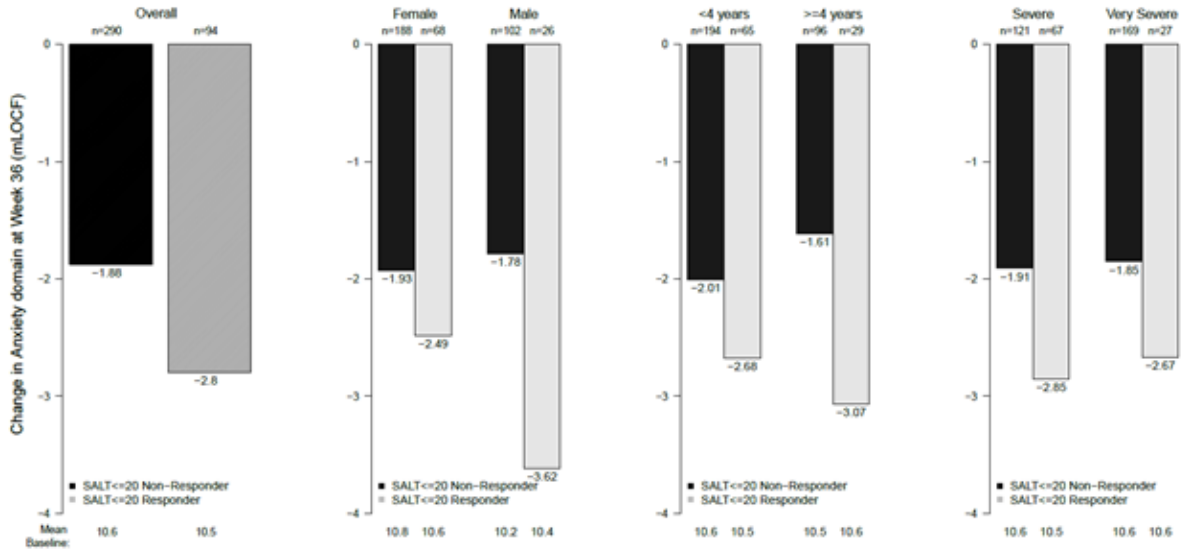


Figure 16 Change from baseline in HADS Anxiety by SALT status at Week 36 and baseline characteristics (mLOCF) in patients with baseline HADS-Anxiety score of ⩾8.

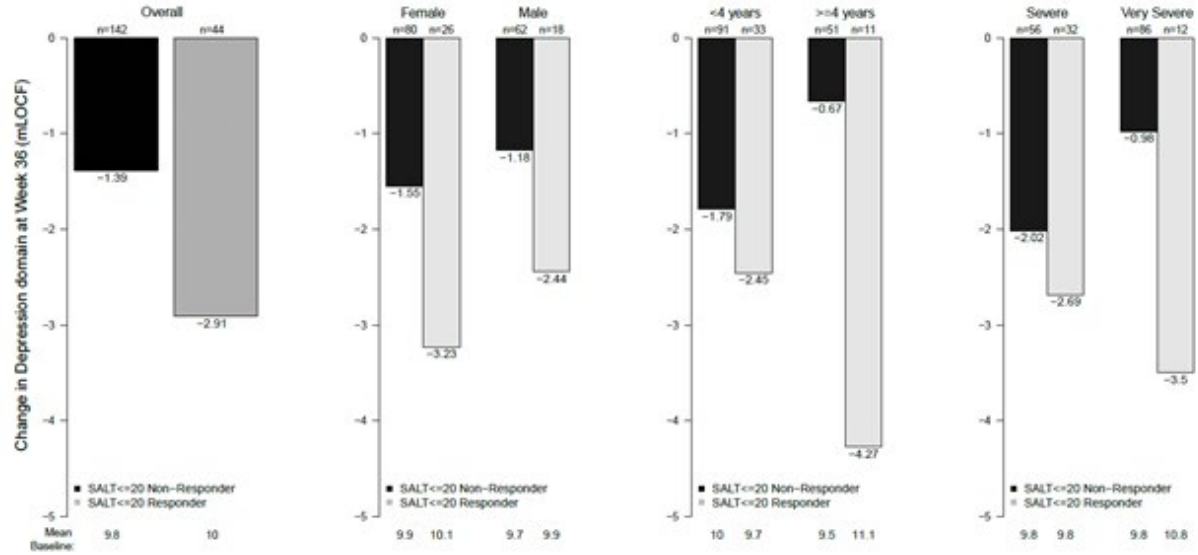


Figure 17 Change from baseline in HADS Depression by SALT status at Week 36 and baseline characteristics (mLOCF) in patients with baseline HADS-Depression score of ⩾8.

Patient-Reported Outcome Measures for Eyebrow and Eyelash Hair Loss

In Study JAHO, for the PRO Measure for EB Hair Loss 0 or 1 with ≥2-point improvement from baseline, both baricitinib 2-mg and baricitinib 4-mg demonstrated a statistically significant improvement compared to placebo from Week 12 to Week 36. This was also seen for the PRO Measure for EL Hair Loss 0 or 1 with ≥2-point improvement from baseline, as both baricitinib 2-mg and 4-mg demonstrated a statistically significant improvement compared to placebo from Week 12 to Week 36.

In Study JAIR, for the PRO Measure for EB Hair Loss 0 or 1 with ≥2-point improvement from baseline baricitinib 4-mg demonstrated a statistically significant improvement compared to placebo from Week 12 to Week 36. In comparison, baricitinib 2-mg demonstrated a statistically significant improvement compared to placebo from Week 16 to Week 36. For the PRO Measure for EL Hair Loss 0 or 1 with ≥2-point improvement from baseline, baricitinib 4-mg demonstrated a statistically significant improvement

compared to placebo from Week 12 to Week 36, while baricitinib 2-mg only demonstrated a statistically significant improvement compared to placebo at Week 36.

Table 22 Proportion of Patients Achieving PRO Measures for Eyebrow Hair Loss 0 or 1 with ≥2-Point Improvement from Baseline FAS Population among Patients with Score ≥2 at Baseline

	Phase 3 Portion of Study JAHO			Study JAIR		
	PBO N=189	BARI 2-mg N=184	BARI 4-mg N=281	PBO N=156	BARI 2-mg N=156	BARI 4-mg N=234
Week 16						
Response, n/N2 (%) 95% CI	1/130 (0.8) (0.1, 4.2)	10/141 (7.1) (3.9, 12.6)	26/184 (14.1) (9.8, 19.9)	1/107 (0.9) (0.2, 5.1)	8/108 (7.4) (3.8, 13.9)	29/165 (17.6) (12.5, 24.1)
Difference vs placebo, % (95% CI)	NA	6.3 (1.6, 11.8)	13.4 (7.8, 19.2)	NA	6.5 (1.0, 13.1)	16.6 (10.1, 23.2)
p-value vs placebo[a]	NA	0.028	0.001	NA	0.042	<0.001
Week 24						
Response, n/N2 (%) 95% CI	3/130 (2.3) (0.8, 6.6)	17/141 (12.1) (7.7, 18.5)	38/184 (20.7) (15.4, 27.1)	3/107 (2.8) (1.0, 7.9)	13/108 (12.0) (7.2, 19.5)	48/165 (29.1) (22.7, 36.4)
Difference vs placebo, % (95% CI)	NA	9.7 (3.6, 16.3)	18.3 (11.6, 24.9)	NA	9.2 (2.2, 16.9)	26.3 (18.1, 33.9)
p-value vs placebo[a]	NA	0.007	<0.001	NA	0.019	<0.001
Week 36						
Response, n/N2 (%) 95% CI	4/130 (3.1) (1.2, 7.6)	23/141 (16.3) (11.1, 23.3)	59/184 (32.1) (25.7, 39.1)	5/107 (4.7) (2.0, 10.5)	16/108 (14.8) (9.3, 22.7)	59/165 (35.8) (28.8, 43.3)
Difference vs placebo, % (95% CI)	NA	13.2 (6.3, 20.5)	29.0 (21.2, 36.3)	NA	10.1 (2.2, 18.5)	31.1 (22.1, 39.1)
p-value vs placebo[a]	NA	0.001	<0.001	NA	0.017	<0.001

Table 23 Proportion of Patients Achieving PRO Measures for Eyelash Hair Loss 0 or 1 with ≥2-Point Improvement from Baseline FAS Population among Patients with Score ≥2 at Baseline

	Phase 3 Portion of Study JAHO			Study JAIR		
	PBO N=189	BARI 2-mg N=184	BARI 4-mg N=281	PBO N=156	BARI 2-mg N=156	BARI 4-mg N=234
Week 16						
Response, n/N2 (%) 95% CI	2/100 (2.0) (0.6, 7.0)	11/112 (9.8) (5.6, 16.7)	22/161 (13.7) (9.2, 19.8)	1/89 (1.1) (0.2, 6.1)	4/90 (4.4) (1.7, 10.9)	25/133 (18.8) (13.1, 26.3)
Difference vs placebo, % (95% CI)	NA	7.8 (1.3, 14.9)	11.7 (5.0, 18.0)	NA	3.3 (-2.3, 9.8)	17.7 (10.1, 25.2)
p-value vs placebo[a]	NA	0.035	0.006	NA	0.238	0.002
Week 24						

Response, n/N2 (%) 95% CI	1/100 (1.0) (0.2, 5.4)	17/112 (15.2) (9.7, 23.0)	38/161 (23.6) (17.7, 30.7)	1/89 (1.1) (0.2, 6.1)	4/90 (4.4) (1.7, 10.9)	34/133 (25.6) (18.9, 33.6)
Difference vs placebo, % (95% CI)	NA	14.2 (7.1, 22.0)	22.6 (15.2, 29.8)	NA	3.3 (-2.3, 9.8)	24.4 (16.1, 32.5)
p-value vs placebo[a]	NA	0.004	<0.001	NA	0.258	<0.001
Week 36						
Response, n/N2 (%) 95% CI	2/100 (2.0) (0.6, 7.0)	22/112 (19.6) (13.3, 28.0)	48/161 (29.8) (23.3, 37.3)	1/89 (1.1) (0.2, 6.1)	17/90 (18.9) (12.1, 28.2)	46/133 (34.6) (27.0, 43.0)
Difference vs placebo, % (95% CI)	NA	17.6 (9.6, 26.1)	27.8 (19.6, 35.4)	NA	17.8 (9.4, 27.1)	33.5 (24.4, 41.9)
p-value vs placebo[a]	NA	<0.001	<0.001	NA	0.002	<0.001

Ancillary analyses

MAH performed subgroup analyses on the Pooled Week 36 Efficacy Population to investigate the effects of various demographic and baseline characteristics on the key, the predefined endpoint of SALT ≤20 at Week 36. These subgroups were based upon gender, age, weight, eGFR, race, geographic region, baseline diseases severity (SALT category) and current AA episode duration category.

As seen with the overall population, a higher proportion of patients in the baricitinib 4-mg group demonstrated SALT ≤20 at Week 36 compared to baricitinib 2-mg in each of the subgroups.

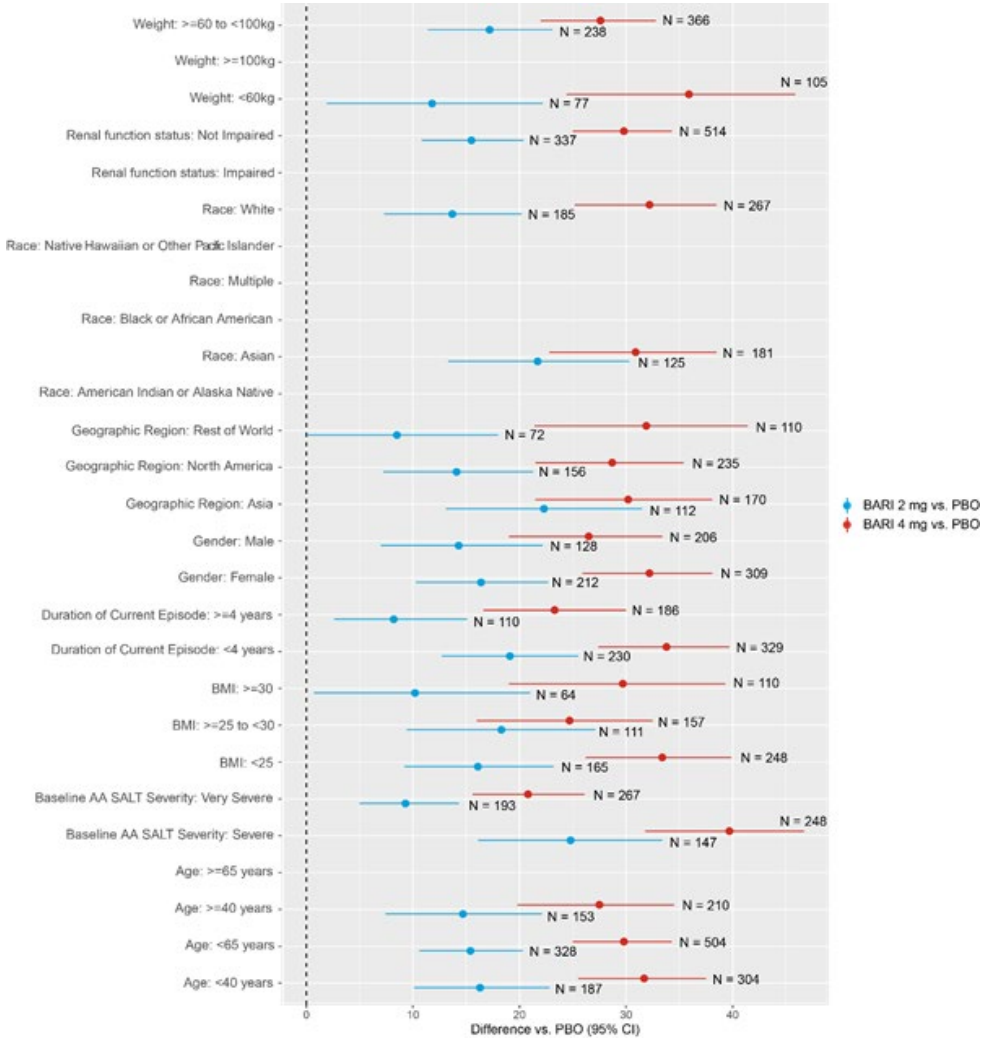


Figure 18 Proportion of patients with SALT ≤20 at Week 36 by subgroup. Pooled Week 36 Efficacy Population, primary censoring rule (NRI).

A significant treatment-by-subgroup interaction was only obtained for the renal function subgroup (patients with eGFR <60 mL/min/1.73 m2 = 6 in total across all treatment groups).

Table 24 Treatment-by-Subgroup Interaction for Pooled Week 36 Efficacy Population for SALT ≤20 at Week 36

Subgroup	Categories	Treatment/Subgroup Interaction p-value[a]
Gender	Male and Female	0.986
Age (years)	<40, ≥40	0.642
	<65, ≥65	0.989
Weight (kg)	<60, ≥60 to <100, ≥100	0.271
BMI (kg/m2)	<25, ≥25 to <30, ≥30	0.571
Renal function (mL/min/1.73 m2)	<60, ≥ 60	<0.001
Race	Asian, Black or African American, White, Native Hawaiian or other Pacific Islander, American Indian or Alaska native and Multiracial	NA
Race[b]	Asian, Black or African American, White and Other	0.499
Geographic region	North America, Asia and Rest of Worldc	0.356
Baseline SALT category	Severe and Very severed	0.427
Duration of current episode of AA category (years)	<4, ≥4	0.426

Abbreviations: AA = alopecia areata; BMI = body mass index; NA = not applicable; SALT = Severity of Alopecia Tool.
a p-value from logistic regression model.
b Post hoc analysis conducted on race with a reduced number of categories.
c Asia includes South Korea in Study JAHO and Japan, China, Taiwan and South Korea in Study JAIR. Rest of World includes Mexico in Study JAHO and Australia, Brazil, Argentina and Israel in Study JAIR.
d Severe and very severe AA are defined as SALT 50-94 and SALT 95-100, respectively.
Note: Values in bold are statistically significant (p<0.1). The p-value is presented as NA if the model did not converge.

Efficacy Results for Disease Severity and Duration Subpopulations

To determine the effect of baseline AA disease severity and episode duration on the efficacy of baricitinib, MAH compared efficacy results for the following subpopulations of patients:

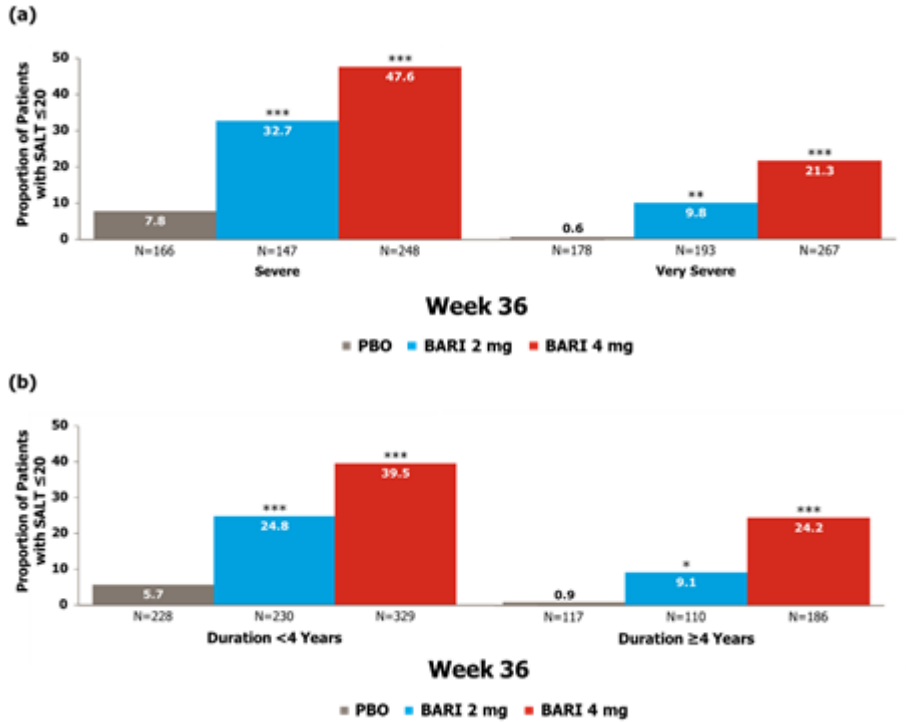
- patients with severe AA (SALT 50-94) versus very severe (SALT 95-100) and
- patients with current duration of AA episode <4 years versus ≥4 years.

These analyses were conducted using the Pooled Week 36 Efficacy Population as well as the FAS for each individual study.

Analysis of the Pooled Week 36 Efficacy Population demonstrated a statistically significant improvement compared to placebo for both baricitinib 4-mg and 2-mg in SALT ≤20 at Week 36 across both AA disease severity and episode duration subpopulations. At both the pooled-database level and

the individual-study level, baricitinib 4-mg consistently achieved a higher response rate than baricitinib 2-mg, regardless of baseline disease severity or episode duration.

For both doses of baricitinib, patients with severe AA or duration <4 years achieved a higher response rate for SALT ≤20 at Week 36 compared to those with very severe AA or duration ≥4 years, respectively.



Abbreviations: BARI = baricitinib; N = number of patients in the analysis population; NRI = nonresponder imputation; PBO = placebo; SALT = Severity of Alopecia Tool; Severe = SALT 50-94; Very Severe = SALT 95-100.
*p-value for baricitinib versus placebo ≤0.05.
**p-value for baricitinib versus placebo ≤0.01.
***p-value for baricitinib versus placebo ≤0.001.

Figure 19 Proportion of patients with SALT ≤20 at Week 36 by (a) baseline disease severity and (b) baseline episode duration. Pooled Week 36 efficacy population, primary censoring rule (NRI).

Regarding key secondary endpoints Baricitinib 4-mg achieved a statistically significant improvement compared to placebo for each of these endpoints across both AA disease severity and episode duration subpopulations. The results for baricitinib 2-mg were less consistent. Baricitinib 2-mg achieved a statistically significant improvement compared to placebo for:

- SALT percent change from baseline for all disease severity and episode duration subpopulations
- ClinRO Measures for EB Hair Loss 0 or 1 at Week 36 for the very severe (SALT 95-100), duration <4 years, and ≥4 years subpopulations and
- ClinRO Measures for EL Hair Loss 0 or 1 at Week 36 for the very severe (SALT 95-100) subpopulation.

Baricitinib 4-mg consistently achieved a higher response than 2-mg across the studied endpoints, regardless of baseline disease severity or episode duration.

Efficacy over time

Baricitinib 4-mg demonstrated a statistically significant improvement compared to placebo in SALT ≤20 as early as Week 16 in Study JAHO and as early as Week 24 in Study JAIR, after adjustment for multiplicity (Figure 19). Baricitinib 2-mg demonstrated a statistically significant improvement compared to placebo in SALT ≤20 at Week 24 and Week 36 in Study JAHO, and only at Week 36 in Study JAIR, after adjustment for multiplicity.

For earlier timepoints not in the graphical testing procedure, baricitinib 4-mg demonstrated a statistically significant improvement compared to placebo in SALT ≤20 as early as Week 8 in Study JAHO and Week 12 in Study JAIR. Baricitinib 2-mg demonstrated a statistically significant improvement compared to placebo in SALT ≤20 starting at Week 24 in Study JAHO and Week 16 in Study JAIR.

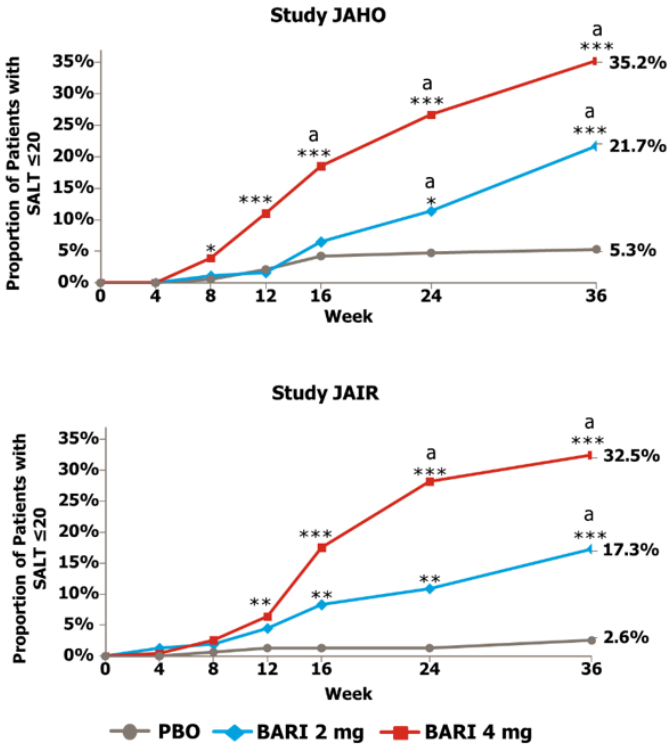


Figure 20 Proportion of patients achieving SALT ⩽20 through Week 36 FAS population, primary censoring rule (NRI).

Time Needed to Observe Hair Re-growth: Stopping Rule in the Absence of Response

In AA, the hair follicles are preserved and, therefore, the potential for recovery of hair growth is in theory maintained over life. However, due to the scarcity of clinical research in AA, very little is known about the time to response for the treatments currently used.

Patients enrolled in the AA clinical programme had severe AA for at least 6 months. However, hair growth being driven by the cyclic functioning of the hair follicles, the amount of hair of a patient may slightly vary over time. Therefore, "no significant response" was defined as the failure to reach a reduction of at least 30% from baseline of the total SALT score ($SALT_{30}$) during the 52 week treatment period. $SALT_{30}$ was the clinical response endpoint used for dose selection after 12 weeks of treatment in the Phase 2 portion of the Study JAHO that informed the choice of dose for Phase 3 (King et al. 2021). $SALT_{30}$ was also selected as the threshold for efficacy assessment in other Phase 2 studies:

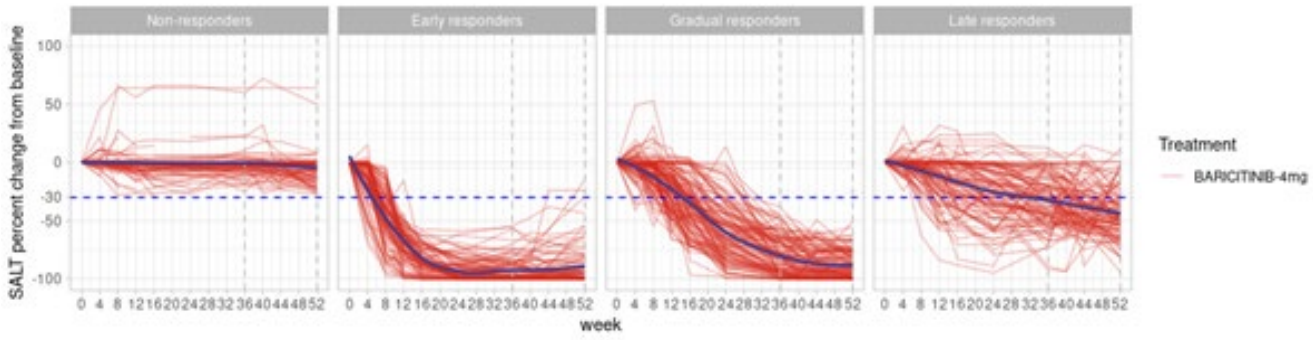
- one evaluating ritlecitinib and brepocitinib in patients with severe AA (SALT score ≥50) (Peeva et al. 2021), and
- one evaluating dupilumab in patients with ≥30% scalp hair loss (Guttman-Yassky et al. 2021).

With this rationale, the MAH analysed the patients randomly assigned to baricitinib 4 mg at Week 0 and divided them into 2 categories:

- $SALT_{30}$ Non-responders (n = 160, 31%) who never achieved $SALT_{30}$ over the 52 week period. Although SALT scores may have fluctuated over the 52 weeks, overall there was no trend towards improvement.
- $SALT_{30}$ Responders (n = 355, 69%) achieved $SALT_{30}$ at any time over the 52 week period.

The unsupervised machine learning method growth mixture model (GMM; Jung and Wickrama 2008; Proust-Lima et al. 2017) is a novel method of latent class mixed model, to identify distinct clusters based on the similarity in the individual patient trajectories overtime. Further, within the category of $SALT_{30}$ Responders, trajectory analysis using GMM allowed grouping of patients into 3 subcategories according to 3 different patterns of response (Figure 20):

- Early responders (n = 102, 20%) for whom improvement was observed soon after treatment initiation (4 to 12 weeks)
- Gradual responders (n = 143, 28%) for whom the threshold of 30% improvement was reached between 12 to 36 weeks, and
- Late responders (n = 110, 21%) had longer response time and may have included periods of relapse after early improvement. Overall, hair re-growth occurred at later time points such that the proportion of patients reaching $SALT_{30}$ continued to increase until Week 52



Abbreviation: SALT = severity of alopecia tool.
Note: Red lines represent individual trajectories. The dotted blue line represents 30% improvement from the baseline. The continuous blue line represents SALT percentage change from baseline for the respective groups.

Figure 21 Patterns of response.

Predictor analysis

Within the $SALT_{30}$ Responders group, about two-third (early- and gradual- responder groups) will achieve $SALT_{30}$ within the first 9 months (36 weeks) of the treatment. The objective of the post-hoc predictor analysis is, therefore, to provide guidance on discontinuing treatment before Week 52 for the non-responder group.

To evaluate a potential stopping rule for the non-responder group, 2 parameters were tested to predict the lack of response up to Week 52 (final time point tested in these datasets) ; (1) magnitude of SALT improvement (20% and 25% improvement from baseline), and time points (namely Weeks 24 and 36). Predictors were evaluated by how well these could identify potential non-responders.
The corresponding prediction accuracy (sensitivity, specificity, PPV, and NPV) is shown in Table 25.

PPV is the probability that the patients who reach 20% or 25% improvement of SALT score at Week 24 or Week 36, will become $SALT_{30}$ Responders by Week 52.

NPV is the probability that patients who did not achieve 20% or 25% improvement of SALT score at Week 24 or Week 36 will also be non-responders who would never achieve $SALT_{30}$ by Week 52. The higher the NPV, the higher the likelihood of identifying true non-responders (who should therefore be discontinued) rather than mistakenly identifying a late responder, who would benefit from continuing treatment.

The NPVs at Week 36 were higher than those at Week 24, for both 20% and 25% improvement of SALT from baseline (Table 25). Therefore, Week 36 is a more appropriate time point to predict later non-response and make a treatment decision, such as discontinuation.

The highest NPV (75.2%) and overall highest prediction accuracy (combination of highest sensitivity, specificity, PPV, and NPV) in predicting non-responders was associated with no response 20% improvement from baseline in SALT score ($SALT_{20}$) at Week 36 (Table 25).

Not achieving a response of 25% at Week 36 was associated with a lower NPV (71.6%), that is, $SALT_{25}$ improvement cut off might be too high a threshold at Week 36 for some late responders. More late responders would be discontinued based on this rule, despite the potential for response by Week 52.

The NPVs from Week 24 are much lower compared with Week 36, indicating that it would not be recommended to establish a discontinuation rule as early as Week 24, as this would lead to patients being discontinued from treatment early, despite the potential for response by Week 52.

Table 25 Predictor Parameters

Time Point (week)	SALT Improvement	Sensitivity	Specificity	PPV	NPV
36	SALT ≥ 20% improvement from baseline	0.854	0.988	0.993	0.752
36	SALT≥25% improvement from baseline	0.823	0.994	0.997	0.716
24	SALT≥20% improvement from baseline	0.783	0.975	0.986	0.670
24	SALT≥25% improvement from baseline	0.758	0.988	0.993	0.648

Abbreviations: NPV = negative predictive value; PPV = positive predictive value; SALT = Severity of Alopecia Tool.

To support the above analysis and conclusion, the proportion of patients reaching SALT ≤20 (primary endpoint) over time among patients who met, and did not meet, the predictor criterion $SALT_{20}$ at Week 36 was assessed. As shown in Figure 21, the use of $SALT_{20}$ at Week 36 for prediction confirms that few patients identified as non-responders will improve further with longer duration of treatment by Week 52.

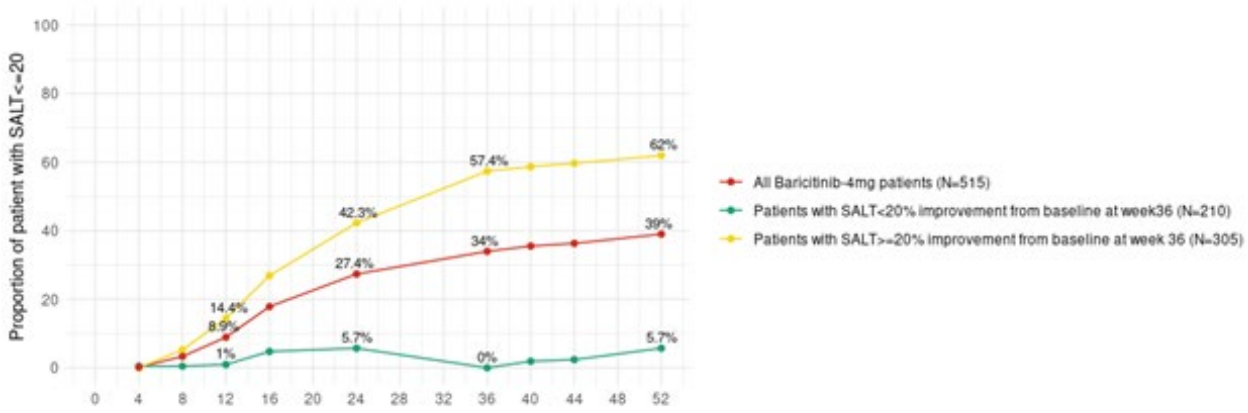


Figure 22 Proportion of patients achieving SALT =<20 over time.

Based on this data, failure to reach $SALT_{20}$ at Week 36 could be used as a criterion to identify patients who will not present a significant response and for whom treatment discontinuation could be considered.

Maintenance of Efficacy after Randomised Down-Titration

All patients randomly assigned at baseline (Week 0) to baricitinib 4 mg in Study JAIR and who reached SALT =<20 at Week 52 were eligible for inclusion in the randomised down-titration period, irrespective of the timing of reaching SALT =<20. At Week 52, 86 patients were re-randomised in a 1:1 ratio to remain on 4 mg (44 patients) or to be down-titrated to 2 mg (42 patients). At the data cutoff date, the analysis set included 83 patients (96.5%) who had completed Week 76, and 3 patients (3.5%) who had discontinued after Week 52 and prior to Week 76

Table 26 Summary of Results for Key Endpoints Randomised Down-Titration
Tertiary Censoring Rule (NRI) Week 76

	BARI 4 mg to BARI 4 mg N = 44	**BARI 4 mg to BARI 2 mg N = 42**
Proportion of patients achieving SALT <=20a		
n (%) (95% CI)	42 (95.5) (84.9, 98.7)	31 (73.8) (58.9, 84.7)
Proportion of patients achieving SALT <=10a		
n (%) (95% CI)	37 (84.1) (70.6, 92.1)	21 (50.0) (35.5, 64.5)
Proportion of patients achieving PRO for scalp hair assessment score of 0 or 1b		
n (%) (95% CI)	39 (88.6) (76.0, 95.0)	22 (52.4) (37.7, 66.6)
Proportion of patients achieving ClinRO measure for eyebrow hair loss score of 0 or 1b		
n (%) (95% CI)	41 (93.2) (81.8, 97.7)	28 (66.7) (51.6, 79.0)
Proportion of patients achieving ClinRO Measure for eyelash hair loss score of 0 or 1b		
n (%) (95% CI)	39 (88.6) (76.0, 95.0)	32 (76.2) (61.5, 86.5)

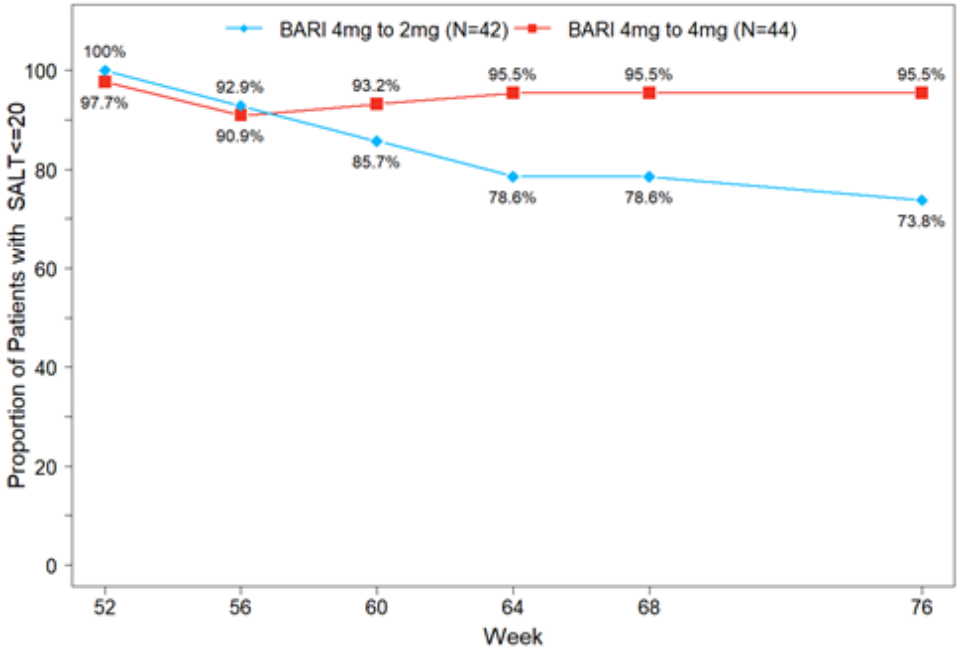
Abbreviations: ClinRO = clinician-reported outcome; N = number of patients in the analysis population; n = number of patients in the specified category; NRI = non-responder imputation; PRO = patient-reported outcome; SALT = Severity of Alopecia Tool.

a Tertiary plus censoring rule excludes data after permanent study drug discontinuation, after retreatment, or when collected at remote visits.
b Tertiary censoring rule excludes data collected after permanent study drug discontinuation or after re-treatment.

SALT =<20 response

At Week 76, an adequate clinical response (SALT ≤20) was achieved by 74% (31 of 42) of the patients who were down-titrated to baricitinib 2 mg, and by 96% (42 of 44) of the patients who remained on baricitinib 4 mg (Figure 22).

Among the 42 patients down-titrated to baricitinib 2 mg, 37 patients had reached SALT ≤20 before or at Week 36 and 30 (81.1%) of them had SALT ≤ 20 at Week 76. Five (5) patients had reached SALT ≤20 for the first time between Week 40 and 52 and only 1 (20%) maintained SALT ≤ 20 at Week 76.



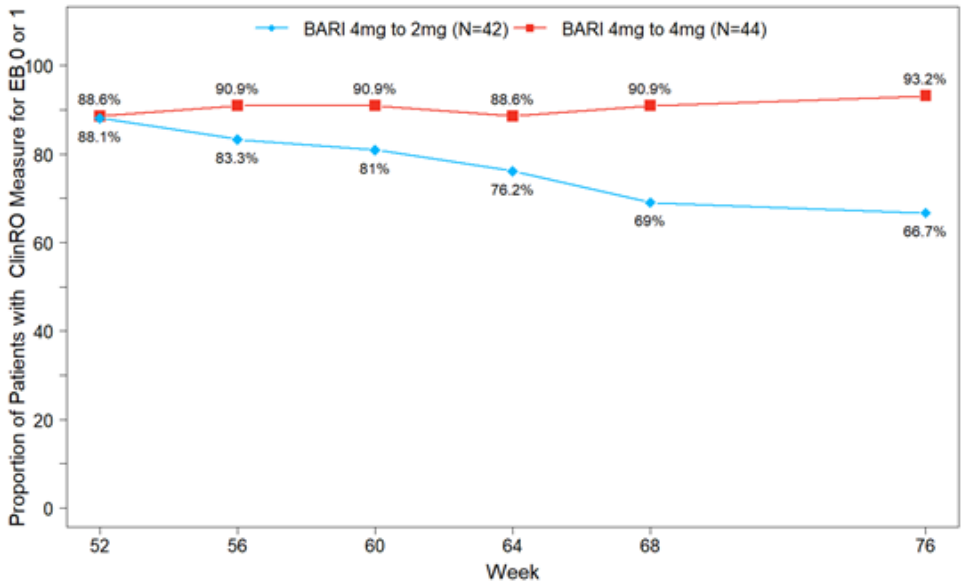
Abbreviations: COVID-19 = coronavirus disease 2019; SALT = Severity of Alopecia Tool.
Note: Data censored after permanent study drug discontinuation, re-treatment with the original dose of baricitinib or data collected during remote visits due to the COVID-19 pandemic.
Patient I4V-MC-JAIR-704-20103 had a virtual visit at Week 52. Per Tertiary Plus censoring rule, this record was censored; thus, the response rate at Week 52 is not 100%.

Figure 23 Maintenance of efficacy through Week 76 following down-titration at Week 52 – from the baricitinib 4 mg Week 52 re-randomised responder population (Study JAIR).

ClinRO measures for EB and EL hair loss

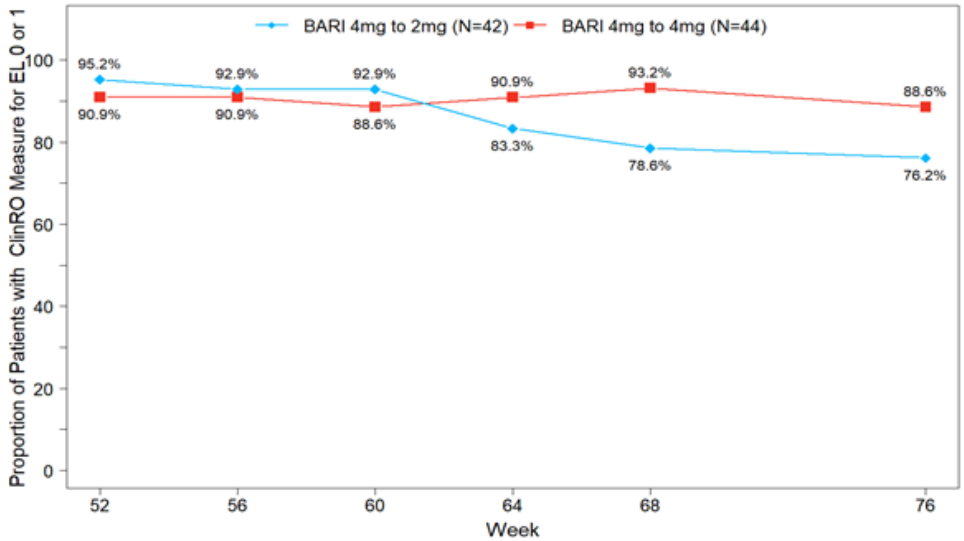
At Week 52, 88% (37 of 40) of the patients who were down-titrated to baricitinib 2 mg and 89% (39 of 44) of the patients who remained on baricitinib 4 mg had a score of 0 or 1 for ClinRO EB. At Week 76, this response was achieved by 67% (28 of 42) of the patients who were down-titrated to baricitinib 2 mg, and increased by 93% (41 of 44) among the patients who remained on baricitinib 4 mg (Figure 23).

At Week 52, 95% (40 of 42) of the patients who were down-titrated to baricitinib 2 mg and 91% (40 of 44) of the patients who remained on baricitinib 4 mg had a score of 0 or 1 for ClinRO EL. At Week 76, this response was achieved by 76% (32 of 42) of the patients who were down-titrated to baricitinib 2 mg, and by 89% (39 of 44) of the patients who remained on baricitinib 4 mg (Figure 24).



Abbreviations: ClinRO = clinician-reported outcome; EL = eyelash; NRI = non-responder imputation.
63.6% of patients on BARI 4 mg to BARI 4 mg had EB score of 2 or 3 at baseline
59.5% of patients on BARI 4 mg to BARI 2 mg had EB score of 2 or 3 at baseline
Score of 2 = significant gaps in eyebrows; Score of 3 = no notable eyebrows
Censored after permanent study drug discontinuation, and re-treatment with the original dose of baricitinib.

Figure 24 Proportion of patients with ClinRO eyebrow (0,1) from Week 52 through Week 76 Randomised down-titration, NRI, Tertiary censoring rule.



47.7% of patients on BARI 4 mg to BARI 4 mg had EL score of 2 or 3 at baseline
54.8% of patients on BARI 4 mg to BARI 2 mg had EL score of 2 or 3 at baseline
Score of 2 = significant gaps in eyelash; Score of 3 = no notable eyelash
Censored after permanent study drug discontinuation, and re-treatment with the original dose of baricitinib.

Figure 25 Proportion of patients with ClinRO Eyelash (0,1) from Week 52 through Week 76 Randomised down-titration, NRI, Tertiary censoring rule.

Data from the randomised down-titration substudy indicate that a majority of patients maintained clinical response after down-titration from baricitinib 4 to 2 mg. Loss of SALT ≤20 was more frequent among subjects who had become responders after Week 36, indicating that it might be beneficial to wait for a few months for patients to reach a stable response (sustained clinical response) before initiating down-titration.

Maintenance of Efficacy after Randomised Withdrawal and Optimal Treatment Duration

All patients randomly assigned at baseline (Week 0) to baricitinib 4 or 2 mg in Study JAHO and who had reached SALT ≤20 at Week 52 were eligible for inclusion in the randomised withdrawal period. At Week 52, 154 (115 on baricitinib 4 mg and 39 on baricitinib 2 mg) eligible patients were re-randomised in a 3:1 ratio to remain on their current dose of baricitinib or transition to placebo. The 3:1 randomisation was selected to limit the number of patients re-randomised to placebo, as it was anticipated that the majority of them would relapse (Zhou et al. 2021) that could have important psychological impact (Aldhouse et al. 2020; Mostaghimi et al. 2021). **Table 27** presents a summary of the key endpoints for the withdrawal period.

Table 27 Summary of Results for Key Endpoints Randomised Withdrawal Tertiary Censoring Rule (NRI) Week 76

	BARI 4 mg to PBO N = 30	**BARI 4 mg to BARI 4 mg N = 85**	**BARI 2 mg to PBO N = 10**	**BARI 2 mg to BARI 2 mg N = 29**
Proportion of patients achieving SALT ≤20a				
n (%) (95% CI)	10 (33.3) (19.2, 51.2)	76 (89.4) (81.1, 94.3)	2 (20.0) (5.7, 51.0)	23 (79.3) (61.6, 90.2)
Proportion of patients achieving SALT ≤10a				
n (%) (95% CI)	8 (26.7) (14.2, 44.4)	66 (77.6) (67.7, 85.2)	1 (10.0) (1.8, 40.4)	20 (69.0) (50.8, 82.7)
Proportion of patients achieving PRO for scalp hair assessment score of 0 or 1b				
n (%) (95% CI)	8 (26.7) (14.2, 44.4)	73 (85.9) (76.9, 91.7)	1 (10.0) (1.8, 40.4)	21 (72.4) (54.3, 85.3)
Proportion of patients achieving ClinRO measure for eyebrow hair loss score of 0 or 1b				
n (%) (95% CI)	11 (36.7) (21.9, 54.5)	71 (83.5) (74.2, 89.9)	2 (20.0) (5.7, 51.0)	21 (72.4) (54.3, 85.3)
Proportion of patients achieving ClinRO measure for eyelash hair loss score of 0 or 1b				
n (%) (95% CI)	14 (46.7) (30.2, 63.9)	71 (83.5) (74.2, 89.9)	4 (40.0) (16.8, 68.7)	21 (72.4) (54.3, 85.3)

Abbreviations: ClinRO = clinician-reported outcome; N = number of patients in the analysis population; n = number of patients in the specified category; NRI = non-responder imputation; PRO = patient-reported outcome; SALT = Severity of Alopecia Tool.

a Tertiary plus censoring rule excludes data after permanent study drug discontinuation, after retreatment, or when collected at remote visits.

b Tertiary censoring rule excludes data collected after permanent study drug discontinuation or after re-treatment.

SALT ≤20 response (Figure 25)

Among patients who achieved adequate clinical response on baricitinib 4 mg at Week 52 (SALT ≤20), this response was reduced by Week 76 in patients who were transitioned to placebo, and was retained in patients who remained on baricitinib 4 mg (Table 27).

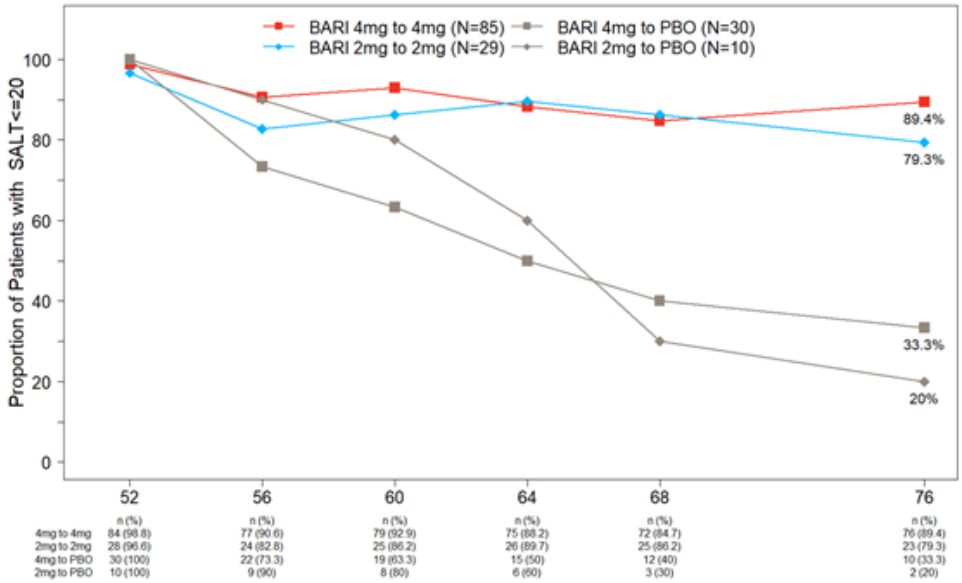
Among patients who achieved adequate clinical response on baricitinib 2 mg at Week 52 (SALT ≤20), this response was reduced by Week 76 in patients who were transitioned to placebo, and was retained in patients who remained on baricitinib 2 mg (Table 27).

Among the 30 patients who were on 4 mg and transitioned to placebo,

- 22 patients had reached SALT ≤20 before or at Week 36 and 8 (36.3%) of them maintained SALT ≤20 at Week 76, and
- 8 patients had reached SALT ≤20 between Week 40 and 52 and only 2 (25%) maintained SALT ≤20 at Week 76.
- Among the 10 patients who were on 2 mg and transitioned to placebo,

- 7 patients had reached SALT ≤20 before or at Week 36 and 1 (14.2%) of them maintained SALT ≤20 at Week 76, and
- 3 patients had reached SALT ≤20 between Week 40 and 52 and 1 (33.3%) maintained SALT ≤20 at Week 76.

Frequency of relapses were comparable between patients who had reached SALT ≤20 before or at Week 36 compared with those who had reached response after Week 36 (up to Week 52).



Abbreviations: COVID-19 = coronavirus disease 2019; NRI = non-responder imputation; SALT = Severity of Alopecia Tool.

Data censored after permanent study drug discontinuation, re-treatment with the original dose of baricitinib and data collected during remote visits due to the COVID-19 pandemic.

Figure 26 Proportion of patents with SALT ≤20 response from Week 52 through Week 76 Randomised withdrawal, NRI, Tertiary plus censoring rule.

ClinRO measures for EB and EL hair loss

The responses on the Clinical assessments for Eyebrow (Figure 26) and for Eyelash hair reduced in the patient groups who were randomized from baricitinib 2 mg and 4 mg to placebo at week 52 (Table 27).

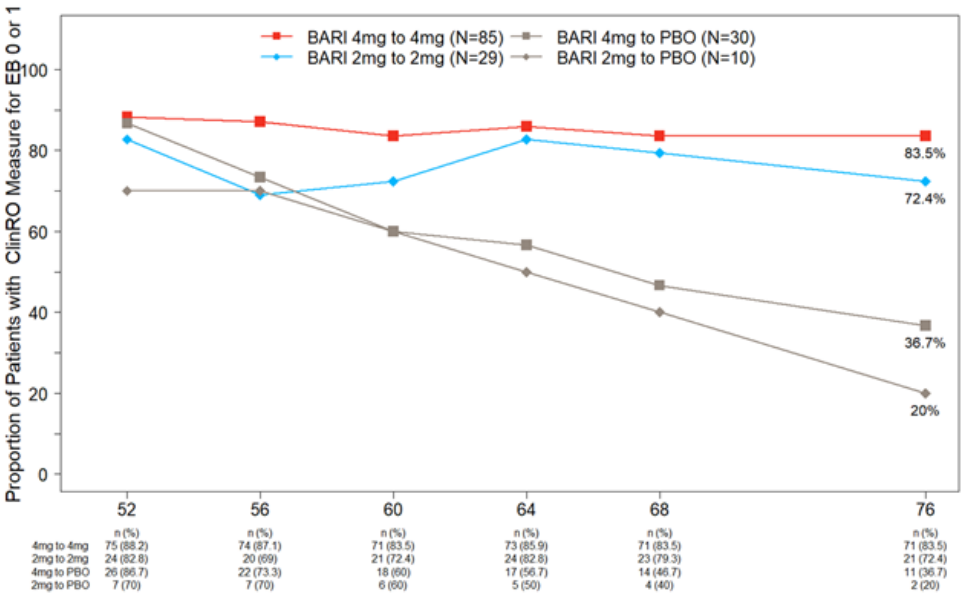


Figure 27 Proportion of patients with ClinRO eyebrow (0,1) from Week 52 through Week 76 Randomised withdrawal, NRI, tertiary censoring rule.

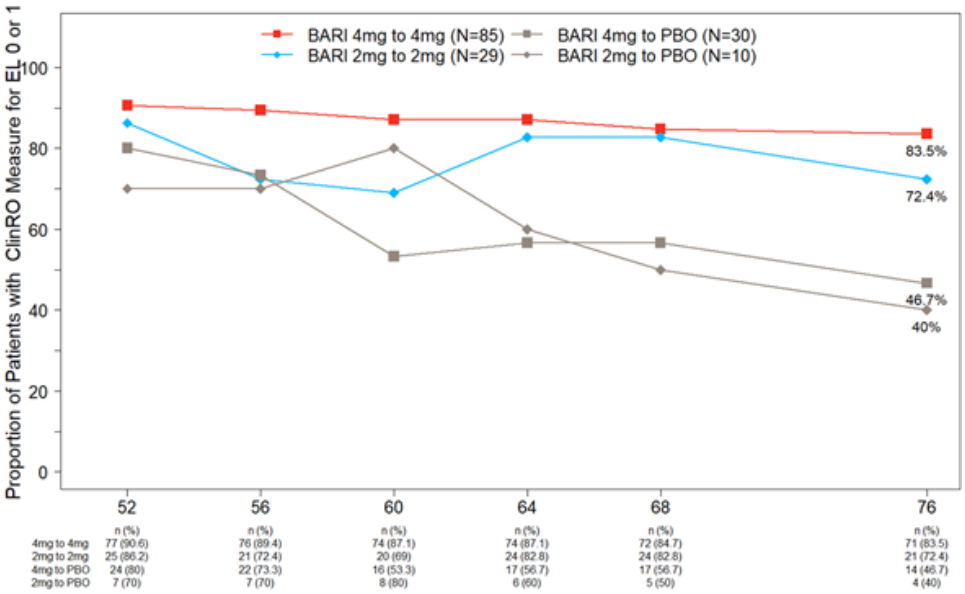


Figure 28 Proportion of patients with ClinRO eyelash (0,1) from Week 52 through Week 76 Randomised withdrawal, NRI, tertiary censoring rule.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections). The Phase 3 portion of JAHO and the JAIR study are comparable in design, with a few notable exceptions.

Table 28 ***Summary of Efficacy for trials JAHO and JAIR***

Title: JAHO (phase 3 portion)				
Study identifier	IND 112543, I4V-MC-JAHO NCT: NCT03570749			
Design	36-week placebo-controlled treatment period (from randomization to end of study period) with primary endpoint assessed at Week 36			
	Duration of main phase:	36 weeks		
	Duration of Run-in phase:	not applicable		
	Duration of Extension phase:	68 weeks		
Hypothesis	4-mg or 2-mg dose of baricitinib is superior to placebo in the treatment of patients with severe or very severe AA			
Treatments groups	Placebo	N= 189		
	Baricitinib 2-mg	N= 184		
	Baricitinib 4-mg	N= 281		
Endpoints and definitions	Primary endpoint	SALT ≤20	Proportion of patients achieving SALT ≤20 at Week 36	
	Key Secondary endpoints	SALT90	– Proportion of patients achieving SALT90 at Week 36	
		PRO scalp hair	– Proportion of patients with PRO for Scalp Hair Assessment score of 0 or 1 with a ≥2-point improvement from Baseline at Week 36 among patients with a score of ≥3 at Baseline	
		ClinRO eyebrows hairloss	– Proportion of patients achieving ClinRO Measure for EB Hair Loss 0 or 1 with ≥2-point improvement from Baseline at Week 36 (among patients with ClinRO Measure for EB Hair Loss ≥2 at Baseline)	
		ClinRO eyelashes hairloss	– Proportion of patients achieving ClinRO Measure for EL Hair Loss 0 or 1 with ≥2-point improvement from Baseline at Week 36 (among patients with ClinRO Measure for EL Hair Loss ≥2 at Baseline)	
Database lock	02 February 2021			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	The full analysis set (FAS) at week 36 of treatment			
Effect estimate per comparison	Treatment group	Placebo	Baricitinib 2-mg	Baricitinib 4-mg
	Number of subject	189	184	281
	SALT ≤20 (primary endpoint)	**10 (5.3)**	**40 (21.7)**	**99 (35.2)**
	p-Value vs. PBO	*NA*	*<0.001*	*<0.001*
	SALT90	6 (3.2)	21 (11.4)	63 (22.4)
	p-Value vs. PBO	*NA*	*0.003*	*<0.001*
	PRO scalp hair	*9 (5.0)*	*28 (16.0)*	*59 (31.4)*
	p-Value vs. PBO	*NA*	*<0.001*	*<0.001*

	ClinRO eyebrows hairloss *p-Value vs. PBO*	4 (3.2) *NA*	26 (19.1) *<0.001*	59 (31.4) *<0.001*
	ClinRO eyelashes hairloss *p-Value vs. PBO*	*3 (3.1)* *NA*	*15 (13.5)* *0.012*	*56 (33.5)* *<0.001*
Notes	52 week results submitted during the review process showed that efficacy parameters continued to improve through Week 52.			

Title: JAIR			
Study identifier	NCT: 03899259		
Design	36-week placebo-controlled treatment period (from randomization to end of study period) with primary endpoint assessed at Week 36		
	Duration of main phase:	36 weeks	
	Duration of Run-in phase:	not applicable	
	Duration of Extension phase:	68 weeks	
Hypothesis	4-mg or 2-mg dose of baricitinib is superior to placebo in the treatment of patients with severe or very severe AA		
Treatments groups	Placebo	N= 156	
	Baricitinib 2-mg	N= 156	
	Baricitinib 4-mg	N= 234	
Endpoints and definitions	Primary endpoint	SALT ≤20	Proportion of patients achieving SALT ≤20 at Week 36
	Key Secondary endpoints	SALT90	– Proportion of patients achieving $SALT_{90}$ at Week 36
		PRO scalp hair	– Proportion of patients with PRO for Scalp Hair Assessment score of 0 or 1 with a ≥2-point improvement from Baseline at Week 36 among patients with a score of ≥3 at Baseline
		ClinRO eyebrows hairloss	– Proportion of patients achieving ClinRO Measure for EB Hair Loss 0 or 1 with ≥2-point improvement from Baseline at Week 36 (among patients with ClinRO Measure for EB Hair Loss ≥2 at Baseline)
		ClinRO eyelashes hairloss	– Proportion of patients achieving ClinRO Measure for EL Hair Loss 0 or 1 with ≥2-point improvement from Baseline at Week 36 (among patients with ClinRO Measure for EL Hair Loss ≥2 at Baseline)
Database lock	19 February 2021		

Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	The full analysis set (FAS) at week 36 of treatment			
Effect estimate per comparison	Treatment group	Placebo	Baricitinib 2-mg	Baricitinib 4-mg
	Number of subject	156	156	234

	SALT ≤20 (primary endpoint)	**4 (2.6)**	**27 (17.3)**	**76 (32.5)**
	p-Value vs. PBO	*NA*	*<0.001*	*<0.001*
	SALT90 *p-Value vs. PBO*	*1* (0.6) *NA*	*13* (8.3) *0.008*	*50* (21.4) *<0.001*
	PRO scalp hair *p-Value vs. PBO*	*6 (4.0)* *NA*	*24 (16.1)* *0.001*	*74 (34.4)* *<0.001*
	ClinRO eyebrows hairloss *p-Value vs. PBO*	*5* (4.5) *NA*	*12* (11.5) *0.076*	56 (34.8) *<0.001*
	ClinRO eyelashes hairloss *p-Value vs. PBO*	*5 (5.6)* *NA*	*9 (10.1)* *0.260*	*48 (34.3)* *<0.001*
Notes	52 week results submitted during the review process showed that efficacy parameters continued to improve through Week 52			

Supportive studies

In 2018, the MAH had performed a patient preference study to understand whether patients with AA would be willing to accept the potential safety risks identified in phase 3 clinical trials of baricitinib in the RA program to achieve the expected level of efficacy of baricitinib in AA.

Methods

The study was designed as a web-based survey to estimate the risk tolerance of patients with at least 50% scalp hair loss due to AA, for an immunosuppressant treatment of their disease by assessing preferences for a 1 in 3 chance of having hair on 80% to 100% of the scalp within 1 year relative to three risks: serious infection, venous thromboembolic event, and malignancy. Basically, patients were asked to choose a preference for one of two states: a reference profile (no treatment and no adverse drug reactions) and a target profile of an immunosuppressive agent. The favourable effect in the target profile (see above) was kept constant and the size of the risks were varied, depending on the preferences that the respondents indicated on the questions. Annual risks were based on the RA trials, and were varied between 1.5% - 6.0% for serious infection; 0.5% - 2% for cancer; 0.2% - 1.0% for VTE. Patient appropriate descriptions were developed and tested for the descriptions of attributes and levels.

The inclusion/exclusion criteria were similar as the main criteria used in the pivotal trials.

The statistical analysis included (1) a baseline choice model that identified the respondent characteristics that are associated with a higher likelihood of choosing the AA medicine, (2) a constant-only interval-regression model that estimated the MAR for each risk, and (3) a covariate-adjusted interval-regression model that estimated the effect of various respondent characteristics on the MAR for each risk.

Results

In total, 701 individuals responded by clicking the link in the e-mail invitation through the National Alopecia Areata Foundation (NAAF); the final sample consists of 178 respondents.

Approximately 90% of the sample was female; the average age was approximately 40 years, with ages ranging from 18 to 70 years. Nearly 75% of the sample described themselves as white or Caucasian. The average time since AA diagnosis was 12 years.

Approximately half (49%) of respondents stated that they would choose an AA medicine with a benefit-risk profile based on the expected benefit of the 4-mg dose of baricitinib in AA and the safety data from the 4-mg dose of baricitinib in the RA phase 3 program in the baseline question: 33% chance on 80%-100% scalp hair coverage in 1 year; 3% risk on serious infection each year; 1% risk on developing cancer each year; 0.5% of getting a blood clot each year.

The averaged maximal acceptable risk (MAR) was similar to the value presented in the baseline question (3.3% for risk of serious infection, 1.2% for risk of cancer, and 0.7% for increased risk of getting a blood clot). However, the distributions of the individually elicited Maximum Acceptable Risks were bimodal for all three risks (Figure 28 below for serious infection). This indicates that about equally large proportions of respondents indicated to accept no risks with the treatment or risks more than the maximum risk specified (empirically based on the RA trials).

Patients who were younger perceived more (physical, social, or emotional) impact of AA, missed hair in all parts of the body, were experienced with prescription medicine, were inclined to accept higher risks.

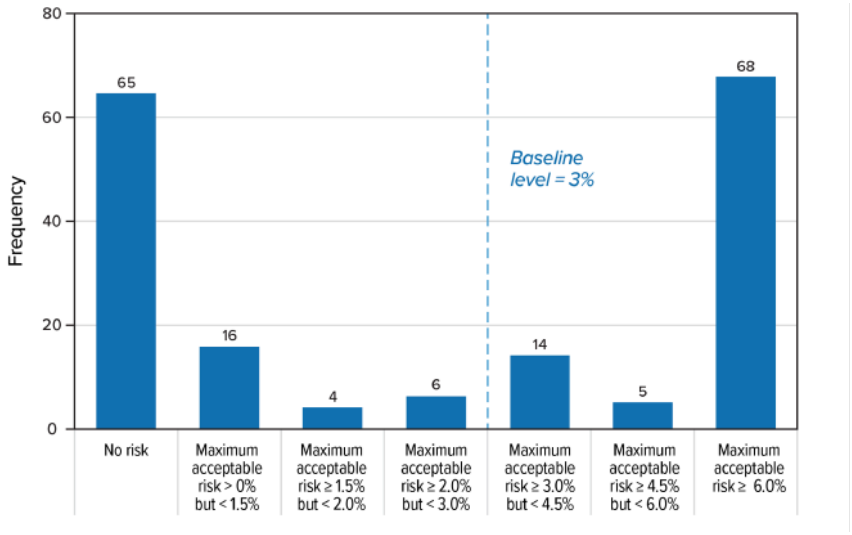


Figure 29 Maximum acceptable risk of serious infection (N=178)

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Overall, the design of JAHO and JAIR clinical trials is acceptable. It is stated that efficacy data of the phase 2 portion in the JAHO study is excluded from overall results, and considering the aim of the phase 2 part (dose-finding) this is agreed. In the 'phase 3' studies, adult patients with severe AA, defined as ≥50% scalp hair loss, and a current episode of more than six months, were randomized to placebo (N=345), baricitinib 2-mg QD (N=340) or 4-mg QD (N=515), for 36 weeks. Patients with other types of alopecia were excluded. This is in line with the intended indication of patients with at

least severe AA. At the CHMP's request, the MAH included in the wording of the indication a reference to the definition of severe AA included in the section 5.1 of the SmPC to ensure that it was clear for the prescriber.

Concomitant therapy with topical or intra-articular corticosteroids (except on scalp, eyebrows and eyelashes) were allowed during pivotal trials. Only 4.3% of patients used concomitant AA therapies during the studies. These concomitant therapies were balanced among treatment groups.

The primary outcome measure was based on the SALT score. The SALT score is often used in clinical practice and scientific research to measure the severity of AA disease. Considering SALT as the primary outcome for the pivotal trials is acceptable. SALT≤ 20 at week 36 was considered as the primary endpoint, corresponding to scalp hair loss of ≤20% or at least 80% scalp hair coverage. The clinical relevance of reaching a SALT≤20 for patients with severe AA was determined using panels from physicians and patients (Wyrwich et al., 2020). The treatment target of the clinician assessed primary outcome SALT<20 aligns with the treatment target of the patient-assessed scalp hair assessment of 0 or 1, which also was found clinical relevant by panel of patients with severe AA taking part in the development (Wyrwich et al. 2020c). This supports the clinical relevance of the primary outcome, and it is considered that the primary endpoint is a clinically relevant outcome for the target population. However, both the clinician-assessed SALT score and the patient assessed Scalp Hair Assessment essentially measure the same measurement concept: the amount of hair (loss). It is acknowledged that the amount of hair drives satisfaction and relevance of treatment effects. Satisfaction with the results also depends on the site of remaining hair loss and was not directly assessed. However, it could be inferred through the results on Skindex-16 subscales and HADS subscales. The MAH has adequately discussed the clinical relevance of the results of Skindex and HADS including relevant subgroups: males/females, severe/very severe, disease duration.

Follow-up of 36 weeks is considered acceptable as AA is a chronic, relapsing disease. 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 months or years after remission (Messenger AG et al., 2012). Therefore, the long-term efficacy results are important for the assessment. An update of the efficacy data, including completed 52-week results, has been provided during the procedure.

No EMA scientific advice for AA has been sought. Based on US FDA recommendations, the MAH developed the Alopecia Areata Investigator's Global Assessment (AA-IGA), the Scalp Hair Assessment PRO™, the ClinRO Measure for Eyebrows Hair Loss™, and the ClinRO Measure for Eyelash Hair Loss™.

The MAH has developed the Scalp Hair Assessment PRO. This measure was intended to confirm the results of SALT score through patients themselves. The measurement properties were only evaluated internally within the two pivotal trials, and no external validation has been performed. In the absence of sensitivity to change, this is considered acceptable.

It is known that AA can cause eyebrow and eyelash loss. ClinRO Measures for Eyebrow and Eyelash Hair Loss, showed a correlation with SALT and PRO scalp measures. However, they were not suitable to distinguish the quality of life differences (measured by the Skindex-16 Emotions Domain Score).

PRO assessments for Eyebrows and Eyelashes are newly introduced measurement tools developed by the MAH. Data on the establishment of validity and reliability and the ability of PRO measures of eyebrows and eyelashes to detect change has been provided. It is considered that comparison of a novel instrument (here Clinician-Reported Outcomes for Eyebrow Hair Loss and Eyelash Hair Loss) with another novel and by MAH developed instrument (here Patient-Reported Outcome Measure for Eyebrows/Eyelashes) is scientifically not ideal and that no external validation was done. However, the results of reliability and validity tests through correlation with other instruments (SALT and Skindex-16

Emotions Domain) are reassuring. Therefore, the selection of these measures as key secondary outcomes is acceptable.

Skindex-16™ and HADS are established assessment scales and clinically relevant because AA affects the quality of life and has a psychological burden on patients. For Skindex-16, the MAH has adapted the wording for AA patients.

Assumptions underlying the sample size calculation were based on studies in other JAK inhibitors, which is a reasonable approach. Given the assumptions made, the calculations are acceptable. As envisioned, the alpha allocation was adjusted before database lock, and testing has been done using the updated significance level of 0.025 for both the high and low dose. The adapted allocation of the significance level is accepted as it provides equal opportunity for the low and high dose to show efficacy. It must be noted that this adaptation has negatively impacted the power for the high dose and positively impacted the power for the low dose. This is not further pursued, as both studies reached significance on the primary endpoint for both doses. The procedures used for randomisation and stratification are adequate. The double-dummy design and measures taken to keep study participants and study personnel blinded appear to be appropriate.

The use of the FAS population for primary efficacy analyses is considered acceptable.

Analysis of dichotomous endpoints was performed using logistic regression with adjustment for baseline value and stratification factors which is considered the standard method of analysis and is acceptable. Analysis of continuous outcomes was performed using ANCOVA with adjustment for baseline value and stratification factors which is considered acceptable.

Both the logistic regression and ANCOVA analyses require imputation of missing outcome data at week 36 for analysis in the FAS. Non-responder imputation (NRI) was used as the primary method for imputation used for the dichotomous outcomes. The modified LOCF was used for imputation of continuous outcomes. Although both these methods for imputation are considered acceptable, sensitivity analyses are required to show the robustness of results to the imputation methods used.

Regarding the multiplicity adjustments, there were some small differences between the graphs used for the hierarchical testing procedure in the two phase 3 trials. In both Studies JAIR and JAHO, graphs in Statistical Analysis Plan differed from the graphs in the original protocols. In addition, the original plan to use the alpha level of 0.04 for the 4-mg dose and 0.01 for the 2-mg dose, was changed to an alpha level of 0.025 for both doses. This change was already discussed when assessing the sample size. As these changes were made before the final database lock, they are considered acceptable.

The assumptions made regarding missing outcomes after permanent discontinuation of study treatment were robust in sensitivity analyses.

For the 2-mg dosing regimen, efficacy could not be declared for some of the secondary endpoints with a nominal p-value below 0.001 because a hypothesis higher in the hierarchy was not rejected. This leaves the efficacy of 2 mg with some uncertainty, and supports choice for 4 mg as the main dose.

No studies were conducted in European countries. PK analysis from other indications has not shown differences between subjects with different ethnicities for baricitinib. Furthermore, efficacy in AA was comparable in the subgroup analysis of different regional groups. Therefore, it is not expected that efficacy will be different in European countries.

Protocol deviations in both studies were mostly dues to misclassification of the current episode. Deviations which violated inclusion/exclusion criteria results are low in numbers and stratified between placebo and treatment arms. The possibility that these deviations have affected the efficacy results is low. Deviations due to non-compliance also occurred in the placebo group at a comparable and small rate.

Overall, rate of discontinuations was comparable between treatment arms and placebo in both studies. The most frequent reasons for discontinuation were withdrawal by subject (3-6%), adverse events (1-3%) and lost to follow up (1-3%). The rates for both reasons were negligible and comparable between all treatment arms.

Efficacy data and additional analyses

The overall patients' characteristics were comparable between the different treatment groups. The largest difference between the trials was observed in geographical regions, as more patients from North America were included in JAHO study compared to JAIR study (around 55% versus around 35%, respectively). This is not supposed to have an impact on efficacy results; it is referred to the subgroup analysis section for more details. The disease baseline characteristics were comparable between placebo and treatment arms. Only the proportion of patients with very severe AA was slightly higher in the baricitinib 2-mg group (57%) compared to baricitinib 4-mg and placebo (52% in both). This difference is considered small, and the probability that it has affected the efficacy results is low. Overall, the investigated population represents the targeted population (patients with severe AA).

Most of the patients (around 90%) in both placebo and treatment arms had prior therapy with systemic immunosuppressants/immunomodulator therapy or topical treatments. In total only 23, 33 and 57 treatment naïve patients are included in placebo, baricitinib 2-mg and baricitinib 4-mg arms in pivotal studies, respectively. It is not expected that concomitant medication use had affected the final results.

The primary endpoint was met ($p<0.001$) in both baricitinib treatment groups (both 4-mg and 2-mg dosing regimens) in both pivotal studies. The treatment effect calculated from pooled data analysis was 15.6 (95%CI: 11,20.5) and 29.9 (25.2,34.4) for baricitinib 2-mg and 4-mg, respectively. The proportion of patients achieving SALT $\leq$20 at W36 in treatment and placebo groups was slightly higher in JAHO phase 3 compared to JAIR study (around 3-4% higher). However, the effect size was comparable between the two studies. The effect size in baricitinib 2-mg group was significantly smaller than baricitinib 4-mg in both studies (16.4% and 14.7% compared to 29.9% and 29.9.% in JAHO and JAIR studies, respectively). The difference with placebo arm was still significant for the baricitinib 2-mg group. The outcome of the sensitivity analyses was largely consistent with the outcome of the primary analysis.

The majority of included patients were Caucasian. The response in Black/African American patients is comparable to the overall results. The 2 mg dosing regimen appears to be less effective and does not show a significant improvement compared to the placebo group. However, the numbers are limited, and no firm conclusions can be made.

Numerous secondary and additional outcomes are calculated. ClinRO and PRO measures are essentially the same instrument measured by different investigators (physician or patient himself). Percentages of change in SALT score is more sensitive than dichotomous SALT, but that is not of additional value in these studies. Therefore the most relevant measures are considered to be the static SALT$\leq$0 (indicating almost full remission), which is almost similar to the change measure $SALT_{90}$, the PRO Scalp instrument (indicating the amount of hair loss from the patient perspective) and ClinRO EB and EL (considering the importance of hair regrowth in eyebrows and eyelashes), for these outcomes efficacy was robust for baricitinib 2-mg and 4-mg. According to the results on the primary and key secondary outcomes, baricitinib 4-mg was more effective than 2-mg.

The MAH has proposed a dose of 4-mg for the intended indication, in line with the efficacy results. The 4-mg dose was more effective than the 2-mg dose, but also, the lower dose can be considered more effective than placebo. Initially, no proposals were made for stopping treatment or down titration to 2-

mg in responding patients treated with baricitinib 4-mg, or for when to stop treatment in patients with an insufficient response. As the disease may recover spontaneously and given the safety profile of JAK inhibitors like baricitinib, the CHMP requested that guidance should be provided regarding treatment continuation and when to stop treatment.

Accordingly, the Section 4.2 of the SmPC has been updated to reflect that a dose of 2 mg once daily may be appropriate for patients such as those aged ≥ 75 years and for patients with a history of chronic or recurrent infections. A dose of 2 mg once daily may also be considered for patients who have achieved sustained control of disease activity with 4 mg once daily and are eligible for dose tapering.

Because data of the stop and dose reduction sub-studies of the trials became available, the MAH provided data driven proposals. After down titration to 2-mg in responding patients, efficacy was reduced. In another sub-study, responders were re-randomised to stop or continuation of the 4-mg or 2-mg dose. According to the results, only 33% and 20% of responders stayed in remission until week 76 if baricitinib 4mg and 2mg were withdrawn, respectively. This indicates a higher chance of flare if treatment is stopped. Therefore, stopping baricitinib in case of maintained good response seems not advisable based on the efficacy results of the stop study since a majority of patients lost response within 24 weeks after discontinuation. On the other hand, considering the safety profile of baricitinib, the exposure should be reduced when possible. At the CHMP's request, Section 4.2 of the SmPC was updated to include the following guidance which was considered acceptable to the CHMP:

"Once a stable response has been achieved, it is recommended to continue treatment for at least several months, in order to avoid relapse. The benefit risk of treatment should be re assessed at regular intervals on an individual basis."

Overall, the additional efficacy endpoints have demonstrated a comparable trend as key secondary endpoints. Baricitinib 4-mg dose has shown more significant results than the 2-mg dosing regimen. For HADS at week 36, no subcategories were statistically different from placebo in baricitinib 2-mg group. The primary outcome has shown the efficacy of baricitinib 2-mg in regrowing the hair of scalp, the significance of which is not as much as 4-mg dosing regimen, and therefore additional endpoints in measuring the overall health of the patient score less than the primary endpoint. Some secondary and additional endpoints were not significant for the baricitinib 2-mg treatment group, especially in the JAIR study. For Skindex functioning and symptoms domain, no significant difference has been found between baricitinib 2-mg and placebo.

There is support for the clinical relevance of the primary outcome (see the section on 'design and conduct' above). The PRO measures support the change in the extent of hair loss from the patient perspective, and patient and physician views aligned. In line with primary outcome, emotion and functioning domain of Skindex-AA show a reduction in baricitinib groups (proportionally better response in 4mg group) compared to the placebo. No minimal clinically important change has been defined by the MAH, which makes interpretations of these results difficult. However, it can be agreed that an overall better response has been observed in treatment groups, which is reassuring. After stratification, it has been observed that females had a better response in symptom domain of Skindex-AA and depression domain of HADS but slightly lesser response at emotion and functioning domains of Skindex-AA and Anxiety domain of HADS, compared to male patients, as cosmetic results are relatively more important for female patients. Improvement of all domains of Skindex-AA and HADS in females is considered reassuring. Patients with episodes <4 years and severe AA at baseline had better responses in all Skindex-AA domains. Only non-responders with very severe disease at baseline and/or duration of episode longer than 4 years and only in symptom domain of Skindex-AA had unfavourable results, which is expected. Other subgroups have shown a reduction in all Skindex-AA domains and HADS domains, which is in line with the overall results.

Subgroup analysis has shown that 4-mg dose is more effective compared to 2-mg dosing regimen.

This included predefined subgroups of patients who: weigh more than 100kg; had impaired renal function; were older than 65 years status. Patients with severe AA at baseline had a better response (47.6%) compared to patients with very severe AA (21.3%). This is expected mainly because the primary endpoint is static and includes complete and near-complete hair regrowth. Long-term efficacy data shows response rate increase from 34% at week 36 to 39% at week 52 for 4-mg group. After week 52, responders were re-randomised for down-titration or continuation on 4mg. The results show that 96% of the patients who remained on baricitinib 4 mg and 74 % of the patients who were re-randomised to baricitinib 2 mg maintained their response week 76.

Patients with a disease duration lower than 4 years had a better response compared to patients with a longer disease duration. This can be expected and is comparable in placebo and baricitinib 2-mg treatment groups.

It has been demonstrated that improvement in SALT starts between week 8-16 of treatment and increases until week 36, with a higher response in the baricitinib 4-mg group. Secondary endpoints showed comparable results.

Predictor analysis has shown that 36 weeks is a more appropriate time point to stop treatment in non-responders than 24 weeks. Therefore, Section 4.2 of the SmPC has been updated as follows:

"*Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit after 36 weeks of treatment*."

2.4.4. Conclusions on the clinical efficacy

In both pivotal studies in patients with severe AA, the primary endpoint (SALT≤20 at week 36) was met. The outcome of sensitivity analysis is largely consistent with the outcome of the primary analysis. The dosing regimen of 4-mg was more effective than the 2-mg dose, but also the lower dose was more effective than placebo, in the primary endpoint. These results were supported by the results on key secondary outcomes, notably by: the proportion of patients with a $SALT_{90}$ at week 36; the proportion of patients with a PRO Scalp Hair Assessment score of 0 or 1 with a ≥2-point improvement; and the proportions of patients with a response (0 or 1 with ≥2-point improvement) on the eyebrow or eyelash hair growth. Clinical relevance of the treatment effects is supported by the definition SALT≤20 as a clinically relevant treatment effect by patients and physicians in the development of SALT. Subgroup analysis by gender shows robust effects.

The statistical methods and analysis populations are considered acceptable.

The CHMP concluded that the efficacy data supports the following indication: Baricitinib is indicated for the treatment of severe alopecia areata in adult patients (see section 5.1).

2.5. Clinical safety

Introduction

Olumiant is available as 2-mg and 4-mg tablets. It is currently indicated to treat adult Rheumatoid arthritis and adult Atopic dermatitis (it is referred to the SmPC for more details). The currently known safety profile, contra-indications and warnings, are coming from those two indications.

Contra-indications

Baricitinib is contra-indicated in pregnancy and in known cases of hypersensitivity to the active substance or any of the excipients.

Warnings

The SmPC includes warnings regarding the occurrence of infections, viral reactivation, haematological abnormalities, venous thromboembolism, lipids, hepatic transaminase elevations, malignancy, hypersensitivity, diverticulitis. The SmPC also includes warnings regarding vaccination, guidance for laboratory monitoring (lipids, absolute neutrophil count, absolute lymphocyte count, haemoglobin, hepatic transaminases), concomitant treatment with other immunosuppressive drugs.

Baricitinib is associated with an increased rate of infections such as upper respiratory tract infections compared to placebo. In patients with active, chronic or recurrent infections, the risks and benefits of treatment with Olumiant should be carefully considered. If an infection develops and the patient is not responding to standard therapy, treatment with baricitinib should be temporarily interrupted.

In relation to haematological abnormalities, treatment should not be initiated, or should be temporarily interrupted, in patients with an ANC < 1 x 109 cells/L, ALC < 0.5 x 109 cells/L or haemoglobin < 8 g/dL.

Cases of viral reactivation, including herpes virus reactivation, were reported in clinical studies.

Dose-dependent increases in hepatic transaminase (ALT and AST) were reported in patients treated with baricitinib compared to placebo. If drug-induced liver injury is suspected, treatment with baricitinib should be temporarily interrupted.

Events of venous thromboembolism (deep venous thrombosis and pulmonary embolism) have been reported in patients receiving baricitinib. Olumiant should be used with caution in patients with risk factors for DVT/PE, such as older age, obesity, a medical history of DVT/PE, or patients undergoing surgery and immobilisation. If clinical features of DVT/PE occur, Olumiant should be discontinued.

Unfavourable effects

In patients with Rheumatoid arthritis and with Atopic dermatitis, the most commonly reported Adverse drug reactions were increased LDL cholesterol, upper respiratory tract infections, and headache. Among the 'common' Adverse drug reactions are viral reactivation (herpes) and pneumonia, while deep venous thrombosis and pulmonary embolism were 'uncommon'.

Overview of safety data

This application includes safety data from baricitinib treated adult patients with severe AA from two multicentre, randomised, double-blind, placebo-controlled studies. Study JAHO is an adaptive Phase 2 and Phase 3 study, and study JAIR is a Phase 3 study. The safety population is defined as all patients who received at least 1 dose of study treatment.

Safety data are included from the 36-week placebo-controlled periods and from the extended period including week 52, with database cut off dates of 23 August 2021 for Study JAHO and 30 August 2021 for Study JAIR.

Adverse events were classified based on the MedDRA Version 23.1. A TEAE was defined as an event that first occurred or worsened in severity after baseline during the analysis period. The analysis period is defined as the treatment period plus up to 30 days after the last dose date of the study drug.

Table 29 Treatment Period, Analysis Population, Treatment Groups, and Comparisons for Each Integrated AA Analysis Set.

	BARI AA PC	Ext BARI AA	All BARI AA	All BARI 2-mg AA	All BARI 4-mg AA
Studies included	JAHO and JAIR				
Time period	36 weeks	Starting from randomisation up to the data cutoff date. Includes all patients who were exposed to PBO, BARI 2-mg, or BARI 4-mg dose from randomisation until dose or treatment change.	Includes all patients who were exposed to any BARI dose at any time during the studies either from randomisation or from switch or rescue from PBO.	Includes all patients who were exposed to BARI 2-mg at any time during the studies either from randomisation or from switch or rescue from treatment other than BARI 2-mg.	Includes all patients who were exposed to BARI 4-mg at any time during the studies either from randomisation or from switch or rescue from treatment other than BARI 4-mg.
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 placebo and 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 patients treated with any dose of baricitinib that might require further evaluation and discussion.	Enable an assessment of potential safety differences in patients primarily exposed to BARI 2-mg compared with patients exposed to any dose of baricitinib (All BARI AA).	Enable an assessment of potential safety differences in patients primarily exposed to BARI 4-mg compared with patients exposed to any dose of baricitinib (All BARI AA).
Treatment groups	PBO BARI 2-mg BARI 4-mg	PBO BARI 2-mg BARI 4-mg Data censored at dose or treatment change.	BARI 1 mg BARI 2-mg BARI 4-mg	BARI 2-mg	BARI 4-mg
Treatment comparisons	BARI 2-mg vs PBO BARI 4-mg vs PBO BARI 4-mg vs BARI 2-mg	BARI 4-mg vs BARI 2-mg	NA	NA	NA

The data sets of both trials were integrated for the safety assessment (Table 29). The data set 'BARI AA PC' includes the 36 weeks placebo-controlled periods and includes placebo, baricitinib 2-mg and 4-mg. Data set 'Ext BARI AA' includes all data from randomisation up to data cut-off, censored at dose or treatment change. The 'All BARI AA' set includes all doses of baricitinib, 1 mg, 2-mg and 4-mg.

In addition, a pooled RA/AD/AA dataset, which includes all RA and AD patients treated with baricitinib in the16-week placebo-controlled periods, and all AA patients treated with baricitinib in the 36-week placebo-controlled period, was used to determine the frequency of Adverse Drug Reactions.

Patient exposure

As of the data cut-off date of 31 March 2021, the AA safety database included 1244 patients exposed to baricitinib at any dose. Overall exposure was 1362 patient-years. The database included 845 (68%) patients with at least 52 weeks of cumulative exposure to baricitinib at any dose, and 516 (55%) patients treated with baricitinib 4-mg who completed at least 52 weeks of treatment.

A total of 28 patients were exposed to baricitinib 1-mg, in the phase 2 portion of study JAHO. A total of 564 patients were exposed to baricitinib 2-mg for 488.9 PY and a total of 938 patients were exposed to baricitinib 4-mg for 858.9 PY. Patients with 52 weeks of exposure (at least 358 days) were: 317 patients (All BARI 2-mg) and 516 patients (All BARI 4-mg).

In the 36-week placebo-controlled comparison, there were 371 patients exposed to placebo, 365 patients exposed to baricitinib 2-mg, and 540 exposed to baricitinib 4-mg (Table 30). About 90% in all three treatment groups were exposed for at least 36 weeks and about 87% were exposed to baricitinib for at least 52 weeks (extended BARI AA).

Table 30 Summary of baricitinib exposure.

	36-Week Placebo-Controlled BARI AA			Extended BARI AA		All BARI AA	All BARI 2-mg AA	All BARI 4-mg AA
	PBO N = 371	BARI 2-mg N = 365	BARI 4-mg N = 540	BARI 2-mg N = 365	BARI 4-mg N = 540	All Doses N = 1244	BARI 2-mg N = 564	BARI 4-mg N = 951
Mean days exposure (SD)	239.4 (49.68)	240.8 (50.16)	245.8 (39.24)	402.4 (169.3)	487.5 (195.3)	489.9 (209.9)	373.5 (170.8)	414.5 (209.4)
Weeks of exposure, n (%)								
>0	371 (100)	365 (100)	540 (100)	365 (100)	540 (100)	1244 (100)	564 (100)	951 (100)
≥4	369 (99.5)	360 (98.6)	536 (99.3)	360 (98.6)	536 (99.3)	1234 (99.2)	558 (98.9)	940 (98.8)
≥8	363 (97.8)	353 (96.7)	533 (98.7)	353 (96.7)	533 (98.7)	1218 (97.9)	546 (96.8)	930 (97.8)
≥12	357 (96.2)	349 (95.6)	528 (97.8)	349 (95.6)	528 (97.8)	1204 (96.8)	537 (95.2)	916 (96.3)
≥16	351 (94.6)	348 (95.3)	523 (96.9)	348 (95.3)	523 (96.9)	1197 (96.2)	534 (94.7)	898 (94.4)
≥24	341 (91.9)	341 (93.4)	514 (95.2)	341 (93.4)	514 (95.2)	1169 (94.0)	520 (92.2)	848 (89.2)
≥36	270 (72.8)	260 (71.2)	403 (74.6)	332 (91.0)	502 (93.0)	1115 (89.6)	476 (84.4)	732 (77.0)
≥52 [a]	–	–	–	307 (84.1)	479 (88.7)	948 (76.2)	361 (64.0)	610 (64.1)
≥76	–	–	–	67 (18.4)	230 (42.6)	586 (47.1)	91 (16.1)	293 (30.8)

	36-Week Placebo-Controlled BARI AA			Extended BARI AA		All BARI AA	All BARI 2-mg AA	All BARI 4-mg AA
	PBO N = 371	BARI 2-mg N = 365	BARI 4-mg N = 540	BARI 2-mg N = 365	BARI 4-mg N = 540	All Doses N = 1244	BARI 2-mg N = 564	BARI 4-mg N = 951
≥104	–	–	–	20 (5.5)	68 (12.6)	158 (12.7)	24 (4.3)	85 (8.9)
Total patient-years	243.2	240.6	363.4	402.1	720.7	1668.4	576.7	1079.2

Abbreviations: AA = alopecia areata; N = number of patients in the safety analysis set; n = number of patients in the specified category.

Notes: 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. Total patient-years is calculated as sum of duration of exposure in days for all patients in dosing regimen / 365.25.

[a] Cumulative exposure ≥358 days due to the protocol-allowed 7-day visit window.

Adverse events

Summary of Adverse Events

In the 36-week placebo-controlled period, the frequencies of TEAEs, SAEs, and AEs leading to permanent discontinuation from study drug were numerically higher in the baricitinib groups compared to placebo (Table 31). Most TEAEs were mild or moderate in severity. The frequency of TEAEs, SAEs and of severe TEAEs was highest in the baricitinib 4-mg group, in the placebo-controlled data as well as in the extended data set.

Table 31 Adverse Events Summary from the 36-Week Placebo-Controlled Period, Extended, and All BARI Analysis Sets.

	36-Week Placebo-Controlled BARI AA			Extended BARI AA		All BARI AA	All BARI 2-mg AA	All BARI 4-mg AA
	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]	BARI 2-mg N = 365 PYE = 402.1 n (%) [IR]	BARI 4-mg N = 540 PYE = 720.7 n (%) [IR]	All Doses N = 1244 PYE = 1668.4 n (%) [IR]	BARI 2-mg N = 564 PYE = 576.7 n (%) [IR]	BARI 4-mg N = 951 PYE = 1079.2 n (%) [IR]
Deaths	0	0	0	0	0	0	0	0
SAE	6 (1.6) [2.5]	8 (2.2) [3.3]	14 (2.6) [3.9]	9 (2.5) [2.1]	25 (4.6) [3.4]	54 (4.3) [3.2]	18 (3.2) [3.0]	36 (3.8) [3.3]
TEAE [a]	211 (56.9) [153.1]	221 (60.5) [160.9]	341 (63.1) [172.1]	246 (67.4) [129.5]	399 (73.9) [132.7]	872 (70.1) [118.5]	351 (62.2) [119.0]	604 (63.5) [115.9]
Mild	122 (32.9) [66.2]	136 (37.3) [76.2]	200 (37.0) [75.1]	132 (36.2) [43.4]	205 (38.0) [38.9]	466 (37.5) [38.3]	198 (35.1) [45.2]	329 (34.6) [40.6]
Moderate	78 (21.0) [36.8]	79 (21.6) [37.7]	120 (22.2) [37.7]	105 (28.8) [30.9]	162 (30.0) [27.1]	349 (28.1) [25.2]	141 (25.0) [28.2]	230 (24.2) [24.9]
Severe	11 (3.0) [4.6]	6 (1.6) [2.5]	21 (3.9) [5.8]	9 (2.5) [2.1]	32 (5.9) [4.4]	57 (4.6) [3.4]	12 (2.1) [2.0]	45 (4.7) [4.1]

Permanent DC from study drug due to AE	6 (1.6) [2.5]	8 (2.2) [3.3]	12 (2.2) [3.3]	9 (2.5) [2.1]	19 (3.5) [2.6]	33 (2.7) [1.9]	10 (1.8) [1.6]	23 (2.4) [2.1]
DC from study due to AE	6 (1.6) [2.5]	8 (2.2) [3.3]	8 (1.5) [2.2]	7 (1.9) [1.6]	18 (3.3) [2.4]	29 (2.3) [1.7]	7 (1.2) [1.2]	22 (2.3) [2.0]

Abbreviations: AA = alopecia areata; DC = discontinuation; IR = incidence rate; n = number of patients in the specified category; N = number of patients in the analysis population; PYE = patient-year exposure; PYR = patient-years at risk.

[a] Patients with multiple occurrences of the same event are counted under the highest severity.

Note: IRs are calculated based on PYR.

Adverse events by SOC

In the placebo-controlled period, the most frequently reported SOCs with TEAEs occurring in 10% of patients or more in any treatment group were Infections and infestations, Skin and subcutaneous tissue disorders, Investigations, Nervous system disorders, Gastrointestinal disorders, and Musculoskeletal and connective tissue disorders (Table 32).

Table 32 Summary of most occurring (>10%) Treatment-Emergent Adverse Events by PT within System Organ Class from the 36-Week Placebo-Controlled Period, Extended, and All BARI Analysis Sets

System Organ Class	36-Week Placebo-Controlled Period			Extended BARI AA		All BARI AA	All BARI 2-mg AA	All BARI 4-mg AA
	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]	BARI 2-mg N = 365 PYE = 402.1 n (%) [IR]	BARI 4-mg N = 540 PYE = 720.7 n (%) [IR]	All Doses N = 1244 PYE = 1668.4 n (%) [IR]	BARI 2-mg N = 564 PYE = 576.7 n (%) [IR]	BARI 4-mg N = 951 PYE = 1079.2 n (%) [IR]
Patients with ≥1 TEAE	211 (56.9) [153.1]	221 (60.5) [160.9]	341 (63.1) [172.1]	246 (67.4) [129.5]	399 (73.9) [132.7]	872 (70.1) [118.5]	351 (62.2) [119.0]	604 (63.5) [115.9]
Infections and infestations	108 (29.1) [55.5]	118 (32.3) [62.9]	165 (30.6) [57.3]	150 (41.1) [51.6]	227 (42.0) [44.4]	509 (40.9) [43.3]	201 (35.6) [45.7]	334 (35.1) [41.4]
Skin and subcutaneous tissue disorders	44 (11.9) [19.5]	45 (12.3) [20.1]	77 (14.3) [23.1]	61 (16.7) [16.4]	122 (22.6) [19.1]	241 (19.4) [16.3]	84 (14.9) [15.5]	162 (17.0) [16.6]
Investigations	19 (5.1) [7.9]	26 (7.1) [11.2]	65 (12.0) [18.9]	33 (9.0) [8.3]	81 (15.0) [12.1]	155 (12.5) [9.9]	48 (8.5) [8.4]	111 (11.7) [10.9]
Nervous system disorders	29 (7.8) [12.4]	28 (7.7) [12.1]	54 (10.0) [15.8]	39 (10.7) [9.9]	75 (13.9) [11.1]	152 (12.2) [9.7]	52 (9.2) [9.1]	101 (10.6) [9.8]
Gastrointestinal disorders	40 (10.8) [17.8]	41 (11.2) [18.3]	52 (9.6) [15.2]	53 (14.5) [14.0]	72 (13.3) [10.7]	171 (13.7) [11.2]	71 (12.6) [12.9]	101 (10.6) [10.0]

System Organ Class	36-Week Placebo-Controlled Period			Extended BARI AA		All BARI AA	All BARI 2-mg AA	All BARI 4-mg AA
	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]	BARI 2-mg N = 365 PYE = 402.1 n (%) [IR]	BARI 4-mg N = 540 PYE = 720.7 n (%) [IR]	All Doses N = 1244 PYE = 1668.4 n (%) [IR]	BARI 2-mg N = 564 PYE = 576.7 n (%) [IR]	BARI 4-mg N = 951 PYE = 1079.2 n (%) [IR]
Musculoskeletal and connective tissue disorders	31 (8.4) [13.4]	27 (7.4) [11.6]	44 (8.1) [12.6]	46 (12.6) [11.7]	68 (12.6) [9.9]	139 (11.2) [8.7]	60 (10.6) [10.6]	82 (8.6) [7.8]
Respiratory, thoracic, and mediastinal disorders	18 (4.9) [7.6]	20 (5.5) [8.5]	36 (6.7) [10.2]	31 (8.5) [7.7]	48 (8.9) [6.8]	98 (7.9) [6.0]	38 (6.7) [6.6]	60 (6.3) [5.6]

Abbreviations: AA = alopecia areata; IR = incidence rate; N = number of patients in the analysis population; n = number of patients in the specified category; PT = preferred term; PYE = patient-years of exposure.

Common adverse events

Common TEAEs are defined as those reported at a frequency of greater than or equal to 2%, before rounding in any treatment group, including placebo. The occurrence of common TEAEs is presented in Table 33.

In the placebo controlled phase, usually the 'common AEs' occurred most frequently in the baricitinib 4-mg group, numerically somewhat less in the 2-mg group, and least in the placebo group, with some exceptions (Table 33). The most common AEs that were numerically more frequent in baricitinib treatment groups included (placebo versus 2-mg versus 4-mg): upper respiratory tract infections (7.0% vs 6.6% vs 7.6%) and viral upper respiratory tract infections (1.6% vs 2.2% vs 1.5%), nasopharyngitis (5.1% vs 4.4% vs 6.9%), headache (5.4% vs 5.5% vs 6.7%), acne (1.1% vs 5.8% vs 5.6%), blood CPK increased (1.3% vs 0.8% vs 4.3%), urinary tract infection (1.6% vs 3.8% vs 3.3%), influenza (1.9% vs 1.6% vs 2.6%), fatigue (1.1% vs 0.8% vs 2.2%), folliculitis (0.8% vs 1.4 vs 2.2%), nausea (1.6% vs 2.7% vs 2.0%) and vulvovaginal candidiasis (0% vs 2.6% vs 1.2%).

Table 33 Summary of Common Treatment-Emergent Adverse Events from the 36-Week Placebo-Controlled Period, Extended, and All BARI Analysis Sets.

	36-Week Placebo-Controlled BARI AA			Extended BARI AA		All BARI AA	All BARI 2-mg AA	All BARI 4-mg AA
	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]	BARI 2-mg N = 365 PYE = 402.1 n (%) [IR]	BARI 4-mg N = 540 PYE = 720.7 n (%) [IR]	All Doses N = 1244 PYE = 1668.4 n (%) [IR]	BARI 2-mg N = 564 PYE = 576.7 n (%) [IR]	BARI 4-mg N = 951 PYE = 1079.2 n (%) [IR]
Upper respiratory tract infection	26 (7.0) [11.2]	24 (6.6) [10.3]	41 (7.6) [11.8]	37 (10.1) [9.4]	52 (9.6) [7.6]	113 (9.1) [7.1]	47 (8.3) [8.3]	65 (6.8) [6.2]
Nasopharyngitis	19 (5.1) [8.0]	16 (4.4) [6.8]	37 (6.9) [10.7]	22 (6.0) [5.4]	45 (8.3) [6.5]	79 (6.4) [4.9]	23 (4.1) [3.9]	54 (5.7) [5.1]
Headache	20 (5.4) [8.4]	20 (5.5) [8.5]	36 (6.7) [10.4]	27 (7.4) [6.7]	48 (8.9) [6.9]	95 (7.6) [5.9]	34 (6.0) [5.8]	61 (6.4) [5.7]
Acne	4 (1.1) [1.6]	21 (5.8) [9.0]	30 (5.6) [8.5]	24 (6.6) [5.9]	35 (6.5) [5.0]	77 (6.2) [4.8]	28 (5.0) [4.8]	48 (5.0) [4.5]
Blood CPK increased	5 (1.3) [2.0]	3 (0.8) [1.2]	23 (4.3) [6.4]	3 (0.8) [0.7]	34 (6.3) [4.7]	53 (4.3) [3.2]	7 (1.2) [1.2]	46 (4.8) [4.3]
Urinary tract infection	6 (1.6) [2.5]	14 (3.8) [5.9]	18 (3.3) [5.0]	21 (5.8) [5.1]	27 (5.0) [3.7]	69 (5.5) [4.2]	28 (5.0) [4.7]	40 (4.2) [3.7]
Hypertension	9 (2.4) [3.7]	2 (0.5) [0.8]	14 (2.6) [3.9]	3 (0.8) [0.7]	17 (3.1) [2.3]	31 (2.5) [1.8]	7 (1.2) [1.2]	23 (2.4) [2.1]
Influenza	7 (1.9) [2.9]	6 (1.6) [2.5]	14 (2.6) [3.9]	7 (1.9) [1.7]	18 (3.3) [2.5]	29 (2.3) [1.7]	8 (1.4) [1.3]	21 (2.2) [1.9]
Pruritus	8 (2.2) [3.3]	1 (0.3) [0.4]	13 (2.4) [3.6]	5 (1.4) [1.2]	17 (3.1) [2.3]	29 (2.3) [1.7]	8 (1.4) [1.3]	21 (2.2) [1.9]
Cough	7 (1.9) [2.9]	5 (1.4) [2.1]	12 (2.2) [3.3]	7 (1.9) [1.7]	13 (2.4) [1.8]	26 (2.1) [1.5]	10 (1.8) [1.7]	16 (1.7) [1.4]
Fatigue	4 (1.1) [1.6]	3 (0.8) [1.2]	12 (2.2) [3.3]	4 (1.1) [0.9]	16 (3.0) [2.2]	24 (1.9) [1.4]	4 (0.7) [0.7]	20 (2.1) [1.8]
Folliculitis	3 (0.8) [1.2]	5 (1.4) [2.1]	12 (2.2) [3.3]	6 (1.6) [1.4]	16 (3.0) [2.2]	32 (2.6) [1.9]	8 (1.4) [1.3]	24 (2.5) [2.2]
Nausea	6 (1.6) [2.5]	10 (2.7) [4.2]	11 (2.0) [3.1]	12 (3.3) [2.9]	13 (2.4) [1.8]	39 (3.1) [2.3]	19 (3.4) [3.2]	19 (2.0) [1.7]

	36-Week Placebo-Controlled BARI AA			Extended BARI AA		All BARI AA	All BARI 2-mg AA	All BARI 4-mg AA
	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]**	**BARI 2-mg N = 365 PYE = 402.1 n (%) [IR]**	**BARI 4-mg N = 540 PYE = 720.7 n (%) [IR]**	**All Doses N = 1244 PYE = 1668.4 n (%) [IR]**	**BARI 2-mg N = 564 PYE = 576.7 n (%) [IR]**	**BARI 4-mg N = 951 PYE = 1079.2 n (%) [IR]**
Back pain	12 (3.2) [5.0]	6 (1.6) [2.5]	10 (1.9) [2.8]	8 (2.2) [1.9]	19 (3.5) [2.6]	32 (2.6) [1.9]	10 (1.8) [1.7]	22 (2.3) [2.0]
Arthralgia	8 (2.2) [3.3]	7 (1.9) [2.9]	9 (1.7) [2.5]	14 (3.8) [3.4]	15 (2.8) [2.0]	38 (3.1) [2.3]	21 (3.7) [3.5]	17 (1.8) [1.5]
Diarrhoea	8 (2.2) [3.3]	2 (0.5) [0.8]	9 (1.7) [2.5]	4 (1.1) [0.9]	12 (2.2) [1.6]	18 (1.4) [1.1]	4 (0.7) [0.7]	14 (1.5) [1.3]
Viral upper respiratory tract infection	6 (1.6) [2.5]	8 (2.2) [3.4]	8 (1.5) [2.2]	8 (2.2) [1.9]	10 (1.9) [1.4]	21 (1.7) [1.2]	9 (1.6) [1.5]	12 (1.3) [1.1]
Oral herpes	9 (2.4) [3.7]	6 (1.6) [2.5]	7 (1.3) [1.9]	7 (1.9) [1.7]	13 (2.4) [1.8]	25 (2.0) [1.5]	7 (1.2) [1.2]	18 (1.9) [1.6]
Vulvovaginal candidiasis[a]	0	6 (2.6) [4.0]	4 (1.2) [1.8]	6 (2.6) [2.2]	6 (1.8) [1.3]	16 (2.1) [1.5]	7 (1.9) [1.8]	8 (1.4) [1.2]
COVID-19	2 (0.5) [0.8]	1 (0.3) [0.4]	1 (0.2) [0.3]	7 (1.9) [1.7]	20 (3.7) [2.7]	57 (4.6) [3.4]	15 (2.7) [2.5]	43 (4.5) [3.9]
Dermatitis contact	4 (1.1) [1.6]	7 (1.9) [2.9]	4 (0.7) [1.1]	8 (2.2) [1.9]	11 (2.0) [1.5]	24 (1.9) [1.4]	9 (1.6) [1.5]	15 (1.6) [1.4]
Dyslipidaemia	3 (0.8) [1.2]	0	9 (1.7) [2.5]	0	14 (2.6) [1.9]	18 (1.4) [1.1]	3 (0.5) [0.5]	15 (1.6) [1.4]
Gastroenteritis	6 (1.6) [2.5]	6 (1.6) [2.5]	4 (0.7) [1.1]	8 (2.2) [1.9]	6 (1.1) [0.8]	19 (1.5) [1.1]	9 (1.6) [1.5]	10 (1.1) [0.9]
Herpes zoster	2(0.5) [0.8]	5 (1.4) (2.1)	5 (0.9) (1.4)	9 (2.5) [2.1]	11 (2.0) [1.5]	30 (2.4) [1.8]	11 (2.0) [1.8]	19 (2.0) [1.7]
Sinusitis	6 (1.6) [2.5]	4 (1.1) [1.7]	5 (0.9) (1.4)	7 (1.9) [1.7]	11 (2.0) [1.5]	21 (1.7) [1.2]	8 (1.4) [1.3]	12 (1.3) [1.1]
Eczema	5 (1.3) [2.1]	3 (0.8) [1.2]	4 (0.7) [1.1]	8 (2.2) [1.9]	7 (1.3) [0.9]	20 (1.6) [1.2]	10 (1.8) [1.7]	10 (1.1) [0.9]

Abbreviations: AA = alopecia areata; COVID-19 = coronavirus disease 2019; CPK = creatine phosphokinase; IR = incidence rate; n = number of patients in the specified category; N = number of patients in the safety analysis set; PYE = patient-years exposure; PYR = patient-years at risk.

Note: IRs are calculated based on PYR.

[a] Denominator and IR adjusted because event is gender specific.

Serious adverse events and deaths

No deaths were reported in the AA clinical trial programme through the data cut-off date.

Serious AEs were reported according to the International Conference on Harmonisation (ICH) E2A guidelines (ICH 1994).

In the 36-Week placebo-controlled period, in the baricitinib 2-mg and 4-mg groups there were 2.2% and 2.6% of patients reporting at least one SAE, compared to 1.6% in the placebo group (Table 34). Over the extended treatment period, most (≥3 patients) SAEs were in the Injury, poisoning and procedural complications, Infections and infestations, Cardiac Disorders and Gastrointestinal disorders SOCs.

Within the Injury, poisoning and procedural complications SOC, fractures were the most frequently reported SAEs for baricitinib-treated patients. In the placebo-controlled period, there were 3 fractures reported in the placebo group, fractures in 8 patients in the baricitinib 2-mg group and in 7 patients in the baricitinib 4-mg group. In the extended data set, 11 patients on 2-mg (3.0%) and 12 patients on 4-mg (2.2%) of baricitinib reported fractures.

In the Infections SOC, two events of pyelonephritis were reported, one in each baricitinib dose group. There were 6 cases of Covid-19 in the All BARI data set, 3 of them with pneumonia. In the extended data set there were SAE's of diverticulitis (n=1), appendicitis (n=2), appendicitis perforated (n=1), and a SAE of herpes zoster in the baricitinib 4-mg group. Pneumonia, diverticulitis and herpes zoster are known as ADRs of baricitinib, gastrointestinal perforation is an important identified risk.

In the SOC for Cardiac disorders, there were 4 SAEs reported: ventricular tachycardia, acute myocardial infarction, congestive cardiac failure, aortic valve incompetence, in the baricitinib groups and none in the placebo group (Table 34).

The SAEs in the Gastrointestinal disorders SOC were diverse, though 2 were gastric in nature (gastric stenosis, obstruction gastric) in the baricitinib 2-mg group (Table 34), apart from the three appendicitis cases alluded to above in the infections paragraph. Regarding Hepatobiliary disorders, there was one SAE of acute cholecystitis in the placebo group and two in the baricitinib groups, with an additional SAE of acute hepatitis in the extended BARI data set (Table 34).

There were two cases of Venous thrombotic events (one Pulmonary embolism and one Deep vein thrombosis) that both occurred after database lock. VTE is a known ADR of baricitinib.

For a complete listing of the important potential risks of baricitinib it is referred to Table 34. In the baricitinib groups and seen over the All BARI data set: there was one SAE of B-cell lymphoma; there were serious infections but there was no occurrence of tuberculosis or serious candida infections or PML; three SAEs of acute hepatitis/acute cholecystitis; two SAEs that refer to MACE (acute myocardial infection and congestive heart failure); two cases of venous thrombotic events; one case of gastro-intestinal perforation. In the baricitinib treated groups there were no SAEs of myelosuppression, or of myopathy including rhabdomyolysis. Pregnancy outcomes are discussed in the section on 'Special populations' further below.

Table 34 Summary of Serious Adverse Events by Preferred Term within System Organ Class from the 36 Week Placebo-Controlled Period, Extended, and All BARI Analysis Sets

System Organ Class Preferred Term	36-Week Placebo-Controlled			Extended BARI AA		All BARI AA	All BARI 2-mg AA	All BARI 4-mg AA
	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]	BARI 2-mg N = 365 PYE = 402.1 n (%) [IR]	BARI 4-mg N = 540 PYE = 720.7 n (%) [IR]	All Doses N = 1244 PYE = 1668.4 n (%) [IR]	BARI 2-mg N = 564 PYE = 576.7 n (%) [IR]	BARI 4-mg N = 951 PYE = 1079.2 n (%) [IR]
Patients with ≥1 SAE	6 (1.6) [2.5]	8 (2.2) [3.3]	14 (2.6) [3.9]	9 (2.5) [2.1]	25 (4.6) [3.4]	54 (4.3) [3.2]	18 (3.2) [3.0]	36 (3.8) [3.3]
Gastrointestinal disorders	1 (0.3) [0.4]	0	2 (0.4) [0.5]	0	2 (0.4) [0.3]	4 (0.3) [0.2]	2 (0.4) [0.3]	2 (0.2) [0.2]
Food poisoning	0	0	1 (0.2) [0.3]	0	1 (0.2) [0.1]	1 (0.1) [0.1]	0	1 (0.1) [0.1]
Inguinal hernia	0	0	1 (0.2) [0.3]	0	1 (0.2) [0.1]	1 (0.1) [0.1]	0	1 (0.1) [0.1]
Strangulated umbilical hernia	1 (0.3) [0.4]	0	0	0	0	0	0	0
Flatulence	0	0	0	0	0	1 (0.1) [0.1]	1 (0.2) [0.2]	0
Gastric stenosis	0	0	0	0	0	1 (0.1) [0.1]	1 (0.2) [0.2]	0
Obstruction gastric	0	0	0	0	0	1 (0.1) [0.1]	1 (0.2) [0.2]	0
Injury, poisoning, and procedural complications	1 (0.3) [0.4]	3 (0.8) [1.2]	2 (0.4) [0.5]	4 (1.1) [0.9]	6 (1.1) [0.8]	15 (1.2) [0.9]	8 (1.4) [1.3]	7 (0.7) [0.6]
Ankle fracture	0	2 (0.5) [0.8]	0	2 (0.5) [0.5]	1 (0.2) [0.1]	4 (0.3) [0.2]	3 (0.5) [0.5]	1 (0.1) [0.1]
Foot fracture	0	1 (0.3) [0.4]	0	1 (0.3) [0.2]	0	2 (0.2) [0.1]	2 (0.4) [0.3]	0
Facial bones fracture	0	0	1 (0.2) [0.3]	0	2 (0.4) [0.3]	2 (0.2) [0.1]	0	2 (0.2) [0.2]
Hand fracture	0	1 (0.3) [0.4]	0	1 (0.3) [0.2]	0	1 (0.1) [0.1]	1 (0.2) [0.2]	0
Lumbar vertebral fracture	0	0	1 (0.2) [0.3]	0	1 (0.2) [0.1]	1 (0.1) [0.1]	0	1 (0.1) [0.1]
Humerus fracture	1 (0.3) [0.4]	0	0	0	0	0	0	0
Ligament sprain	0	0	0	0	0	2 (0.2) [0.1]	1 (0.2) 0.2]	1 (0.1) [0.1]

System Organ Class Preferred Term	36-Week Placebo-Controlled			Extended BARI AA		All BARI AA	All BARI 2-mg AA	All BARI 4-mg AA
	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]	BARI 2-mg N = 365 PYE = 402.1 n (%) [IR]	BARI 4-mg N = 540 PYE = 720.7 n (%) [IR]	All Doses N = 1244 PYE = 1668.4 n (%) [IR]	BARI 2-mg N = 564 PYE = 576.7 n (%) [IR]	BARI 4-mg N = 951 PYE = 1079.2 n (%) [IR]
Radius fracture	0	0	0	1 (0.3) [0.2]	0	1 (0.1) [0.1]	1 (0.2) [0.2]	0
Thermal burn	0	0	0	0	1 (0.2) [0.1]	1 (0.1) [0.1]	0	1 (0.1) [0.1]
Anastomotic ulcer	0	0	0	0	0	1 (0.1) [0.1]	1 (0.2) [0.2]	0
Clavicle fracture	0	0	0	0	1 (0.2) [0.1]	1 (0.1) [0.1]	0	1 (0.1) [0.1]
Cardiac disorders	0	2 (0.5) [0.8]	1 (0.2) [0.3]	2 (0.5) [0.5]	2 (0.4) [0.3]	4 (0.3) [0.2]	2 (0.4) [0.3]	2 (0.2) [0.2]
Ventricular tachycardia	0	0	1 (0.2) [0.3]	0	1 (0.2) [0.1]	1 (0.1) [0.1]	0	1 (0.1) [0.1]
Acute myocardial infarction	0	1 (0.3) [0.4]	0	1 (0.3) [0.2]	0	1 (0.1) [0.1]	1 (0.2) [0.2]	0
Cardiac failure congestive	0	1 (0.3) [0.4]	0	1 (0.3) [0.2]	0	1 (0.1) [0.1]	1 (0.2) [0.2]	0
Aortic valve incompetence	0	0	0	0	1 (0.2) [0.1]	1 (0.1) [0.1]	0	1 (0.1) [0.1]
General disorders and administration site conditions	0	1 (0.3) [0.4]	1 (0.2) [0.3]	1 (0.3) [0.2]	2 (0.4) [0.3]	4 (0.3) [0.2]	2 (0.4) [0.3]	2 (0.2) [0.2]
Chest pain	0	0	1 (0.2) [0.3]	0	1 (0.2) [0.1]	1 (0.1) [0.1]	0	1 (0.1) [0.1]
Asthenia	0	1 (0.3) [0.4]	0	1 (0.3) [0.2]	0	1 (0.1) [0.1]	1 (0.2) [0.2]	0
Cyst	0	0	0	0	1 (0.2) [0.1]	1 (0.1) [0.1]	0	1 (0.1) [0.1]
Drug withdrawal syndrome	0	0	0	0	0	1 (0.1) [0.1]	1 (0.2) [0.2]	0
Hepatobiliary disorders	1 (0.3) [0.4]	1 (0.3) [0.4]	1 (0.2) [0.3]	1 (0.3) [0.2]	2 (0.4) [0.3]	3 (0.2) [0.2]	1 (0.2) [0.2]	2 (0.2) [0.2]
Cholecystitis acute	1 (0.3) [0.4]	1 (0.3) [0.4]	1 (0.2) [0.3]	1 (0.3) [0.2]	1 (0.2) [0.1]	2 (0.2) [0.1]	1 (0.2) [0.2]	1 (0.1) [0.1]
Hepatitis acute	0	0	0	0	1 (0.2) [0.1]	1 (0.1) [0.1]	0	1 (0.1) [0.1]

System Organ Class Preferred Term	36-Week Placebo-Controlled			Extended BARI AA		All BARI AA	All BARI 2-mg AA	All BARI 4-mg AA
	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]	BARI 2-mg N = 365 PYE = 402.1 n (%) [IR]	BARI 4-mg N = 540 PYE = 720.7 n (%) [IR]	All Doses N = 1244 PYE = 1668.4 n (%) [IR]	BARI 2-mg N = 564 PYE = 576.7 n (%) [IR]	BARI 4-mg N = 951 PYE = 1079.2 n (%) [IR]
Infections and infestations	0	2 (0.5) [0.8]	1 (0.2) [0.3]	2 (0.5) [0.5]	5 (0.9) [0.7]	14 (1.1) [0.8]	3 (0.5) [0.5]	11 (1.2) [1.0]
Pyelonephritis	0	1 (0.3) [0.4]	1 (0.2) [0.3]	1 (0.3) [0.2]	1 (0.2) [0.1]	2 (0.2) [0.1]	1 (0.2) [0.2]	1 (0.1) [0.1]
COVID-19 pneumonia	0	1 (0.3) [0.4]	0	1 (0.3) [0.2]	0	3 (0.2) [0.2]	1 (0.2) [0.2]	2 (0.2) [0.2]
COVID-19 [a]	0	0	0	0	1 (0.2) [0.1]	3 (0.2) [0.2]	1 (0.2) [0.2]	2 (0.2) [0.2]
Diverticulitis	0	0	0	0	1 (0.2) [0.1]	1 (0.1) [0.1]	0	1 (0.1) [0.1]
Herpes zoster	0	0	0	0	1 (0.2) [0.1]	1 (0.1) [0.1]	0	1 (0.1) [0.1]
Varicella	0	0	0	0	0	1 (0.1) [0.1]	0	1 (0.1) [0.1]
Appendicitis	0	0	0	0	1 (0.2) [0.1]	3 (0.2) [0.2]	0	3 (0.3) [0.3]
Investigations	0	0	1 (0.2) [0.3]	0	0	0	0	0
SARS-CoV-2 test positive [a]	0	0	1 (0.2) [0.3]	0	0	0	0	0
Neoplasms benign, malignant, and unspecified	1 (0.3) [0.4]	0	1 (0.2) [0.3]	0	2 (0.4) [0.3]	3 (0.2) [0.2]	1 (0.2) [0.2]	2 (0.2) [0.2]
B-cell lymphoma	0	0	1 (0.2) [0.3]	0	1 (0.2) [0.1]	1 (0.1) [0.1]	0	1 (0.1) [0.1]
Prostate cancer[b]	1 (0.7) [1.0]	0	0	0	0	0	0	0
Chronic lymphocytic leukaemia	0	0	0	0	0	1 (0.1) [0.1]	1 (0.2) [0.2]	0
Uterine leiomyoma[b]	0	0	0	0	1 (0.3) [0.2]	1 (0.1) [0.1]	0	1 (0.2) [0.1]
Nervous system disorders	0	0	1 (0.2) [0.3]	0	2 (0.4) [0.3]	3 (0.2) [0.2]	0	3 (0.3) [0.3]
Guillain-Barre syndrome	0	0	1 (0.2) [0.3]	0	1 (0.2) [0.1]	1 (0.1) [0.1]	0	1 (0.1) [0.1]

System Organ Class Preferred Term	36-Week Placebo-Controlled			Extended BARI AA		All BARI AA	All BARI 2-mg AA	All BARI 4-mg AA
	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]	BARI 2-mg N = 365 PYE = 402.1 n (%) [IR]	BARI 4-mg N = 540 PYE = 720.7 n (%) [IR]	All Doses N = 1244 PYE = 1668.4 n (%) [IR]	BARI 2-mg N = 564 PYE = 576.7 n (%) [IR]	BARI 4-mg N = 951 PYE = 1079.2 n (%) [IR]
Sciatica	0	0	0	0	1 (0.2) [0.1]	2 (0.2) [0.1]	0	2 (0.2) [0.2]
Pregnancy, puerperium, and perinatal conditions	0	0	1 (0.2) [0.3]	0	1 (0.2) [0.1]	2 (0.2) [0.1]	1 (0.2) [0.2]	1 (0.1) [0.1]
Abortion missed[b]	0	0	1 (0.3) [0.4]	0	1 (0.3) [0.2]	1 (0.1) [0.1]	0	1 (0.2) [0.1]
Abortion spontaneous[b]	0	0	0	0	0	1 (0.1) [0.1]	1 (0.3) [0.3]	0
Product issues	0	0	1 (0.2) [0.3]	0	1 (0.2) [0.1]	1 (0.1) [0.1]	0	1 (0.1) [0.1]
Device dislocation	0	0	1 (0.2) [0.3]	0	1 (0.2) [0.1]	1 (0.1) [0.1]	0	1 (0.1) [0.1]
Vascular disorders	0	0	1 (0.2) [0.3]	0	1 (0.2) [0.1]	1 (0.1) [0.1]	0	1 (0.1) [0.1]
Hypertension	0	0	1 (0.2) [0.3]	0	1 (0.2) [0.1]	1 (0.1) [0.1]	0	1 (0.1) [0.1]
Musculoskeletal and connective tissue disorders	1 (0.3) [0.4]	0	0	0	0	0	0	0
Rhabdomyolysis	1 (0.3) [0.4]	0	0	0	0	0	0	0
Renal and urinary tract disorders	1 (0.3) [0.4]	0	0	0	0	0	0	0
Nephrolithiasis	1 (0.3) [0.4]	0	0	0	0	0	0	0
Eye disorders	0	0	0	0	1 (0.2) [0.1]	1 (0.1) [0.1]	0	1 (0.1) [0.1]
Glaucoma	0	0	0	0	1 (0.2) [0.1]	1 (0.1) [0.1]	0	1 (0.1) [0.1]
Psychiatric disorders	0	0	0	0	0	1 (0.1) [0.1]	0	1 (0.1) [0.1]
Depression	0	0	0	0	0	1 (0.1) [0.1]	0	1 (0.1) [0.1]

System Organ Class Preferred Term	36-Week Placebo-Controlled			Extended BARI AA		All BARI AA	All BARI 2-mg AA	All BARI 4-mg AA
	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]	BARI 2-mg N = 365 PYE = 402.1 n (%) [IR]	BARI 4-mg N = 540 PYE = 720.7 n (%) [IR]	All Doses N = 1244 PYE = 1668.4 n (%) [IR]	BARI 2-mg N = 564 PYE = 576.7 n (%) [IR]	BARI 4-mg N = 951 PYE = 1079.2 n (%) [IR]
Reproductive system and breast disorders	0	0	0	0	0	1 (0.1) [0.1]	0	1 (0.1) [0.1]
Vaginal dysplasia[b]	0	0	0	0	0	1 (0.1) [0.1]	0	1 (0.2) [0.1]
Surgical and medical procedures	0	0	0	0	0	1 (0.1) [0.1]	0	1 (0.1) [0.1]
Gastrectomy	0	0	0	0	0	1 (0.1) [0.1]	0	1 (0.2) [0.1]

Abbreviations: AA = alopecia areata; COVID-19 = coronavirus disease 2019; IR = incidence rate; n = number of patients in the specified category; N = number of patients in the analysis population; PC = placebo-controlled; PYE = patient-years exposure; PYR = patient-years at risk; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: IRs are calculated based on PYR.

[a] Denominator and IR adjusted because event is gender specific.

[b] 'SARS-CoV-2 test positive' term in PC period was recoded to 'COVID-19' for the Extended and All BARI analysis sets.

Adverse Events of Special Interest

Safety topics of special interest were selected and closely monitored in the 'phase 3' studies based on: the established safety profile in the RA and AD indications for baricitinib; the baricitinib Phase 2 clinical study in AA; the mechanism of action for baricitinib; information from literature.

The safety topics of special interest discussed by the MAH in the SCS are: infections, haematologic changes, lipid increases, MACE, VTE, ATE, CPK increases and muscle-related symptoms, NMSC and malignancy other than NMSC, abnormal hepatic tests, effects on renal function, GI perforation, depression and suicidality, allergic reactions or hypersensitivity, and photosensitivity reactions.

Infections, including opportunistic infections

The mode-of-action of baricitinib could lead to an increased sensibility to acquire infections in users. The SmPC of baricitinib includes infection in the Warnings and Precautions section, upper respiratory tract infections, herpes, gastroenteritis, urinary tract infections, and pneumonia are ADR, and serious infections are an important potential risk of baricitinib. In the AA clinical programme, patients were excluded if they had

- history of eczema herpeticum in the last 12 months or 2 previous episodes, or
- current or recent and/or clinically serious viral, bacterial, fungal, or parasitic infection.

Potential opportunistic infections (OIs) were identified using a list of MedDRA PTs, in line with the consensus recommendations for reporting OIs (Winthrop et al. 2015). There were 3 modifications to this approach:

- Candidiasis infections involving only the oral cavity and pharynx were not considered OIs; except if also involving infection of the oesophagus or below.
- Localised herpes zoster infections were not considered OIs; only multidermatomal or disseminated infections, or both, were considered OIs.
- Treatment-emergent, active TB infection was considered an OI.

In the placebo-controlled period, there were no large differences between placebo and baricitinib treatment groups for Treatment-Emergent infections, serious infections, temporary interruptions, and permanent discontinuations of study drug due to infections (Table 35). Infections that were reported by more than 1% of patients in any baricitinib group and that were more frequent with baricitinib compared to placebo were urinary tract infection, folliculitis, bronchitis, herpes zoster, and vulvovaginal candidiasis. Differences were not significant except for vulvovaginal candidiasis. No patients with placebo and 3 patients in the baricitinib groups reported serious infections.

These were a pyelonephritis with baricitinib 2-mg and baricitinib 4-mg each, and a COVID-19 pneumonia with baricitinib 2-mg, which did not result in study drug discontinuation. All patients recovered.

Herpes zoster was the most frequently reported infection resulting in a temporary interruption of study drug in baricitinib-treated patients as mandated in the protocol. One patient discontinued study drug due to infection (a patient with lower respiratory tract infection in the baricitinib 2-mg group).

In the Extended BARI AA analysis set, no dose differences were seen for TE infections, serious infections, temporary interruptions, and discontinuations from study drug due to infections (Table 35). The IRs of TE infections in the baricitinib 2-mg and 4-mg dose groups of the Extended BARI AA analysis set were similar to or lower compared to the respective dose groups in the placebo-controlled

period. There were no consistent dose-differences for the infection events with the highest IRs: upper respiratory tract infections, nasopharyngitis, and urinary tract infection (Table 35).

Table 35 Infections from the 36-Week Placebo-Controlled Period, Extended, and All BARI Analysis Sets

	36-Week Placebo-Controlled BARI AA			Extended BARI AA		All BARI AA	All BARI 2-mg AA	All BARI 4-mg AA
	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]	BARI 2-mg N = 365 PYE = 402.1 n (%) [IR]	BARI 4-mg N = 540 PYE = 720.7 n (%) [IR]	All Doses N = 1244 PYE = 1668.4 n (%) [IR]	BARI 2-mg N = 564 PYE = 576.7 n (%) [IR]	BARI 4-mg N = 951 PYE = 1079.2 n (%) [IR]
Patients with ≥1 TEAE	108 (29.1) [55.5]	118 (32.3) [62.9]	165 (30.6) [57.3]	150 (41.1) [51.6]	227 (42.0) [44.4]	509 (40.9) [43.3]	201 (35.6) [45.7]	334 (35.1) [41.4]
SAE	0	2 (0.5) [0.8]	1 (0.2) [0.3]	2 (0.5) [0.5]	5 (0.9) [0.7]	14 (1.1) [0.8]	3 (0.5) [0.5]	11 (1.2) [1.0]
Permanent DC from study drug due to AE	0	1 (0.3) [0.4]	0	1 (0.3) [0.2]	1 (0.2) [0.1]	2 (0.2) [0.1]	1 (0.2) [0.2]	1 (0.1) [0.1]
Temporary interruption from study drug due to AE	10 (2.7) [4.1]	12 (3.3) [5.0]	11 (2.0) [3.0]	16 (4.4) [3.9]	24 (4.4) [3.3]	69 (5.5) [4.1]	28 (5.0) [4.7]	41 (4.3) [3.8]

Abbreviations: AA = alopecia areata; DC = discontinuation; IR = incidence rate; n = number of patients in the specified category; N = number of patients in the safety analysis set; PYE = patient-years of exposure.
Note: IRs are calculated based on patient-years at risk.

No confirmed Opportunistic Infections and no TB infections were reported in the AA clinical trials.

The established safety profile for baricitinib includes viral reactivation, including Herpes virus reactivation in the Warnings and Precautions section, and herpes zoster is a recognised ADR for baricitinib. Patients were excluded from the AA clinical trial programme if they had a symptomatic herpes zoster infection within 12 weeks prior to screening or if they had a history of disseminated or complicated herpes zoster. If patients developed herpes zoster during the course of the study, the protocol mandated temporary interruption of study drug. The established safety profile for baricitinib includes viral reactivation in the Warnings and Precautions section. This includes herpes virus reactivation and hepatitis infections. In the placebo-controlled data set and in the extended BARI data set, no patients had detectable postbaseline HBV DNA. In the all BARI data set 2 cases of positivity of HBV DNA occurred, but no patients had a reactivation of HBV.

In the placebo-controlled period, Herpes zoster infections were numerically more frequent with baricitinib 2-mg and baricitinib 4-mg compared to placebo (Table 36). No dose differences were observed. All were localised non-multidermatomal infections of mild or moderate severity. No patient reported a severe or serious herpes zoster infection or discontinued study drug due to the infection.

In the Extended BARI AA analysis set, no dose differences were observed for herpes zoster infections (Table 36). The IRs of TE herpes zoster in the baricitinib 2-mg and 4-mg dose groups of the Extended

BARI AA analysis set were similar to the respective dose groups in the placebo-controlled period. All were localised non-multidermatomal infections. One patient, treated with baricitinib 4-mg, reported a severe herpes zoster infection of 9 days duration that was also serious. The patient recovered.

Herpes simplex is a recognised ADR for baricitinib. Patients were excluded from the AA clinical trial programme if they had a history of eczema herpeticum in the last 12 months or 2 previous episodes or if they had a symptomatic herpes simplex infection at the time of randomisation. In the placebo-controlled phase, the occurrence of herpes simplex (oral herpes, genital herpes, herpes simplex, genital herpes simplex) was more frequent in the placebo group as compared to baricitinib 2-mg and 4-mg (3.2% vs 2.5% vs 1.3%). In the extended BARI AA set, the IRs for the herpes simplex cluster were similar for both dose groups.

Table 36 Herpes Zoster from the 36-Week Placebo-Controlled Period, Extended, and All BARI Analysis Sets

	36-Week Placebo-Controlled BARI AA			Extended BARI AA		All BARI AA	All BARI 2-mg AA	All BARI 4-mg AA
	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]	BARI 2-mg N = 365 PYE = 371.5 n (%) [IR]	BARI 4-mg N = 540 PYE = 624.3 n (%) [IR]	All Doses N = 1244 PYE = 1362.2 n (%) [IR]	BARI 2-mg N = 564 PYE = 488.9 n (%) [IR]	BARI 4-mg N = 938 PYE = 858.9 n (%) [IR]
TE herpes zoster	2 (0.5) [0.8]	5 (1.4) [2.1]	5 (0.9) [1.4]	9 (2.5) [2.1]	11 (2.0) [1.5]	30 (2.4) [1.8]	11 (2.0) [1.8]	19 (2.0) [1.7]

Abbreviations: AA = alopecia areata; IR = incidence rate; n = number of patients in the specified category; N = number of patients in the safety analysis set; PYE = patient-years of exposure; PYR = patient-years at risk; TE = treatment-emergent.

Note: IRs are calculated based on PYR.

In the 36-Week placebo-controlled period, there appears to be a higher frequency of folliculitis with baricitinib 2-mg (1.4%, IR 2.1) and baricitinib 4-mg (2.2%, IR 3.3) compared to placebo (0.8%, IR 1.2). The IRs of folliculitis were 1.5 with baricitinib 2-mg and 2.4 with baricitinib 4-mg and are similar to or lower than what was observed in the placebo-controlled period. In the All BARI AA analysis set, the IRs of folliculitis were 1.4 in the All BARI 2-mg AA analysis set, and 2.5 in the All BARI 4-mg AA analysis set. Of the 32 patients who reported folliculitis in the All BARI AA analysis set: the scalp was involved in 75% of patients, no events were serious or severe and 87% were mild and 13% were of moderate intensity. The majority of the folliculitis cases on the scalp (71%) occurred in patients who were experiencing scalp hair re growth at the time of the event or who became responders shortly thereafter. Most (70%) of patients recovered or were recovering from their folliculitis, and no patient interrupted or discontinued study drug due to the AE.

Folliculitis may have infectious causes or may be due to irritation of the hair follicle from regrowing hair. The hair follicle has a particular microbiome, different from the microbiome observed at the skin surface. Dysregulation of the hair follicle microbiome has been reported as a potential cause, or consequence, of the inflammatory process involved in AA pathogenesis (Lousada et al. 2021). Given that the majority of folliculitis cases in the All BARI AA analysis set involved the scalp, according to the MAH it can be hypothesised that these folliculitis cases are linked to a change in the local microbiome in response to the resolution of the inflammation in the follicle, or secondary to a mechanical irritation by the regrowing hair. The mechanical irritation would then be similar to the situation described as pseudofolliculitis on various body areas after shaving or waxing, when the growing hair does not exit

correctly through the ostium (Khanna et al. 2013; Gray and McMichael 2016). If folliculitis was indicative of infections due to local immunosuppression, the MAH anticipates that it would affect various areas of the body and would be observed in a comparable manner among responders and non-responders. In the AD and RA indications, where the recovery of the hair follicle does not play a role, the frequency of folliculitis was similar in baricitinib- and placebo-treated patients and no dose-response was noted.

In the 36-Week placebo-controlled period, vulvovaginal candidiasis and mycotic infections as a cluster term were reported more frequently with baricitinib 2-mg and baricitinib 4-mg compared to placebo : 0.5% (n=1, IR=0.7) vs 3.0% (n=7, IR=4.7) vs 3.0% (n=7, IR=3.1). In the extended BARI set, the IRs for baricitinib 2-mg and 4-mg were similar (IR=2.6 and IR=2.0, respectively) , which was also seen in the All BARI data set. Of the 22 patients reporting 26 events in the All BARI AA analysis set: no events were serious or severe, 69% were mild, and 31% were of moderate intensity. All patients except 1 recovered, and no patient interrupted or permanently discontinued study drug due to the AE.

When considering data from the AD and RA populations, in AD no patients reported vulvovaginal candidiasis in the 16-week placebo-controlled period in the baricitinib groups, compared to 1 patient in the placebo group. Furthermore, there was 1 patient with vulvovaginal mycotic infection in the baricitinib 4-mg group in AD and no patients in the baricitinib 2-mg and placebo groups. In the 16-week placebo-controlled period in RA, the frequency of vulvovaginal candidiasis was higher with baricitinib (2-mg: 0.8%, 4-mg: 0.5%) compared to placebo (0%) but overall low. The frequencies of vulvovaginal mycotic infection were not higher with baricitinib (2-mg: 0.3%, 4-mg: 0.1%) compared to placebo (0.5%).

Given that vulvovaginal candidiasis and mycotic infections (cluster term) were reported by only 1 patient each in the baricitinib and placebo groups in the placebo-controlled period in AD, that differences between treatment groups were small for RA and that no dose response was observed, the differences between treatment groups in the AA clinical trials were not considered causally associated with baricitinib treatment.

Haematologic changes

Treatment-emergent laboratory abnormalities occurring at any time during the treatment period and shift tables of baseline to maximum Grade during the treatment period were tabulated. Planned and unplanned measurements were included. Box plots for mean changes from baseline at scheduled visit had also been provided (not shown).

This section concentrates on the haematologic changes: neutrophil count decreased, lymphocyte count decreased, haemoglobin level decreased, and platelet count increased. Neutropenia and thrombocytosis are known ARDs of baricitinib and there are warnings for increased infections with the use of baricitinib, and not to use baricitinib with low haemoglobin levels.

In the placebo-controlled period, decreased neutrophil count and lymphocyte count, decreased haemoglobin levels, and increased platelet counts were more frequent in the baricitinib 4-mg and 2-mg as compared to placebo, in a dose-dependent way (Table 37). The IRs remained similar, or reduced somewhat, in the extended BARI set as compared to the placebo-controlled set.

In the All BARI AA analysis set, 13 patients (1%, IR 0.9) reported TEAEs of anaemia: no events were serious, all events were mild to moderate in severity. Two patients temporarily interrupted study drug due to anaemia. One patient with a Grade 4 haemoglobin shift discontinued study drug due to anaemia.

Confounders or alternative causes were present in 12 of the 13 patients who reported anaemia and included medical history of GI bleeding, vitamin B12 deficiency, haemoglobinopathy, anaemia, and iron

deficiency. Other patients had low haemoglobin at baseline, or anaemia was associated with vaginal bleeding, liposuction, and penicillin use or with dysmenorrhoea.

Although low haemoglobin and related haematology analyte changes were seen with a higher frequency in baricitinib-treated patients compared to placebo and more frequently in the baricitinib 4-mg compared to the 2-mg group, most haemoglobin increases were to CTCAE Grade 1 or 2, and mean decreases from baseline were small and not clinically meaningful. Anaemia is a common comorbidity reported in the literature in the AA population. In the All BARI AA analysis set, the IR of anaemia was 0.9 per 100 PYR, and all events were nonserious and mild or moderate in intensity. The majority of patients with Grade ≥2 shifts in haemoglobin had confounding factors or alternative causes.

Table 37 Haematologic Changes in from the 36-Week Placebo-Controlled Period, Extended, and All BARI Analysis Sets

	36-Week Placebo-Controlled BARI AA			Extended BARI AA		All BARI AA	All BARI 2-mg AA	All BARI 4-mg AA
	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]	BARI 2-mg N = 365 PYE = 402.1 n (%) [IR]	BARI 4-mg N = 540 PYE = 720.7 n (%) [IR]	All Doses N = 1244 PYE = 1668.4 n (%) [IR]	BARI 2-mg N = 564 PYE = 576.7 n (%) [IR]	BARI 4-mg N = 951 PYE = 1079.2 n (%) [IR]
Neutrophil count decreased								
Any CTCAE Grade increase	47 (12.8) [19.3]	57 (15.8) [23.7]	107 (20.0) [29.4]	65 (18.1) [16.2]	128 (23.9) [17.8]	260 (21.1) [15.6]	86 (15.5) [14.9]	172 (18.3) [15.9]
Increase to CTCAE Grade ≥3 (<1.0 × 10^9/L)	0	2 (0.6) [0.8]	5 (0.9) [1.4]	4 (1.1) [1.0]	10 (1.9) [1.4]	19 (1.5) [1.1]	4 (0.7) [0.7]	15 (1.6) [1.4]
Lymphocyte count decreased								
Any CTCAE Grade increase	30 (8.2) [12.3]	34 (9.4) [14.1]	59 (11.0) [16.2]	43 (11.9) [10.7]	115 (21.5) [16.0]	208 (16.8) [12.5]	61 (11.0) [10.6]	147 (15.6) [13.6]
Increase to CTCAE Grade ≥3 (<0.5 × 10^9/L)	0	0	2 (0.4) [0.6]	0	3 (0.6) [0.4]	3 (0.2) [0.2]	0	3 (0.3) [0.3]
Haemoglobin decreased								
Any CTCAE Grade increase	17 (4.6) [7.0]	27 (7.5) [11.2]	59 (11.0) [16.2]	34 (9.4) [8.5]	95 (17.7) [13.2]	175 (14.2) [10.5]	49 (8.8) [8.5]	123 (13.1) [11.4]
Increase to CTCAE Grade ≥3 (<8.0 g/dL)	0	0	2 (0.4) [0.6]	0	2 (0.4) [0.3]	2 (0.2) [0.1]	0	2 (0.2) [0.2]
Platelet count increased								
Thrombocytosis (>400 × 10^9/L)	16 (4.6) [6.6]	32 (9.2) [13.3]	74 (14.2) [20.4]	38 (11.0) [9.5]	105 (20.2) [14.6]	208 (17.7) [12.5]	51 (9.8) [8.9]	150 (17.1) [13.9]
Thrombocytosis (>600 × 10^9/L)	0	1 (0.3) [0.4]	2 (0.4) [0.6]	2 (0.6) [0.5]	3 (0.6) [0.4]	7 (0.6) [0.4]	2 (0.4) [0.3]	5 (0.5) [0.5]

Abbreviations: AA = alopecia areata; CTCAE = Common Terminology Criteria for Adverse Events; N = number of patients in the safety analysis set; n = number of patients in the specified category; PYE = patient-years of exposure.
Notes: Percentages for CTCAE increases are based on number of patients at risk for specified abnormality. IRs are calculated based on PYE.

Blood lipid changes

Hypercholesterolaemia and hypertriglyceridaemia are recognised as ADRs for baricitinib. Lipid parameters were assessed 12 weeks following the initiation of baricitinib in the AA clinical programme.

An increase of mean LDL-C, HDL-C, and, consequently, total cholesterol was observed in the first 12 weeks of treatment with baricitinib. Compared to the placebo group, there were no differences in mean triglycerides nor in percentage of categorical shifts for triglycerides.

Although some increases in mean LDL-C were seen after Week 12 in both baricitinib 2-mg and 4-mg groups, the proportion of patients with shifts to high or very high LDL-C after Week 12, with a normal level at baseline and Week 12, was small (1.5% in the baricitinib 4-mg group at Week 36).

In the baricitinib 4-mg group, AEs of hyperlipidaemia were more frequently reported than in the placebo and 2-mg groups, which had similar frequencies. With a longer exposure, the IR in the baricitinib 4-mg group went from 10.2 in the placebo-controlled period to 7.7 in the Extended BARI AA analysis set.

Major Adverse Cardiovascular Events

MACE were identified by the investigative site or through medical review and were sent to a blinded, external Clinical Event Committee for adjudication. These events included: potential MACE (cardiovascular death, myocardial infarction, and stroke), other cardiovascular events (transient ischaemic attack, hospitalisation for unstable angina, hospitalisation for heart failure, serious arrhythmia, resuscitated sudden death, cardiogenic shock, and coronary revascularizations), VTEs and ATEs, and non-cardiovascular deaths.

In the placebo-controlled period, there was 1 MACE that occurred in the baricitinib 2-mg group.

- A reported acute myocardial infarction approximately 9 months after starting baricitinib 2-mg. The patient had multiple risk factors such as current tobacco use, obesity (BMI 34 kg/m2 at baseline), hypercholesterolaemia, atrial fibrillation, and hypertension (treated with lisinopril). The patient had low HDL-C and high triglycerides at study entry. Study drug was interrupted for 4 days while patient underwent a coronary revascularization procedure (reported as other cardiovascular event) and then resumed. The patient recovered from the event.

There were 2 other cardiovascular events, both serious arrythmias.

- One case of ventricular tachycardia in a patient with obesity (BMI 32 kg/m2 at baseline) was reported 15 weeks after the start of baricitinib.The patient was randomly assigned to the 4-mg dose but received the 2-mg dose due to renal impairment (eGFR <60 mL/min/1.73 m2). The patient had hyperlipidaemia and palpitations in the medical history and was taking multiple concomitant medications including fexofenadine and epinephrine. The patient reported AEs of sinus tachycardia and palpitations 9 weeks into the study that were ongoing at the time of the SAE of ventricular tachycardia. The patient discontinued study drug due to the SAE and then discontinued from the study. The patient recovered from the event after 6 days.
- One case of ventricular extrasystoles in a, overweight, patient was reported 18 weeks after the starting baricitinib 4-mg. The medical history did not mention any cardiac disorder, and was

not taking any concomitant medication in the 3 weeks before the start of the event. The patient had not recovered from the event. No action was taken with study drug. An AE of acute stress disorder was reported 1 week later that was ongoing at the time of the data cutoff date. This cardiovascular event was positively adjudicated as serious arrythmia after the database lock for the placebo-controlled period and was included here for completeness.

In the Extended baricitinib 2-mg and 4-mg AA analysis set and in the All BARI AA analysis set, one additional cardiovascular event was reported (aortic valve incompetence, non-MACE).

Venous thrombotic events

Pulmonary embolism and DVT are recognised as ADRs for baricitinib, and VTE is an important potential risk for baricitinib. Patients with a history of VTE or at high risk for VTE were excluded from the AA clinical studies. Possible VTEs were identified by the investigative site or through medical review and were sent to a blinded, external Clinical Event Committee for adjudication, as described above in the MACE search strategy. There have been 2 patients with SAEs of VTE in the AA clinical trial programme after the database cutoff dates for the updated safety database, one case of PE and one of DVT/PE, both patients were treated with baricitinib 2 mg. The patient with DVT/PE also had obesity (BMI 35.8) and used oral contraceptives, the other patient with PE concomitantly had COVID-19 pneumonia and acute respiratory failure, and also a genetic predisposition (prothrombine gene heterozygosity (c.*97 G>A variant).

Creatine Phosphokinase Changes and Muscle-Related Symptoms

CPK increases of more than 5 x ULN are recognised as ADRs for baricitinib. No relationship to muscle symptoms was identified in the baricitinib RA and AD clinical programmes. In the AA clinical studies, treatment-emergent AEs related to increased CPK were reviewed to identify any additional elevations in CPK that were not captured by laboratory values.

In the placebo-controlled period, the percentage of patients with any CTCAE grade increase (reflecting an increase in CPK) was higher in baricitinib 2-mg and baricitinib 4-mg compared to placebo, and dose-related differences were observed (Table 38). Most increases were to Grade 1 or 2.

In the Extended BARI AA analysis set, the percentage of patients with any CTCAE grade increase (reflecting an increase in CPK) was higher in the baricitinib 4-mg group compared to the baricitinib 2-mg group, and frequencies for both doses were higher in the Extended BARI AA analysis set compared to the placebo-controlled period. The IRs for baricitinib 4-mg were numerically higher than for 2-mg dose.

Table 38 CPK Changes from the 36-Week Placebo-Controlled Period, Extended, and All BARI Analysis Sets

	36-Week Placebo-Controlled BARI AA			Extended BARI AA		All BARI AA	All BARI 2-mg AA	All BARI 4-mg AA
	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]	BARI 2-mg N = 365 PYE = 402.1 n (%) [IR]	BARI 4-mg N = 540 PYE = 720.7 n (%) [IR]	All Doses N = 1244 PYE = 1668.4 n (%) [IR]	BARI 2-mg N = 564 PYE = 576.7 n (%) [IR]	BARI 4-mg N = 951 PYE = 1079.2 n (%) [IR]
Any CTCAE increase	65 (17.9) [26.7]	82 (22.7) [34.1]	185 (34.8) [50.9]	119 (32.9) [29.6]	257 (48.4) [35.7]	495 (40.5) [29.7]	144 (26.0) [25.0]	349 (37.6) [32.3]
Increase to CTCAE Grade ≥3 (>5 x ULN)	13 (3.6) [5.3]	8 (2.2) [3.3]	27 (5.1) [7.4]	13 (3.6) [3.2]	42 (8.0) [5.8]	72 (6.0) [4.3]	18 (3.3) [3.1]	53 (5.8) [4.9]

Abbreviations: AA = alopecia areata; CPK = creatine phosphokinase; CTCAE = Common Terminology Criteria for Adverse Events; IR = incidence rate; n = number of patients in the specified category; N = number of patients in the safety analysis set; PYE = patient-years of exposure.

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

Treatment-emergent AEs identified by the Rhabdomyolysis/myopathy SMQ were reviewed to determine if the patient had an increased CPK at or near the time of the event onset. If an increased CPK was identified, the patient's data were medically reviewed to see if the patient reported an AE that was clearly associated with the CPK elevation.

In the placebo-controlled period, the percentages and numbers of patients who reported 1 or more TEAE potentially related to muscle symptoms/with accompanying elevations in CPK were: n=3/0 on placebo, n=3/1 on baricitinib 2-mg, and n=5/3 on baricitinib 4-mg. In the placebo group, of the 3 patients with reported muscle symptoms there was 1 patient with rhabdomyolysis and normal CPK. Rhabdomyolysis did not occur in the other treatment groups. In the baricitinib 4-mg group, most (4/5) of the patients had muscle spasms, and there was 1 patient with myalgia.

In the extended treatment period, in the baricitinib 2-mg group there were 4 additional patients reporting muscle symptoms, which included 2 patients with muscle spasms and 2 patients with myalgia; three of the patients had a raised CPK. In the baricitinib 4-mg group, 5 additional patients reported muscle symptoms, which included 1 patient with muscle spasms, 3 patients with myalgia, and 1 patient with myofascial pain syndrome; all with normal CPK.

In the All BARI AA analysis set, there were 20 patients with TEAEs related to muscle symptoms (IR 1.2) and 35% (7/20) had an associated increases in CPK. The IRs were similar for the All BARI 2-mg (IR 1.5) and All BARI 4-mg (IR 1.0) analysis sets.

Most (65%, 13/20) of the patients reported a muscle AE that did not coincide with a CPK increase. The events for TEAEs related to muscle symptoms in All BARI AA were (35%, 7/20):

- 4 of the 7 patients with coincident muscle AEs and CPK increases had an increase to CTCAE Grade 3 or greater. Of these, 2 patients reported engaging in intense physical exercise near the time of the CPK increase and 2 patients denied any physical exercise.

- The 3 remaining patients had CTCAE increases to Grade 1 and one of these patients reported engaging in physical exercise.

An analysis was performed in the n=64 patients with a CPK >5 x ULN (Grade 3 or Grade 4) at any time in the All BARI AA analysis set. The mean age of patients was 32 years and ~50% were female. In these group, 64% (41/64) of patients had normal baseline CPK. Time to onset of the >5 x ULN was a mean of 238.0 days, a median of 249.0 days, and a range of 29 to 561 days. Creatine phosphokinase returned to baseline values in 81% of patients, and the mean time to return to baseline was 34 days, with a range of 7 to 223 days. Three patients temporarily interrupted treatment (4.7%) due to CPK laboratory results, and no patient permanently discontinued treatment as a result of the increased CPK. Seven patients reported muscular symptoms, 4 of them (6.2%) from the Rhabdomyolysis/myopathy SMQ.

Malignancies

Malignancies were identified using terms from the malignant tumours SMQ (20000194). Malignancies excluding NMSCs and NMSCs are reported separately.

The number of malignancies (n=3) and NMSC (n=2) in the AA programme was small in patients exposed to baricitinib for over 104 weeks (13%) in the All BARI AA analysis set, with 490 days of mean exposure (Table 39). In the placebo-controlled period, one event of prostate cancer was reported for placebo and 1 event of B-cell lymphoma was reported for baricitinib 4-mg. In the Extended BARI AA analysis set, breast cancer had occurred in a patient of the baricitinib 4-mg group. Also in the Extended BARI AA analysis set, for two patients in the baricitinib 2-mg group NMSC was reported, and there was one case of B-cell lymphoma also on 2-mg of baricitinib.

Table 39 Malignancies from the 36-Week Placebo-Controlled Period, Extended, and All BARI Analysis Sets

	36-Week Placebo-Controlled BARI AA			Extended BARI AA		All BARI AA	All BARI 2-mg AA	All BARI 4-mg AA
	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]	BARI 2-mg N = 365 PYE = 402.1 n (%) [IR]	BARI 4-mg N = 540 PYE = 720.7 n (%) [IR]	All Doses N = 1244 PYE = 1668.4 n (%) [IR]	BARI 2-mg N = 564 PYE = 576.7 n (%) [IR]	BARI 4-mg N = 951 PYE = 1079.2 n (%) [IR]
Malignancies other than NMSC	1 (0.3) [0.4]	0	1 (0.2) [0.3]	0	2 (0.4) [0.3]	3 (0.2) [0.2]	1 (0.2) [0.2]	2 (0.2) [0.2]
NMSC	0	0	0	1 (0.3) [0.2]	0	2 (0.2) [0.1]	2 (0.4) [0.3]	0

Abbreviations: AA = alopecia areata; IR = incidence rate; n = number of patients in the specified category; N = number of patients in the safety analysis set; NMSC = non-melanoma skin cancers; PYE = patient-years of exposure.

Abnormal hepatic tests

ALT and AST increases of 3 or more times the ULN are recognised as ADRs for baricitinib; with hepatotoxicity being an important potential risk for baricitinib.

In the placebo-controlled period, mean AST and ALT in the baricitinib 4-mg group increased slightly over the duration of the placebo-controlled period (+2.6 IU for ALT and +3.1 for AST) while the median remained stable (+1 IU for ALT and +2 IU for AST). The mean and median values in the 2-mg

group remained stable and similar to the mean in the placebo group. The frequency of an increase of ALT or AST to ≥3 x ULN and ≥5 x ULN was lower in the baricitinib groups than in the placebo group (Table 40).

There were no elevations of bilirubin ≥2 x ULN in the 2-mg group, and in the 4-mg group, the frequency was uncommon and similar to the placebo group. Elevations of ALP ≥1.5 x ULN were more frequent in the 2-mg group than in the placebo and 4-mg groups, but the frequency in the baricitinib 4-mg group was uncommon and not increased compared to the placebo group.

In the Extended BARI AA analysis sets, there were 5 patients with increases in AST ≥5 x ULN in the 4-mg group and 2 additional patients in the 2-mg group. There were 2 patients with increases in ALT ≥5 x ULN, one each in the 2-mg and 4-mg dose groups. Among all these cases, there was 1 patient on 4-mg with an AE of acute hepatitis; this case will be further discussed in this section as potentially meeting Hy's Law criteria. The other cases reported no AEs associated with the transaminase increase. There were 4 cases of increase of ALT or AST ≥10 x ULN in the All BARI 4-mg analysis set.

There was 1 patient who met the laboratory criteria for potential Hy's Law (SCS APP.2.7.4.7.9.8.1). This had ALT, AST, and ALP >5 x ULN, and total bilirubin >2 x ULN, 13 months after starting baricitinib 4-mg. Internal The MAH liver and infection experts concluded that the hepatic abnormality was due to syphilitic hepatitis secondary to a preexisting syphilis infection.

Alanine aminotransferase, AST, and ALP were normal at entry into the study and up to the event. A rash was diagnosed 3 weeks after the presentation of the hepatitis event as syphilis based on a positive treponema test and the histology of the skin lesions. The patient recovered from the liver injury, and liver enzymes were within normal limits 4 weeks after the start of the penicillin treatment, which supported the syphilitic aetiology of the hepatic injury.

Table 40 Abnormal Postbaseline Elevations in Hepatic Laboratory Tests from the 36-Week Placebo-Controlled Period, Extended, and All BARI Analysis Sets

	36-Week Placebo-Controlled BARI AA			**Extended BARI AA**		**All BARI AA**	**All BARI 2-mg AA**	**All BARI 4-mg AA**
	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]**	**BARI 2-mg N = 365 PYE = 402.1 n (%) [IR]**	**BARI 4-mg N = 540 PYE = 720.7 n (%) [IR]**	**All Doses N = 1244 PYE = 1668.4 n (%) [IR]**	**BARI 2-mg N = 564 PYE = 576.7 n (%) [IR]**	**BARI 4-mg N = 951 PYE = 1079.2 n (%) [IR]**
ALT ≥3 x ULN	10 (2.7) [4.1]	7 (1.9) [2.9]	7 (1.3) [1.9]	11 (3.0) [2.7]	16 (3.0) [2.2]	40 (3.2) [2.4]	17 (3.0) [2.9]	22 (2.3) [2.0]
ALT ≥5 x ULN	3 (0.8) [1.2]	1 (0.3) [0.4]	0	3 (0.8) [0.7]	4 (0.7) [0.6]	11 (0.9) [0.7]	5 (0.9) [0.9]	6 (0.6) [0.6]
ALT ≥10 x ULN	1 (0.3) [0.4]	0	0	0	1 (0.2) [0.1]	2 (0.2) [0.1]	0	2 (0.2) [0.2]
AST ≥3 x ULN	8 (2.2) [3.3]	4 (1.1) [1.7]	6 (1.1) [1.7]	7 (1.9) [1.7]	14 (2.6) [1.9]	32 (2.6) [1.9]	11 (2.0) [1.9]	20 (2.1) [1.9]
AST ≥5 x ULN	4 (1.1) [1.6]	0	2 (0.4) [0.6]	2 (0.6) [0.5]	5 (0.9) [0.7]	8 (0.6) [0.5]	2 (0.4) [0.3]	6 (0.6) [0.6]
AST ≥10 x ULN	0	0	1 (0.2) [0.3]	0	1 (0.2) [0.1]	2 (0.2) [0.1]	0	2 (0.2) [0.2]
Bilirubin ≥2 x ULN	2 (0.5) [0.8]	0	3 (0.6) [0.8]	0	7 (1.3) [1.0]	8 (0.6) [0.5]	1 (0.2) [0.2]	7 (0.7) [0.6]

ALP ≥1.5 x ULN	2 (0.5) [0.8]	5 (1.4) [2.1]	1 (0.2) [0.3]	7 (1.9) [1.7]	2 (0.4) [0.3]	13 (1.1) [0.8]	7 (1.3) [1.2]	7 (0.7) [0.6]

Abbreviations: AA = alopecia areata; ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; IR = incidence rate; n = number of patients who have ≥1 measure falling into both the baseline and postbaseline categories; N = number of patients in the safety analysis set; PYE = patient-years of exposure; ULN = upper limit of normal.

Notes: Percentages are based on the number of patients with ≥1 baseline and 1 postbaseline measurement. IR are calculated based on PYE.

Laboratory findings

Laboratory findings for haematological changes (neutrophils, lymphocytes, haemoglobin, and platelets), lipid changes, CPK elevations, abnormal hepatic tests are discussed in the section on AESI's.

The chemistry, haematology, immunoglobulin, and urinalysis analytes discussed in this section are those where significant differences were observed in frequency and for which frequencies were higher: in the baricitinib groups compared to the placebo group or in the baricitinib 4-mg compared to the baricitinib 2-mg group in the placebo-controlled or Extended BARI AA analysis set.

In the placebo-controlled period, the percentages of patients with TE high serum albumin were higher in the baricitinib groups compared to the placebo group: 1.4% (IR 2.1) on placebo, 3.9% (IR 5.8) on baricitinib 2-mg, and 5.0% (IR 7.2) on baricitinib 4-mg. The maximum mean increases from baseline in serum albumin were: no increases seen in placebo, 0.66 g/L on baricitinib 2-mg, and 0.85 g/L on baricitinib 4-mg.

In the Extended BARI AA analysis set before the data update, incidence rates for TE high serum albumin were: IR 3.7 on baricitinib 2-mg, and IR 5.6 on baricitinib 4-mg.

In the placebo-controlled period, the percentage of patients with TE low monocytes was higher in the baricitinib 4-mg group compared to the placebo and baricitinib 2-mg groups: 10.7% (IR 14.8) on placebo, 11.7% (IR 15.8) on baricitinib 2-mg, and 17.1% (IR 22.8) on baricitinib 4-mg. The maximum mean decreases from baseline in monocytes were small, with -0.01 × 109/L on placebo, no decreases in baricitinib 2-mg, and -0.01 × 109/L on baricitinib 4-mg.

In the Extended BARI AA analysis set, the IRs of TE low monocytes were higher in the baricitinib 4-mg compared to the baricitinib 2-mg group: 12.6 on baricitinib 2-mg, and 20.2 on baricitinib 4-mg.

Vital signs

Blood pressure

In the placebo-controlled period, the frequency of high systolic blood pressure was numerically higher in baricitinib-treated patients compared to placebo with no dose differences. Hypertension as a PT was reported at similar frequency with placebo (2.4%) and baricitinib 4-mg (2.6%) and less frequently with baricitinib 2-mg (0.5%). Maximum mean changes from baseline in baricitinib-treated patients were small (less than 2 mm Hg) for both dose groups. No differences among treatment groups were noted for high systolic blood pressure; maximum mean changes from baseline in baricitinib-treated patients were small (less than 1 mm Hg) for both dose groups.

Pulse

In the placebo-controlled period, the frequency of low pulse rate was similar with baricitinib 4-mg and placebo, and lower with baricitinib 2-mg. High pulse rate was numerically more frequent in baricitinib-treated patients compared to placebo. Maximum mean changes from baseline in baricitinib-treated patients were small (less than 2 bpm) and did not increase compared to placebo-treated patients (2.57 bpm) for both dose groups.

Weight

In the placebo-controlled period, the frequency of weight loss (≥7% decrease) was higher with placebo compared to the baricitinib 2-mg and 4-mg groups. A similar proportion of patients across all treatment groups had weight gain of ≥7%. Weight increased as a PT was reported at higher frequency in the baricitinib 2-mg (1.6%) and 4-mg (0.9%) groups compared to placebo (0.3%). Maximum mean changes from baseline were 1.15 kg with baricitinib 2-mg and 1.78 kg with baricitinib 4-mg compared to 0.62 kg with placebo.

Safety in special populations

Age

Age categories were defined as <65 years and ≥65 years. Study inclusion criteria was at least 18 years and ≤60 years for males, and ≤70 years for females at the time of informed consent. In total, out of 1244 patients, there were: 1214 (97.6%) patients aged less than 65 years, and 30 (2.4%) patients aged 65 years and older (Table 41). The frequencies and IRs of TEAEs and SAEs in the ≥65 years age group were higher compared to the younger age group.

Table 41 Summary of AEs by Age Category in the All BARI AA Analysis Set

	<65 years N=1214 n (%) [IR]	**≥65 years N=30 n (%) [IR]**
Total TEAEs	849 (69.9) [117.5]	23 (76.7) [175.7]
SAEs	51 (4.2) [3.1]	3 (10.0) [7.3]
Deaths	00	0
VTE		0
Infections and infestations SOC	502 (41.4) [44.3]	17 (56.7) [71.2]
Hyperlipidaemia	86 (7.1) [5.4]	6 (20.0) [16.1]

Abbreviations: AA = alopecia areata; IR = incidence rate; n = patients with ≥1 event; N = number of patients in the safety analysis set; PYE = patient-years of exposure; SOC = System Organ Class; VTE = venous thromboembolism.

Note: IRs are calculated based on PYE.

The majority (77%) of patients in the ≥65 years age group reported more than 1 TEAE, and the SOC with the most events reported was the Infections and infestations SOC. Three patients in the ≥65 years age group reported SAEs, 1 each with ankle fracture, COVID-19, and ventricular tachycardia. There were no deaths reported in any age group in the AA clinical trial programme. The frequencies and IRs of events in the Infections and infestations SOC and events of hyperlipidaemia were higher in the >65 age group compared to the <65 years age group.

Renal function

In the AA clinical programme, only 2 patients with an eGFR between 40 and 60 mL/min/1.73 m2 at baseline were randomly assigned to the baricitinib 4-mg dose, and these patients received the 2-mg dose in line with the dose recommendations in the SmPC.

Other intrinsic and extrinsic factors

No clinically meaningful differential treatment effects were noted for common TEAEs in any of the subgroups for gender, race, ethnicity, baseline weight, or baseline BMI. For most TEAEs, the numbers were too small for meaningful comparison. No clinically meaningful differential treatment effects were found for common TEAEs in any of the geographical region subgroups or for patients with prior versus no prior systemic therapy. However, numbers were small.

Pregnancy

In the approved RA and AD SmPC, baricitinib is contraindicated during pregnancy.

The JAK-STAT pathway has been shown to be involved in cell adhesion and cell polarity, which can affect early embryonic development. Effects of baricitinib on human foetal development are not known; however studies in rats and rabbits have shown teratogenicity. Findings of maternal and embryo-foetal toxicities, including skeletal anomalies at doses higher than maximum human exposure, indicate that baricitinib may have an adverse effect on bone development in utero. As foetal malformation following exposure in utero is an important potential risk, and baricitinib is contraindicated during pregnancy in the SmPC, women and men with reproductive potential enrolled in the AA clinical programme were required to use a reliable method of birth control during the clinical studies and for at least 4 weeks following the last dose of study drug. Pregnancy is a criterion for permanent discontinuation from study drug in all baricitinib studies.

As of 13 February 2021, there were 56 women who became pregnant, and 11 pregnancies were reported for partners of male patients while in any baricitinib clinical trial, including trials in RA, AD, systemic lupus erythematosus, AA, and psoriasis.

As of 13 February 2021, 6 women had become pregnant during AA study participation. The outcome included: 1 elective termination, 1 spontaneous abortion, 1 missed abortion, and 3 pregnancies still in utero. There were no pregnancies in partners of male patients exposed to baricitinib during participation in an AA study. No congenital anomalies were reported in the three pregnancies that came to an end early; there was a predisposing medical history in the two women who had a spontaneous abortion. There were no cases reported of baricitinib use during breast-feeding in AA clinical trials.

Safety related to drug-drug interactions and other interactions

The known drug-drug interaction (DDI) 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 DDI studies were completed as part of the AA clinical programme. Baricitinib does not affect cytochrome P450 enzymes or CYP3A substrate inhibitors. The only known DDI for baricitinib is with organic anion transporter 3 inhibitors with a strong inhibition potential, such as probenecid.

Discontinuation due to adverse events

Permanent discontinuation

By protocol, patients were required to discontinue study drug in case of certain laboratory abnormalities, pregnancy, malignancy, HBV DNA detection above limit of quantification, prohibited medications, or development of a VTE.

In the placebo-controlled period, across all 3 treatment groups, fewer than 2.5% of patients discontinued study drug because of AEs and fewer than 1% of patients discontinued because of SAEs.

All AE PTs and all SAE PTs resulting in discontinuation of study drug were single events spread across the treatment groups with no cluster of events to indicate a specific safety issue, in both the placebo-controlled period as well as the extended BARI analysis set.

Temporary discontinuation

Criteria for temporary interruption of study drug included the following laboratory findings: abnormal blood counts, low eGFR, ALT or AST>5 x UL, haemoglobin<8 g/dl, in line with the warnings and recommendations in the SmPC. The occurrence of Herpes zoster, infections (if needed), VTE, suicidal related behaviours also led to treatment interruption.

In the placebo-controlled period, the percentage of patients with ≥1 temporary interruption was similar in the baricitinib 2-mg, baricitinib 4-mg, and placebo groups. For most patients, the reason for temporary interruptions were AEs, irrespective of the treatment group. Events in the Infections and infestations SOC were responsible for most of the temporary interruptions. Herpes zoster and influenza were the most frequently reported PTs in baricitinib-treated patients that resulted in a temporary interruption of study drug.

Table 42 Summary of Temporary Interruptions of Study Drug from the 36-Week Placebo-Controlled Period, Extended, and All BARI Analysis Sets

	36-Week Placebo-Controlled BARI AA			**Extended BARI AA**		**All BARI AA**	**All BARI 2-mg AA**	**All BARI 4-mg AA**
	PBO N = 371 PYE = 243.2	**BARI 2-mg N = 365 PYE = 240.6**	**BARI 4-mg N = 540 PYE = 363.4**	**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 = 564 PYE = 576.7**	**BARI 4-mg N = 951 PYE = 1079.2**
Total number study drug interruptions, n	33	30	44	44	82	184	70	114
With resumption of study drug	31	30	43	43	76	175	69	106
Without resumption of study drug	2	0	1	1	6	9	1	8
Number of patients with study drug interruption, n (%)								
≥1	26 (7.0)	24 (6.6)	39 (7.2)	35 (9.6)	69 (12.8)	153 (12.3)	56 (9.9)	97 (10.2)
≥2	7 (1.9)	4 (1.1)	4 (0.7)	6 (1.6)	10 (1.9)	24 (1.9)	10 (1.8)	14 (1.5)
≥3	0	2 (0.5)	1 (0.2)	2 (0.5)	3 (0.6)	6 (0.5)	3 (0.5)	3 (0.3)
Duration of dose interruptions (days), mean (SD)	13.3 (22.91)	14.6 (16.32)	14.8 (18.15)	11.7 (13.78)	14.8 (15.43)	13.5 (15.83)	13.3 (18.48)	13.7 (13.93)
Reason for study drug interruption, n (%)								
Adverse event	20 (5.4)	18 (4.9)	25 (4.6)	26 (7.1)	51 (9.4)	117 (9.4)	44 (7.8)	73 (7.7)
Abnormal laboratory result	2 (0.5)	2 (0.5)	6 (1.1)	3 (0.8)	8 (1.5)	16 (1.3)	4 (0.7)	12 (1.3)
Per protocol	1 (0.3)	2 (0.5)	0	2 (0.5)	0	2 (0.2)	2 (0.4)	0
Suspected pregnancy	1 (0.3)	0	2 (0.4)	0	2 (0.4)	3 (0.2)	0	3 (0.3)
Investigator decision	1 (0.3)	2 (0.5)	6 (1.1)	2 (0.5)	7 (1.3)	11 (0.9)	3 (0.5)	8 (0.8)

	36-Week Placebo-Controlled BARI AA			Extended BARI AA		All BARI AA	All BARI 2-mg AA	All BARI 4-mg AA
	PBO N = 371 PYE = 243.2	BARI 2-mg N = 365 PYE = 240.6	BARI 4-mg N = 540 PYE = 363.4	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 = 564 PYE = 576.7	BARI 4-mg N = 951 PYE = 1079.2
Subject decision due to epidemic or pandemic	1 (0.3)	0	0	1 (0.3)	0	1 (0.1)	1 (0.2)	0
Travel restrictions due to epidemic or pandemic	1 (0.3)	0	0	0	0	0	0	0
Other epidemic or pandemic reasons or mitigations	0	0	0	1 (0.3)	1 (0.2)	4 (0.3)	2 (0.4)	2 (0.2)
Missing	0	1 (0.3)	0	1 (0.3)	0	1 (0.1)	1 (0.2)	0

Abbreviations: AA = alopecia areata; n = number of patients in the specified category; N = number of patients in the safety analysis set; PYE = patient-year exposure. Sources: Table SCS APP. 2.7.4.7.22 and Table SCS APP. 2.7.4.7.23.

Post marketing experience

Worldwide sales of baricitinib have been collected for the cumulative time period ending on 13 February 2021. As sales data are only available in complete months, the data are reflective of the cumulative time frame ending on 31 January 2021.

Cumulatively, as of 31 January 2021, there has been an estimated 232,500 patients exposed to baricitinib and 138,600 PYE. Approximately 180 patients (0.08%) were exposed to baricitinib 1 mg, 60,400 patients (26.0%) were exposed to baricitinib 2-mg, and approximately 171,900 patients (73.9%) were exposed to baricitinib 4-mg. Since the DLP for this submission, PSUR 08 has been completed and submitted to the EMA.

The MAH concludes that the data available from post-authorisation sources did not reveal any new information. Post-approval, spontaneous AE reports remain consistent with the established safety profile of baricitinib.

Of the cases with an opportunistic infection, most were reported in elderly patients, 36.2% occurred with concomitant disease-modifying antirheumatic drugs, and 32.3% occurred with concomitant corticosteroid use.

Haematologic events were mostly nonserious (84.8%) and included anaemia and white blood cell count decreased as the most frequently reported events. Two serious cases of agranulocytosis were reported.

Potential MACE (139 cases) were uncommonly reported (reporting rate 0.06, 0.10 per 100 PYE) with 49.0% of cases reporting a myocardial infarction/acute myocardial infarction, 28.8% reporting stroke, and 22.3% reporting cardiovascular deaths. Most events were in elderly patients having cardiovascular comorbidities and risk factors.

Deep vein thrombosis and PE were uncommonly reported (reporting rate 0.11, 0.19 per 100 PYE). Of the 261 VTEs, 51.7% were PE, 36.8% were DVT, and 11.5% reported both PE and DVT. Five cases were fatal and were reported in elderly patients with multiple risk factors. Most patients reporting a

VTE had risk factors including age greater than 50 years, history of VTE, lack of mobility, and obesity. From the VTE cases reported, about 58% were from patients receiving baricitinib 4-mg and 21% from patients receiving baricitinib 2-mg, 21% had no dose reported.

Gastrointestinal perforations were rarely reported post-approval (reporting rate 0.017%), and most reports were large intestine perforation or peritonitis. There were 4 fatal cases (1 small intestinal perforation, 1 peritonitis, 1 intestinal perforation, and 1 large intestinal perforation).

Increases in CPK were uncommonly reported (reporting rate 0.08%) and were generally asymptomatic with few details on specific values. In addition, 4 cases (reporting rate 0.0017%) of rhabdomyolysis were reported; however, these were not confirmed reports.

Malignancy was uncommonly reported (reporting rate 0.14%, 0.24 per 100 PYE), with lung neoplasms most often reported (14.0% of malignancy cases), a known risk for the RA population (Smitten et al. 2008). Other frequently reported malignancies included skin neoplasm (10.9%), breast cancer (9.8%), and lymphoma (9.2%). Of all malignancy cases, 11% had fatal outcomes, which were mainly related to the progression of the malignancy or metastases.

Hepatic events have been uncommonly reported (reporting rate 0.35%), 89.7% were nonserious, and most were related to increases in ALT and AST. There were 4 fatal cases reporting the following hepatic events: 1 case of hepatocellular injury and liver metastases, 1 case of hepatic failure and hepatic encephalopathy, with a history of HBV and positive antibodies, 1 case of hepatic failure in a patient taking baricitinib off label for COVID-19 pneumonia, and 1 case of portal hypertension, with a history of alcohol abuse. Among these patients who developed hepatic events, baricitinib-related, drug-induced liver injury could neither be confirmed nor appeared to be likely based on the available information.

2.5.1. Discussion on clinical safety

Olumiant is available as 2-mg and 4-mg tablets, and it is currently indicated to treat adult Rheumatoid arthritis and adult Atopic dermatitis. For both diseases, the recommended dose of Olumiant is 4-mg once daily. A dose of 2-mg once daily is recommended for patients ≥75 years and for patients with a history of chronic or recurrent infections. A dose of 2-mg once daily should also be considered for patients who have achieved sustained disease control with 4-mg once daily.

In the current variation, the proposed indication is 'for the treatment of severe alopecia areata in adult patients'. The recommended dose for the treatment of AA is 4-mg once daily, similar as RA and AD. During the second round of the procedure, the MAH proposed that 'a dose of 2-mg once daily may be appropriate for some patients such as those aged ≥ 75 years and for patients with a history of chronic or recurrent infections'. A dose of 2 mg once daily also is considered for patients who have achieved sustained control of disease activity with 4 mg once daily. After 36 weeks of treatment, consideration should be given to treatment stop in the absence of response. Confinement of the indication to patients with severe AA is relevant for assessing the balance of Risks with Benefits.

Existing safety profile

Baricitinib is contra-indicated in pregnancy and in known cases of hypersensitivity to the product. The SmPC includes warnings regarding the occurrence of infections, viral reactivation, haematological abnormalities, venous thromboembolism, lipids, hepatic transaminase elevations, malignancy, hypersensitivity, diverticulitis. The SmPC also includes warnings regarding vaccination, guidance for laboratory monitoring (lipids, absolute neutrophil count, absolute lymphocyte count, haemoglobin, hepatic transaminases), concomitant treatment with other immunosuppressive drugs. In patients with Rheumatoid arthritis and with Atopic dermatitis, the most commonly reported Adverse drug reactions

were increased LDL cholesterol, upper respiratory tract infections, and headache. Among the 'common' Adverse drug reactions are viral reactivation (herpes) and pneumonia, while deep venous thrombosis and pulmonary embolism were 'uncommon'.

For the extension of indication with AA, the MAH did not propose new contra-indications, warnings, or new ADRs. Where frequencies were notably different for AA as compared to RA or AD, this was annotated as footnotes in the ADR table in section 4.8 of the SmPC. No new important identified risks, important potential risks or missing information, were proposed for the RMP.

As can be derived from the above, baricitinib has a complicated safety profile, with similarities to other JAK inhibitors. From the description of demographic and disease characteristics of patients included in the trials (JAHO and JAIR) it appears that these are relatively younger patients, as compared to patients with RA.

Design

This application includes safety data from baricitinib treated adult patients with severe AA from two multicentre, randomised, double-blind, placebo-controlled studies (see 2.4.). Study JAHO is an adaptive Phase 2 and Phase 3 study, and study JAIR is a Phase 3 study. At baseline of the phase 3 studies, patients were randomized in a 2:2:3 ratio to receive placebo, baricitinib 2-mg or 4-mg dose. After completing the 36 weeks of the placebo-controlled phase, patients entered a long term extension phase of 68 weeks of additional treatment with the allocated baricitinib dose, patients on placebo were re-randomised to 2-mg or 4-mg. The safety population is defined as all patients who received at least 1 dose of study treatment. Safety data are included from the 36-week placebo-controlled periods and from the extended period up to database cut off dates of 24 March 2021 for JAIR and 31 March 2021 for JAHO.

The overall design with two basically identical pivotal studies is considered adequate to assess the short-term (36 weeks) safety of both doses of baricitinib against placebo, and to follow and compare the safety experience with the 2-mg and 4-mg dose over time. The 2:2:3 randomisation at baseline means that the safety sample of the recommended main dose of 4-mg is the largest sample. . The studies are ongoing and will last up to 4 years, but the placebo-controlled phase and the extension phase up to week 52 of the studies has been completed and submitted as part of the procedure.

The posology initially did not indicate whether baricitinib can, or should, be stopped in case of sufficient response or lack of response. The pivotal studies do include a randomised withdrawal phase at week 52, and completed data up to week 76 were submitted. Dose recommendations regarding that baricitinib should be stopped in case of non-response, and that the dose can be reduced if a good response has been reached were included in the SmPC at the CHMP's request (see 2.4.3.).

Sample size and follow-up

As of the data cut-off dates of August 2021, the total database included 610/951 (64%) patients treated with baricitinib 4-mg who completed at least 52 weeks of treatment. Following the original randomisation in the two pivotal studies, 307/365 (84%) of patients were treated with 2-mg for 52 weeks, and 479/540 (89%) were treated with 4-mg for 52 weeks.

Over 80% of patients originally allocated to baricitinib 2-mg or 4-mg in the pivotal studies, completed 52 weeks of follow-up. During the procedure, the MAH updated the safety data with completed 52-week results, and discussed differences with the already submitted safety data. The patient numbers exposed to at least 52 weeks of treatment with baricitinib 2-mg (n=294) or 4-mg (n=459) are expected to be sufficiently large to also detect uncommon adverse events, by roughly relying on the 'rule of three' (Eypasch 1995).

Elderly

The experience in patients with AA >65 years is limited. The mean (SD) age of the included patients was about 37 (13) and only a small portion (2-3%) was ≥65 years of age. This is in line with the inclusion criteria of being at least 18 years of age and ≤60 years of age for males and ≤70 years of age for females. The reason was to avoid noise due to age-related alopecia, which could add noise in the assessment of effect. Consequently, for elderly patients with AA it must have relied on the safety experience in elderly patients with RA. Therefore, the CHMP considered that the dose recommendation of 2-mg also applies to elderly patients with AA, even if there may be not a large demand for treatment of AA in this age group (see 2.4.3.).

Generalisation to clinical practice

The main exclusion criteria (see 2.4.2.) considered the type of alopecia and inadequate wash-out of therapies, and the discontinuation criteria were in line with the warnings and precautions in the baricitinib SmPC. Therefore, it is considered that these criteria were not overly selective, which is supportive for generalisation to clinical practice. Although it was attempted by the MAH to perform a safety analysis by subgroups of the population, the small size of subgroups and the heterogeneous nature of AEs limits the interpretation of these data.

Discontinuations

The number of permanent treatment discontinuations in the placebo-controlled phases of studies JAHO and JAIR was quite low. Between 7% and 11% of patients in baricitinib 2-mg or 4-mg discontinued and in 1.1%-2.6% this was due to an AE (usually infections), similar as in placebo. Stopping baricitinib in case of infections if considered needed, is recommended in the baricitinib SmPC. Overall this means that it is unlikely that the safety experience in AA is distorted by drop-outs, while the low number of discontinuations due to an AE suggests good tolerability of baricitinib in people with AA.

Interactions with co-medication

The only known DDI for baricitinib is with organic anion transporter 3 inhibitors with a strong inhibition potential, such as probenecid.

Adverse events

In the 36-week placebo-controlled phase, the occurrence of AEs was lowest in the placebo group and numerically higher in the baricitinib 2-mg and 4-mg groups (57% versus 61% versus 63%). SAEs were infrequent but occurred less in the placebo group and more frequently in the baricitinib 2-mg and 4-mg groups (1.6% versus 2.2% versus 2.6%). As already pointed to above, few patients discontinued study drug due to AEs. The occurrence of AEs, severe AEs, SAEs and discontinuations in the extended data set, comparing baricitinib 2-mg and 4-mg, is in line with the results of the placebo-controlled phase. In the updated safety database, the occurrence of SAEs, TEAEs, severe TEAEs, and discontinuations from study drug due to AEs for baricitinib 2-mg and 4-mg in the extended AA dataset were basically similar to the initial submission.

In the placebo-controlled period, the most frequently reported SOCs with TEAEs occurring in 10% of patients or more in any treatment group were Infections and infestations, Skin and subcutaneous tissue disorders, Investigations, Nervous system disorders, Gastrointestinal disorders, and Musculoskeletal and connective tissue disorders. This is basically in line with what is known from the safety of baricitinib in RA and AD.

Of the most common AEs that occurred in the placebo-controlled phase, upper respiratory tract infections, urinary tract infections, headache, nausea, acne, CPK increased, are known as ADRs of baricitinib. The occurrence of AEs of folliculitis, fatigue, and vulvovaginal candidiasis was <3%, but

higher on baricitinib 4-mg, in a dose-dependent way for folliculitis. Folliculitis and vulvovaginal candidiasis could be ADRs and are further discussed below. Hypertension and pruritis occurred most frequently in the baricitinib 4-mg group, but at a similar frequency in the placebo group and lower in the baricitinib 2-mg group. In the extended data set, the occurrence of these AEs remained higher in the 4-mg group as compared to the 2-mg group. However, hypertension, fatigue, and pruritis are not regarded as probable ADRs because of the low occurrence in baricitinib that was not clearly different from placebo and a lower occurrence than placebo in the 2-mg dose group.

Serious adverse events and deaths

Even if SAEs in the clinical trials were low, it numerically appears that the occurrence of SAEs of fractures, infections, cardiac disorders, and hepatobiliary disorders was higher for baricitinib than placebo. Except for fractures, these are known risks of baricitinib. MACE as an outcome of hyperlipidaemia is an important potential risk. Infections are a known ADR, and serious infections are an important potential risk of baricitinib. Increases of liver enzymes (ALT ≥3 x ULN and AST ≥3 x ULN) are a known ADR, but DILI is not. Therefore, the apparently higher occurrence of fractures was further discussed during the procedure.

Even at low frequency, the more frequent occurrence of fractures in patients treated with baricitinib, as compared to placebo, is remarkable. Because nearly all fractures occurred in patients treated with baricitinib. At the same time, there was no obvious dose-response relationship, and the fractures did not seem to be 'low impact fractures'. It also must be recognised that the baricitinib 4-mg group was larger than the baricitinib 2-mg and placebo groups. Though, according to non-clinical data, baricitinib may have an effect on bone. In rat and rabbit reproductive toxicology studies, baricitinib was shown to reduce foetal growth/weight and produce skeletal malformations (at exposures of approximately 10 and 39 times the human exposure, respectively) [Baricitinib SmPC]. It is not clear whether baricitinib in doses of 2-mg and 4-mg would lead to relevant bone effects in children or in adults. However, in the scientific literature there currently is a wave of publications that suggest that there is an effect of JAK Inhibitors (notably tofacitinib and baricitinib) to enhance bone formation and bone mass, to be used therapeutically in patients with bone loss due to inflammatory disorders such as Rheumatoid arthritis (e.g. Adam et al. 2021 https://www.scientificarchives.com/article/prospects-of-jak-inhibition-in-the-framework-of-bone-loss). However, the same mechanism might be responsible for increased fracture risk (increasing bone mineralization and reducing elastic properties). However, based on the totality of data including patients at high risk (RA patients) it is considered that fractures should not be considered an ADR of baricitinib based on the available evidence. The main reasons are that: in the RA and AD data there were no differences between baricitinib-treated and placebo-treated patients in occurrence of fractures; in RA, AD and AA there was no suggestion of a dose-response effect; in RA, AD and AA the IR's at follow-up were similar to the IR's of the placebo-controlled phase suggesting no increment in frequencies; the IR's for fractures in the RA, AD and AA trials did not seem to exceed the background risk.

Adverse events of special interest

In the placebo-controlled period, there were no large differences between placebo and baricitinib treatment groups for Treatment-Emergent infections, serious infections, temporary interruptions, and permanent discontinuations of study drug due to infections. No patients with placebo and 3 patients in the baricitinib groups reported serious infections. This is somewhat reassuring, considered that people with AA are relatively healthy, as compared with people having auto-immune diseases like RA and AD. However, it is considered that also for people with AA and a history of chronic or recurrent infections, a dose of 2-mg once daily is more appropriate than the standard dose of 4-mg, which has been included in the SmPC at the CHMP's request.

Infections that were reported by more than 1% of patients in any baricitinib group and that were more frequent with baricitinib compared to placebo were: urinary tract infection, folliculitis, bronchitis, herpes zoster, and vulvovaginal candidiasis. Differences were not significant except for vulvovaginal candidiasis. Of those infections, urinary tract infection, upper respiratory tract infections and herpes zoster are known ADRs of baricitinib. Based on the results of the placebo-controlled trial in AA, folliculitis and vulvovaginal candidiasis could be ADRs, which was further discussed by the MAH during the procedure at the CHMP's request.

In the placebo-controlled phase, there was a higher frequency of folliculitis with baricitinib 2-mg (1.4%) and baricitinib 4-mg (2.2%) compared to placebo (0.8%). The scalp was involved in 80% of patients, no events were serious or severe, most (70%) of patients recovered or were recovering, and no patient interrupted or discontinued study drug due to the AE. Based on the data for RA and AD, there is no association of exposure to baricitinib, versus placebo, and folliculitis. This is notably different to the AA trial data. The MAH makes likely that there is a mechanical explanation for folliculitis due to irritation of the follicle by regrowing hair. In addition, a immunosuppressive cause is unlikely, given the results in the RA and AD trials and given that the predominant place of folliculitis in AA was the scalp (75%) and was experienced by patients who were responders (71%). Consequently, folliculitis in AA is likely due to mechanical irritation by regrowing hair, which is specific for the AA indication. While folliculitis in AA can be viewed as condition-specific ADR, it is considered unlikely that the occurrence of folliculitis will be a limiting factor for many patients. At the CHMP's request, "folliculitis" was added to the table of adverse reactions in Section 4.8 of the SmPC with a frequency "common". The prescribers and patients are now informed in the SmPC/PIL that folliculitis—like eruptions have been reported at the treatment of AA with baricitinib, particularly in the scalp region, but that these eruptions are actually a signal of hair re-growth.

In the placebo-controlled part of the study, vulvovaginal candidiasis occurred more frequently in the baricitinib 2-mg, and 4-mg treated groups as compared to placebo (2.6% vs 1.2% vs 0%). In the placebo-controlled phase, occurrence on baricitinib 2-mg was lower as compared to 4-mg, but this became more similar in the All baricitinib set (IR~2.0 for both dose groups). In most patients these infections had occurred <16 weeks after baseline and no additional cases appeared with the data update. In contrast, in RA and notably in AD, there was no apparent difference in the occurrence of vulvovaginal candidiasis/mycotic infections between baricitinib and placebo and there was no tendency that the occurrence of these infections increased over time. It is of relevance for the distribution of risk factors that the populations of AD and AA are more similar than the generally older RA population. Based on these conflicting results, it is considered that the higher occurrence of these infections in females with AA on baricitinib, as compared to placebo, is likely to be explained by chance.

The changes in blood lipids in the AA trial population are in line with what is known about the product. Hypercholesterolaemia and hypertriglyceridaemia are ADRs of baricitinib.

MACE as an outcome of hyperlipidemia is an important potential risk of baricitinib. In the placebo-controlled period, there was 1 MACE that occurred in the baricitinib 2-mg group. The 2 other cardiovascular events were both serious arrhythmias. Currently, the results do not raise additional concerns regarding MACE in the AA population.

VTE did occur in 2 patients (PE/DVT and PE) in the AA study population, while both patients had multiple risk factors for VTE. However, VTE due to treatment with baricitinib is also considered to be a risk for patients with AA.

CPK increases are a known ADR of baricitinib. According to the results in AA, increases in CPK and increases >5 x ULN were overall more frequent with baricitinib than with placebo, especially with the 4-mg dose. Based on the available data in AA, there appears to be no association of muscle symptoms,

notably of rhabdomyolysis, with elevations in CPK related to baricitinib treatment. Notably, CPK increments is a known class effect of JAK-inhibitors, but neither for the other JAK-inhibitor products than baricitinib an association was found with rhabdomyolysis.

Malignancies did infrequently occur in the AA study population and remain an important potential risk for baricitinib.

ALT and AST increases of 3 or more times the ULN are known ADRs of baricitinib, with hepatotoxicity being an important potential risk for baricitinib. The current results in the AA population are in line with this and do not give rise to additional concerns.

Other laboratory findings, such as high serum albumin and low monocytes, and vital signs, did not give rise to safety concerns.

Safety in special populations

The majority of the study population was <65 years of age, data of elderly patients are limited. At the CHMP's request, the SmPC states that clinical experience in patients ≥ 75 years is very limited and in these patients a starting dose of 2-mg is appropriate. There appears to be no safety reason to limit the upper age to the AA population studied (≤60 years of age for males and ≤70 years of age for females).

There is no relevant new information for other special populations and situations, including hepatic impairment, renal impairment, pregnancy and lactation.

2.5.2. Conclusions on clinical safety

The safety profile of baricitinib appears as overall positive in the data submitted as part of this application. The occurrence of AEs and SAEs was only slightly higher for baricitinib 2-mg and 4-mg as compared to placebo. SAEs and discontinuations due to an AE were infrequent. The safety data are consistent with the known safety profile of baricitinib for the approved indications, including infections, headache, nausea, acne, increased CPK, increased ALT/AST, increased blood lipids. VTE, malignancies, and MACE, occurred in single cases. Fractures and vulvovaginal candidiasis were discussed as ADR using the updated safety data, but it was agreed that these are not to be considered as new ADRs. Folliculitis appears to be an ADR for the treatment of AA only and has been added to the table of adverse reactions in Section 4.8 of the SmPC. No other new safety signals were identified in the treatment of adult patients with severe AA. However, the safety profile of baricitinib is complicated and includes several ADRs concerning laboratory values, most notably of blood lipids, CPK, ALT/AST, of which the long-term results are not exactly clear. It is of relevance from the safety perspective (malignancy, MACE, VTE, infections, …) to avoid unnecessary long-term exposure in relatively young people. During the procedure therefore, proposals for the SmPC regarding when to stop treatment in case of non-response and when to reduce the dose in case of good response were included at the CHMP's request, similarly to what was done for RA and AD.

The CHMP concluded that the safety data for baricitinib was acceptable in the new indication of treatment of severe alopecia areata in adult patients.

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

The PRAC considered that the risk management plan version 12.3 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 12.3 with the following content:

Safety concerns

• **Summary of Safety Concerns**	
• **Important identified risks**	• Herpes zoster • VTE[a]
• **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 • Use in paediatric patients

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

[a]At the request of PRAC, this was re-categorised from an important potential risk to an important identified risk.

Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates •
Category 1 - Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
I4V-MC-B003: Prospective Observational US Postmarketing safety registry (Corrona) (Ongoing)	Primary Objectives: 1) Compare the incidence rates and profiles of the following aggregate outcomes: serious infections (including herpes zoster) and opportunistic infections (including tuberculosis, *Candida* infections, and PML), MACE, malignancies (including lymphoma and typically virus-induced malignancies, such as cervical and many oropharyngeal cancers), and VTE among patients with long-term exposure to baricitinib versus patients with long-term exposure to other medications used for moderate-to-severe RA; 2) Describe the incidence rates of lymphoma, herpes zoster; opportunistic infections (such as tuberculosis, *Candida* infections, and PML), rhabdomyolysis; myelosuppression (agranulocytosis); hyperlipidaemia (hypercholesterolaemia, hypertriglyceridaemia); GI perforations, and evidence of DILI. Secondary Objective:	Important Identified Risks: • Herpes zoster VTE Important potential risks: • Serious and opportunistic infections (including tuberculosis, *Candida* infections, PML) • MACE as an outcome of hyperlipidaemia • Malignancies (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers) • Potential for DILI • Myelosuppression (agranulocytosis) • Myopathy including rhabdomyolysis • GI perforation Missing information: • Long-term safety Use in very elderly (≥75 years	Study progress reports	Annually in PBRER/PSUR submitted in April of each year after start of data collection

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates •
	Describe the incidence of the above outcomes in very elderly patients (aged ≥75 years).			
I4V-MC-B004: Retrospective Observational Safety Study Using an Existing Database (Ongoing)	Primary Objectives: 1) To assess and compare the risk of the following aggregate outcomes: serious infections (including herpes zoster) and opportunistic infections (including tuberculosis, *Candida* infections, PML), MACE, malignancies (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers), and VTE, among patients with long-term exposure to baricitinib compared to similar patients with RA with long-term exposure to other indicated medications. 2) To describe the incidence rates of the following individual outcomes: lymphoma; herpes zoster; opportunistic infections such as tuberculosis, *Candida*, and PML; rhabdomyolysis; myelosuppression (agranulocytosis); hyperlipidaemia (hypercholesterolaemia, hypertriglyceridaemia); GI perforations; and evidence of DILI. Secondary Objective: 3) To describe the incidence of the above outcomes in very	Important Identified Risks • Herpes zoster • VTE Important potential risks: • Serious and opportunistic infections (including tuberculosis, *Candida* infections, PML) • MACE as an outcome of hyperlipidaemia • Malignancies (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers) • Potential for DILI • Myelosuppression (agranulocytosis) • Myopathy including rhabdomyolysis • GI perforation Missing information: • Long-term safety Use in very elderly (≥75 years)	Study progress reports Final Study Report	Annually in PBRER/PSUR submitted in April of each year after start of data collection 30 June 2030

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates •
	elderly patients (aged ≥75 years old).			
I4V-MC-B011: Retrospective Cohort Study to Assess Safety of Baricitinib in Nordic countries (Ongoing in RA, planned in AD)	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); GI perforations; and liver injury. Secondary Objectives:	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) • Myopathy including rhabdomyolysis • GI perforation Missing information: • Long-term safety Use in very elderly (≥75 years)	**For RA study**: Study progress reports Final Report for Objective 4 Final study report (Objectives 1-3*)* **For AD Study:** Study progress reports Final Report	**For RA study:** Annually in PBRER/PSUR submitted in April of each year To be determined based on at least 24 months of data in at least 50% of the discrete healthcare databases 31 December 2027 **For AD Study**: Annually in PBRER/ PSUR submitted in April of each year 31 December 2028

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates •
	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 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. (This objective complements the aims of Study I4V-MC-B010, which aims to assess the effectiveness of risk minimisation activities.)			
I4V-MC-B012 Observational post marketing Surveillance in 3 European Registries (Ongoing)	Primary Objectives: 1) To monitor the incidence rate and profile of the following aggregate outcomes of serious infections (including herpes zoster) and opportunistic infections (including tuberculosis, *Candida* infections, and PML), MACE, malignancies (including lymphoma and typically virus-induced malignancies, such as cervical and many oropharyngeal cancers),	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	Study progress reports Final study report	Annually in PBRER/ PSUR submitted in April of each year 31 March 2024

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates •
	and VTE among patients with long-term exposure to baricitinib compared to patients with long-term exposure to other medications used for moderate-to-severe RA, as possible given the data available in the BSRBR, RABBIT, and ARTIS registries. To describe the occurrence of the following individual outcomes: lymphoma, herpes zoster, opportunistic infections, rhabdomyolysis, agranulocytosis, PML, GI perforations, and evidence of DILI.	infections (including Tuberculosis, *Candida* infections, PML), • Myelosuppression (agranulocytosis) • Myopathy including rhabdomyolysis • Potential for drug-induced liver injury • GI perforation • MACE as an outcome of hyperlipidaemia		
I4V-MC-B016: Assessment of off-label use of baricitinib in the paediatric population in the United Kingdom (Ongoing)	Primary objective: Describe the proportion of baricitinib prescribing that occurs off-label to paediatric patients. Secondary objective: If paediatric use is ≥5 patients, describe paediatric patients who receive a prescription for baricitinib in terms of total number of patients, demographics (age and sex) and select baseline diagnosis codes.	Missing information Use in paediatrics	Study progress reports Interim study report (corresponds to final study report date that was committed to at the time when RA was only approved indication) Final study report (corresponds to new final study report date committed to with addition of AD indication)	Annually in the PSUR, submitted in April each year 31 March 2021 31 March 2023

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates •
I4V-MC-B025: Dermatologist Survey to Assess the Effectiveness of the Baricitinib Risk Minimisation Measures in Prescribers of Patients with Atopic Dermatitis (Planned)	Primary Objective: To assess the understanding of and adherence to the key risk minimisation messages and required mitigating actions in the HCP Educational Material and PAC among a sample of dermatologists, regarding: • Use in pregnancy • Infections • Lipids • VTE	Important Identified Risks • Herpes zoster • VTE Important Potential Risks: • Serious and opportunistic infections (including tuberculosis, *Candida* infections, PML) • MACE as an outcome of hyperlipidaemia • Foetal malformation following exposure in utero	Final study report	30 September 2023

Abbreviations: ARTIS = Antirheumatic Therapies in Sweden; BSRBR = the British Society for Rheumatology Biologics Register; DILI = drug-induced liver injury; EU = European Union; GI = gastrointestinal; HCP = Healthcare Professional; MACE = major adverse cardiovascular events; PAC = Patient Alert Card; PBRER = periodic benefit-risk evaluation report; PML = progressive multifocal leukoencephalopathy; PSUR = periodic safety update report; PV = pharmacovigilance; Q = quarter; RA = rheumatoid arthritis; RABBIT = Rheumatoid Arthritis Observation of Biologic Therapy; US = United States; VTE = venous thromboembolic event.

Risk minimisation measures

Table Part V.3. 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 Section 4.8 • SmPC section 4.4 recommends that if an infection develops, the patient should be monitored carefully, and Olumiant should be	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection • Herpes zoster follow-up form Additional pharmacovigilance activities:

	temporarily interrupted and not be resumed until the infection resolves. There is a further recommendation that, prior to starting treatment, all patients be brought up to date with all immunisations. PIL sections 2 and 4 PL Section 2 advises that the patient should tell their doctor if they develop signs of shingles. [Additional risk minimisation measures:] • Healthcare Professional Educational Material • Patient Alert Card	Observational post-marketing safety studies to monitor the incidence of herpes zoster in patients exposed to baricitinib RA: • National RA registries, such as Corrona • EU registries • An observational database study • Nordic healthcare study AD: • Nordic healthcare study
Malignancies (including lymphoma and typically virus-induced malignancies, such as cervical and many oropharyngeal cancers)	[Routine risk minimisation measures:] SmPC Section 4.4 PIL section 2 PL Section 2 advises patients to tell their doctor or pharmacist before and during treatment if they have cancer. [Additional risk minimisation measures:] None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Cancer/neoplasm follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to compare the incidence of malignancy in patients exposed to baricitinib with patients exposed to other medications used for: Moderate-to-severe RA: • National RA registries, such as Corrona • EU registries • An observational database study • Nordic healthcare study Moderate-to-severe AD: • Nordic healthcare study
Serious and opportunistic infections (including TB *Candida* infections, PML)	[Routine risk minimisation measures:] SmPC Sections 4.4 and 4.8 PL Section 2 SmPC Section 4.4 advises that the risks and benefits of treatment should be considered prior to initiating therapy in patients with active, chronic, or recurrent infections. It also recommends that if an infection develops, the patient should be monitored carefully and	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *Candida* infection follow-up form • Pneumonia follow-up form • Viral reactivation follow-up form • Unspecified infection follow-up form • Extrapulmonary TB follow-up form

	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 be brought up to date with all immunisations. •Section 2 of the PL advises patient that they need to talk to their doctor or pharmacist before and during treatment with Olumiant if they have an infection or if they often get infections. It also advises patents that they should tell their doctor if they get signs of TB, herpes zoster or have, or have previously had, hepatitis B or C. [Additional risk minimisation measures:] • Healthcare Professional Educational Material • Patient Alert Card	• Pulmonary TB follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to compare the incidence of serious and opportunistic infections (including TB, *Candida*, and PML) in patients exposed to baricitinib with patients exposed to other medications used for moderate-to-severe: RA: • National RA registries, such as Corrona • EU registries • An observational database study • Nordic healthcare study AD: • Nordic healthcare study
Myelosuppression (agranulocytosis)	[Routine risk minimisation measures:] SmPC Sections 4.2,4.4, 4.8, and 5.3 PL sections 2 and 4 SmPC Sections 4.2 and 4.4 recommend that treatment should not be initiated or should be temporarily interrupted in patients with white cell counts or a haemoglobin that is below a certain level. PL Section 2 advises patients that they may need blood tests prior to or during treatment to check if they have a low red or white blood cell counts. [Additional risk minimisation measures:] None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Blood and Bone Marrow Disorders follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to monitor the incidence of myelosuppression in patients exposed to baricitinib: RA: • National RA registries, such as Corrona • EU registries • An observational database study • Nordic healthcare study

		AD • Nordic healthcare study
Myopathy including rhabdomyolysis	[Routine risk minimisation measures:] SmPC Section 4.8 (increases in CPK PL Section 4 (increases in CPK) [Additional risk minimisation measures:] None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Rhabdomyolysis follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to monitor the incidence of myopathy including rhabdomyolysis in patients exposed to baricitinib RA: • National RA registries, such as Corrona • EU registries • An observational database study • Nordic healthcare study AD: • Nordic healthcare study
Potential for drug-induced liver injury	[Routine risk minimisation measures:] SmPC Sections 4.2, 4.4, and 4.8 PIL Sections 2 and 4 SmPC Section 4.2 recommends that Olumiant should not be used in patients with severe hepatic impairment. Section 4.4 recommends that if increases in ALT or AST are observed and drug-induced liver injury is suspected, Olumiant should be interrupted. •Section 2 of the PL advises patients to speak to their doctor if they have, or have previously had, hepatitis B or C or if they have poor liver function. [Additional risk minimisation measures:] None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Hepatic disorders follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to monitor the incidence of potential drug-induced liver injury among patients exposed to baricitinib: RA: • National RA registries, such as Corrona • EU registries • An observational database study • Nordic healthcare study 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: • Fistula and/or GI perforation follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to monitor the incidence of GI perforations in patients exposed to baricitinib RA: • National RA registries, such as Corrona • EU registries • An observational database study • Nordic healthcare study AD: • Nordic healthcare study
MACE (as an outcome of hyperlipidaemia)	[Routine risk minimisation measures:] SmPC Sections 4.4 and 4.8 (hypercholesterolaemia and hypertriglyceridaemia) PIL Section 2 and 4 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. PL Section 2 advises patients that they may need blood tests while taking Olumiant to check if they have a high cholesterol level. [Additional risk minimisation measures:] • Healthcare Professional Educational Material (lipid monitoring) • Patient Alert Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Cardiac disorders follow-up form • Cerebrovascular accident follow-up form • Mortality follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to compare the incidence of hyperlipidaemia and MACE among patients exposed to baricitinib: RA: • National RA registries, such as Corrona • EU registries • An observational database study • Nordic healthcare study AD • Nordic healthcare study
Foetal malformation following exposure in utero	[Routine risk minimisation measures:] SmPC Sections 4.3, 4.6, and 5.3 PIL Section 2 SmPC Sections 4.3 and 4.6 state that pregnancy is a contraindication.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

	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. PL Section 2 • States that patients should not take Olumiant if they are pregnant or think that they may be pregnant • Advises patients that if they are pregnant, think they may be pregnant, or are planning to have a baby, they should ask their doctor or pharmacist for advice before taking the medicine • States that patients should use an effective method of contraception to avoid becoming pregnant during treatment and for at least 1 week after the last Olumiant treatment • States that patients must tell their doctor if they become pregnant as Olumiant should not be used during pregnancy [Additional risk minimisation measures:] • Healthcare Professional Educational Material • Patient Alert Card	• Pregnancy data collection – maternal follow-up form • Pregnancy data collection – paternal follow-up form • Pregnancy outcome - maternal follow-up form • Pregnancy outcome - paternal follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to monitor the incidence of foetal malformation following exposure in utero among patients exposed to baricitinib for both RA and AD: • Nordic healthcare study
VTE	[Routine risk minimisation measures:] SmPC Sections 4.4 and 4.8 (DVT and PE) PIL Section 2 SmPC Section 4.4 advises that Olumiant should be used with caution in patients with risk factors for VTE and that if clinical features of VTE occur, treatment should be discontinued and patients should be evaluated promptly and appropriately treated. PL Section 2 advises patients: • To talk to their doctor or pharmacist before and during treatment if they have previously	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Thromboembolic follow-up form • Clotting and/or coagulation disorders follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to compare the incidence of VTE, including VTE validated based on clinical information, among patients exposed to baricitinib being treated for moderate-to-severe: RA:

	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	• National RA registries, such as Corrona • EU registries • An observational database study • Nordic healthcare study AD: • Nordic healthcare study
Long-term safety	[Routine risk minimisation measures:] SmPC Sections 4.4 and 4.8 (hypercholesterolaemia and hypertriglyceridaemia) PL Sections 2 and 4 No additional recommendations are included in the SmPC or PL other than those already stated for malignancy and MACE. [Additional risk minimisation measures:] None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Cardiac disorders follow-up form • Cerebrovascular accident follow-up form • Mortality follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to monitor long-term safety in patients exposed to baricitinib RA: • National RA registries, such as Corrona • EU registries • An observational database study • Nordic healthcare study 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 recommends that in patients, ≥75 years, a starting dose of 2 mg is appropriate.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Observational post-marketing safety studies to monitor the incidence of use in very elderly (≥75 years) in patients exposed to baricitinib: RA: • National RA registry, such as Corrona

	[Additional risk minimisation measures:] None.	• An observational database study • Nordic healthcare study AD: • Nordic healthcare study
Use in patients with evidence of hepatitis B or hepatitis C infection	[Routine risk minimisation measures:] SmPC Section 4.4 PL Section 2 SmPC Section 4.4 recommends that screening for viral hepatitis should be performed before starting treatment and that if the test is positive, a liver specialist should be consulted Section 2 of the PL advises patients to speak to their doctor if they have, or have previously had, hepatitis B or C. [Additional risk minimisation measures:] None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: hepatic disorders follow-up Additional pharmacovigilance activities: None
Use in patients with a history of or current lymphoproliferative disease	[Routine risk minimisation measures:] SmPC Section 4.4 PL Section 2 PL Section 2 advises patients to tell their doctor or pharmacist before and during treatment if they have cancer. [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 PL Section 2 advises patients to tell their doctor or pharmacist before and during treatment if they have cancer. [Additional risk minimisation measures:] None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Use in paediatric patients	[Routine risk minimisation measures:] SmPC Section 4.2 PIL Section 2 PL Section 2 advises that Olumiant is not for use in children and adolescents younger than 18 years old. [Additional risk minimisation measures:]	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities for RA and AD: • Off-label use in children (CPRD database)

	None	

Abbreviations: AD = atopic dermatitis; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; CPRD = Clinical Practice Research Database; DVT = deep vein thrombosis; EU = European Union; GI = gastrointestinal; MACE = major adverse cardiovascular event; PE = pulmonary embolism; PL = 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 consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template.

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 for the following reasons: user consultation has been done during the MAA for Olumiant, the extension of indication has not significantly altered the structure and design of the PL.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The proposed indication is: 'for the treatment of severe alopecia areata in adult patients.'

Baricitinib is an orally available, reversible, adenosine triphosphate (ATP) competitive Janus kinase (JAK) inhibitor. Janus kinases are intracellular enzymes that transmit signals from cytokine or growth factor-receptor interactions on the cellular membrane to influence immune cell functions and haematopoiesis.

Insights into the immunopathogenesis of alopecia areata (AA) began with recognising the hair follicle as 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 utilizes JAK1 and JAK2.

3.1.1. Disease or condition

Alopecia areata (AA) is an autoimmune disease characterized by patches of nonscarring hair loss. AA is associated with atopic diseases such as atopic dermatitis and asthma. Severe AA is defined as scalp hair loss> 50%. Severe AA is recognized 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 alopecia areata, and the disorder occurs at similar rates in males and females (Strazzulla LC et al., 2018). AA has a lifetime prevalence of approximately 2% (Wasserman et al., 2007; Islam et al., 2015; Korta et al., 2018). The mean age for diagnosis of AA is predicted to be of 32 years in males and 36 years in females (Mirzoyev SA et al. 2013). It has a higher psychological and cosmetic burden for women.

3.1.2. Available therapies and unmet medical need

No treatment for AA indication is widely available in the EU through centralized approval. However, some authorized medications are available in individual member states (e.g. in NL methylprednisolone and triamcinolone intra-lesion injections are approved for AA indication). Current guidelines advise on topical (corticosteroids and minoxidil) or systemic therapies (corticosteroids, corticosteroid-sparing agents such as cyclosporin and methotrexate, and biological such as ustekinumab/Stelara) (European Dermatology Forum (EDF): Evidence-based (S3) guideline for the treatment of androgenetic alopecia in women and in men, 2017; British Association of Dermatologists (BAD): Guidelines for the management of alopecia areata, 2012). However, some of those treatments are used off-label. The response to treatment varies widely; few well-designed clinical trials have evaluated these therapies. Therefore, there is an unmet medical need for patients with severe AA.

3.1.3. Main clinical studies

The baricitinib clinical development programme for AA includes 2 pivotal global clinical studies (Study I4V-MC-JAHO [JAHO] and Study I4V-MC-JAIR [JAIR]) to evaluate the safety and efficacy of baricitinib in adult patients with severe AA defined as ≥50% scalp hair loss, a duration of the current episode of at least 6 months. Both studies were multicenter, randomized, double-blind, placebo-controlled, parallel-group, and outpatient. The primary endpoint was a SALT score ≤20 at week 36, which corresponds to a scalp hair loss of ≤20% or at least 80% scalp hair coverage.

Study JAHO was a Phase 2/3, adaptive, and operationally seamless placebo-controlled study. The Phase 2 portion was designed to select up to 2 doses of baricitinib (of 1 mg, 2-mg and 4-mg QD) to be evaluated in the Phase 3 portion of the study.

In the Phase 3 portion of JAHO and in Study JAIR, the efficacy and safety of 2-mg/day and 4-mg/day of baricitinib were compared to placebo in adult patients with severe AA. The current submission includes efficacy data for 855 patients enrolled in the Phase 3 AA studies through Week 36 (placebo-controlled period), and for 629 patients (approximately 74%) randomised to baricitinib through Week 52.

3.2. Favourable effects

Primary outcome (SALT ≤20 at week 36) was met ($p<0.001$) in both baricitinib treatment groups (both 4-mg and 2-mg dosing regimens) in both pivotal studies. The treatment effect on SALT≤20 in the baricitinib 2-mg group was lower compared to baricitinib 4-mg (16.4% versus 29.9.% and 14.7% versus 29.9% in JAHO and JAIR studies, respectively). The treatment effect (difference in proportion with placebo) calculated from pooled data analysis was 16% (95%CI: 11% - 21%) and 30% (25% - 34%) for baricitinib 2-mg and 4-mg, respectively. The results were supported by the results of the provided sensitivity analyses. Lowering the extent of hair loss from 50% to less than 20% of scalp hair

in almost one-third of the patients can be considered clinically relevant. The clinical relevance of SALT<20% is supported by the development of SALT (Wyrwich et al. 2020a).

The most relevant key secondary outcomes: (SALT ≤10 at Week 36 (representing almost full recovery), patient-assessed Scalp Hair Assessment at week 36, clinician assessed Eyebrow Hair Loss at week 36, clinician assessed Eyelash Hair Loss at week 36) demonstrated statistically significant improvements for both baricitinib 4-mg and 2-mg. The Scalp Hair Assessment PRO is considered to support clinical relevance of the primary endpoint (SALT≤20) because the treatment effects are in line with the patient perceptions of the amount of hair loss. The endpoint (0 or 1) in the patient-assessed Scalp Hair assessment was also considered relevant by the patient panel in its development (Wyrwich et al. 2020c). ClinRO EB and EL measure physician assessment on eyebrow and eyelashes hair loss, which has an important cosmetic and clinical importance.

To support clinical relevance, satisfaction with/acceptability of the treatment effect can be indirectly assessed through the results on the emotional and functional subscales of the Skindex questionnaire and the scores on anxiety and depression of the HADS. In Studies JAHO and JAIR, baricitinib 4-mg demonstrated a statistically significant improvement compared to placebo for mean change from baseline in Skindex-16 Emotions and Functioning domains at Week 36. This translates into a decreased psychological burden in treated patients, and this is considered clinically relevant. Furthermore, baricitinib 4-mg demonstrated a statistically significant improvement compared to placebo for mean change from baseline in the HADS Anxiety total score at week 36.

Improvement in SALT started between week 8-16 of treatment and increased until week 52, with higher responses in the baricitinib 4-mg groups. Overall from the results of primary, secondary and additional endpoints, it appears that the 4-mg dose is superior to 2-mg and to placebo. Most of the endpoints also have shown the superiority of the 2-mg dose to placebo.

Pooled data analysis shows 39% response rates in the 4-mg group after 52 weeks of treatment. Thereafter, half of the responders were re-randomized to be down-titrated to 2-mg. SALT ≤20 was achieved by 74% (31 of 42) of the patients who were down-titrated to baricitinib 2 mg, and by 96% (42 of 44) of the patients who remained on baricitinib 4 mg.

Subgroup analysis supports the robustness of the higher responses on baricitinib 4-mg. The Pooled Week 36 Efficacy Population analysis demonstrated a statistically significant improvement in SALT for both baricitinib 4-mg and 2-mg across both AA disease severity and episode duration subpopulations. Baldness is psychologically more important for women (they need a denser hair implant for a cosmetically acceptable hair than men). Subgroup analysis has been provided in Skindex and HADS measures in men and women. Symptom domain of Skindex and depression domain of HADS showed more favourable results for female subjects.

3.3. Uncertainties and limitations about favourable effects

No studies were conducted in European countries. PK analysis from other indications has not shown differences between subjects with different ethnicities for baricitinib. Furthermore, efficacy in AA was comparable in the subgroup analysis of different regional groups. Therefore, it is not expected that efficacy will be different in European countries.

Both the clinician-assessed SALT score and the patient assessed Scalp Hair Assessment are essentially measuring the same measurement concept: the amount of hair (loss). It is acknowledged that the amount of hair drives satisfaction and clinical relevance of treatment effects. However, satisfaction with the results also depends on the site of remaining hair loss, and satisfaction with the treatment

results was not directly assessed. However, it could be inferred through the results on Skindex-16 subscales and HADS subscales.

Some secondary and additional endpoints were not significant for the baricitinib 2-mg treatment group, especially in the JAIR study. For Skindex functioning and symptoms domain, no significant difference has been found between baricitinib 2-mg and placebo. For HADS at week 36, no subcategories were statistically different from placebo in baricitinib 2-mg group. The CHMP concluded that this does not impact the overall efficacy results, as 4 mg is the main dose and there is support for efficacy of the 2 mg dose in SALT<20 response.

Most of the patients (around 90%) in both placebo and treatment arms had prior therapy with systemic immunosuppressants/immunomodulator therapy or topical treatments. In total only 23, 33 and 57 treatment naïve patients are included in placebo, baricitinib 2-mg and baricitinib 4-mg arms in pivotal studies, respectively. The proportion of patients using concomitant medication use was small and comparable between treatment and placebo arms. Therefore it is not expected that concomitant medications use had affected the final results.

The MAH has proposed a dose of 4-mg for the intended indication, in line with the efficacy results. The 4-mg dose was more effective than the 2-mg dose, but also, the lower dose can be considered more effective than placebo. Initially, no proposals were made for stopping treatment or down titration to 2-mg in responding patients treated with baricitinib 4-mg, or for when to stop treatment in patients with an insufficient response. As the disease may recover spontaneously and given the safety profile of JAK inhibitors like baricitinib, the CHMP requested that guidance should be provided regarding treatment continuation and when to stop treatment. At the CHMP's request, the Section 4.2 of the SmPC has been updated to reflect that a dose of 2 mg once daily may be appropriate for patients such as those aged ≥ 75 years and for patients with a history of chronic or recurrent infections. In addition, a dose of 2 mg once daily may also be considered for patients who have achieved sustained control of disease activity with 4 mg once daily and are eligible for dose tapering.

Because data of the stop and dose reduction sub-studies of the trials became available, the MAH provided data driven proposals. After down titration to 2-mg in responding patients, efficacy was reduced. In another sub-study, responders were re-randomised to stop or continuation of the 4-mg or 2-mg dose. According to the results, only 33% and 20% of responders stayed in remission until week 76 if baricitinib 4mg and 2mg were withdrawn, respectively. This indicates a higher chance of flare if treatment is stopped. Therefore, stopping baricitinib in case of maintained good response seems not advisable based on the efficacy results of the stop study since a majority of patients lost response within 24 weeks after discontinuation. On the other hand, considering the safety profile of baricitinib, the exposure should be reduced when possible. At the CHMP's request, Section 4.2 of the SmPC was updated to include the following guidance which was considered acceptable to the CHMP:

"Once a stable response has been achieved, it is recommended to continue treatment for at least several months, in order to avoid relapse. The benefit risk of treatment should be re assessed at regular intervals on an individual basis."

Predictor analysis has shown that 36 weeks is more appropriate time point to stop treatment in non-responders compared to 24 weeks. Therefore, Section 4.2 of the SmPC has been updated as follows: "*Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit after 36 weeks of treatment*."

3.4. Unfavourable effects

The 'phase 3' studies are both ongoing and will last up to 4 years. The data from the placebo-controlled phase from baseline up to week 36 and the extension phase up to week 52 have been completed and were submitted as part of the procedure. Over 80% of patients completed 52 weeks of follow-up.

In the 36-week placebo-controlled phase, the occurrence of AEs was lowest in the placebo group and numerically higher in the baricitinib 2-mg and 4-mg groups (57% versus 61% versus 63%). SAEs occurred less in the placebo group and more frequently in the baricitinib 2-mg and 4-mg groups (1.6% versus 2.2% versus 2.6%). The number of patients who discontinued study drug or study due to AEs, varied from 1.6% - 2.2% over treatment groups. In the extended data set, the occurrence of AEs, severe AEs, SAEs and discontinuations comparing baricitinib 2-mg and 4-mg, was in line with the results of the placebo-controlled phase. No deaths had occurred.

In the placebo-controlled phase, most common AEs (≥2%) were more frequent in the baricitinib 4-mg group, and lest frequent in the placebo group, with some exceptions. Common AEs that were numerically more frequent in baricitinib treatment groups included (placebo versus 2-mg versus 4-mg): upper respiratory tract infections (7.0% vs 6.6% vs 7.6%) and viral upper respiratory tract infections (1.6% vs 2.2% vs 1.5%), nasopharyngitis (5.1% vs 4.4% vs 6.9%), headache (5.4% vs 5.5% vs 6.7%), acne (1.1% vs 5.8% vs 5.6%), blood CPK increased (1.3% vs 0.8% vs 4.3%), urinary tract infection (1.6% vs 3.8% vs 3.3%), influenza (1.9% vs 1.6% vs 2.6%), fatigue (1.1% vs 0.8% vs 2.2%), folliculitis (0.8% vs 1.4 vs 2.2%), nausea (1.6% vs 2.7% vs 2.0%) and vulvovaginal candidiasis (0% vs 2.6% vs 1.2%). Of these AEs, upper respiratory tract infections, urinary tract infections, headache, nausea, acne, CPK increased, are known ADRs of baricitinib. Serious infections are an important potential risk of baricitinib. Increases of liver enzymes (ALT ≥3 x ULN and AST ≥3 x ULN) also are a known ADR, but DILI is not.

Fractures were the most frequently reported SAE for baricitinib-treated patients. In the placebo-controlled period, there were 3 fractures reported in the placebo group, fractures in 8 patients in the baricitinib 2-mg group and in 7 patients in the baricitinib 4-mg group. In the extended data set, 11 patients on 2-mg (3.0%) and 12 patients on 4-mg (2.2%) of baricitinib reported fractures. It is concluded that fractures must not be considered an ADR of baricitinib. The main reasons are that: in the RA and AD data there were no differences between baricitinib-treated and placebo-treated patients in occurrence of fractures; in RA, AD and AA there was no suggestion of a dose-response effect; in RA, AD and AA the IR's at follow-up were similar to the IR's of the placebo-controlled phase suggesting no increment in frequencies; the IR's for fractures in the RA, AD and AA trials did not seem to exceed the background risk. Further, from a non-clinical part of view, there are no concerns that baricitinib would cause fractures in adults.

There were no large differences between placebo and baricitinib treatment groups for overall Treatment-Emergent infections, serious infections, temporary interruptions, and permanent discontinuations of study drug due to infections. However, in the placebo-controlled period, there was a higher frequency of folliculitis with baricitinib 2-mg (1.4%) and baricitinib 4-mg (2.2%) compared to placebo (0.8%); vulvovaginal candidiasis occurred more frequently in the baricitinib 2-mg and 4-mg treated groups as compared to placebo (2.6% vs 1.2% vs 0%). While folliculitis in AA can be viewed as condition-specific ADR, it is considered unlikely that the occurrence of folliculitis will be a limiting factor for many patients. At the CHMP's request, "folliculitis" was added to the table of adverse reactions in Section 4.8 of the SmPC with a frequency "common". Vulvovaginal candidiasis did not appear as potential ADR in RA and AA data. Therefore, it is considered that the higher occurrence of vulvovaginal candidiasis in females with AA on baricitinib, as compared to placebo, is likely to be explained by chance.

Regarding Hepatobiliary disorders, there was one SAE of acute cholecystitis in the placebo group and two in the baricitinib groups, with an additional SAE of acute hepatitis in the extended BARI data set.

In the SOC for Cardiac disorders, there were 4 SAEs reported: ventricular tachycardia, acute myocardial infarction, congestive cardiac failure, aortic valve insufficiency, in the baricitinib groups and none in the placebo group.

There were two SAEs of Venous thrombotic events (Pulmonary embolism or Deep vein thrombosis) in the extended/all BARI data sets, which are known ADRs of baricitinib. Both patients had multiple risk factors for VTE.

The number of malignancies (n=3) and NMSC (n=2) in the AA programme was small in patients exposed to baricitinib for up to 2.5 years in the All BARI AA analysis set. In the placebo-controlled period, one event of prostate cancer occurred with placebo and 1 event of B-cell lymphoma occurred with baricitinib 4-mg.

Regarding laboratory values: haematologic changes (neutrophil count decreased, lymphocyte count decreased, haemoglobin level decreased, and platelet count increased) and blood lipid changes (hyperlipideamia but no hyper-triglyceridaemia), CPK increased, ALT/AST increased are in line with what is known about baricitinib.

3.5. Uncertainties and limitations about unfavourable effects

To reduce lengthy exposure, a stop of treatment with baricitinib in case of maintained good response could be considered. However, stopping baricitinib in case of maintained good response seems not advisable based on the efficacy results of the stop study since a majority of patients lost response within 24 weeks after discontinuation. On the other hand, considering the safety profile of baricitinib, the exposure should be reduced when possible. At the CHMP's request, Section 4.2 of the SmPC was updated to include the following guidance which was considered acceptable to the CHMP: *"Once a stable response has been achieved, it is recommended to continue treatment for at least several months, in order to avoid relapse. The benefit risk of treatment should be re assessed at regular intervals on an individual basis."*

A review of JAK inhibitors in the treatment of inflammatory disorders has been initiated at the request of the European Commission (EC) under Article 20 of Regulation (EC) No 726/2004 and is currently on-going.

3.6. Effects Table

Table 44 ***Effects Table for baricitinib in treatment of Alopecia Areata***

Effect	Short description	Unit	Placebo	Baricitinib 2-mg QD	Baricitinib 4-mg QD	Uncertainties / Strength of evidence	References
			N=345	**N=340**	**N=515**		
	Favourable Effects						
SALT ≤20 (primary endpoint)	Severity of Alopecia Tool	%	4.1	19.7	34	**SoE:** p<0.001 in both 2-mg and 4-mg groups, results for SALT<10; almost complete coverage of the scalp by hair, in line; 2.3, 11.8, 24.9 for PL, B 2-mg, B 4-mg (p<0.001). **Unc**: study ongoing	pooled data of the 36-week placebo-controlled period of JAHO (only phase3 portion) and JAIR
PRO for Scalp Hair Assessment	0 or 1 with ≥2-point improvement	%	4.5	16	33.7	**SoE**: p<0.001 in both 2-mg and 4-mg groups, results for ClinRO for EB hair loss and ClinRO for EL hair loss, in line; EB p<0.001 in both 2-mg and 4-mg groups, EL p<0.001 in 4-mg group **Unc:** study ongoing	
	Unfavourable Effects			**N=371**	**N=365**	**N=540**	
(Viral) Upper respiratory tract infections		%	8.6	8.8	9.1	**SoE:** placebo controlled period completed with ~10% drop-outs. **Unc:** 2 cases of VTE occurred after 52 weeks of exposure. **Unc:** candidiasis did not occur as ADR in RA and AD. **Unc**: only 2% of patients were >65 years of age.	BARI AA PC: pooled data of the 36-week placebo-controlled period of JAHO (both phase 2 and phase 3 portions) and JAIR
Urinary tract infections		%	1.6	3.8	3.3		
Candidiasis		%	0	2.6	1.2		
Investigations	Laboratory	%	5.1	7.1	12		
VTE		%	0	0	0		
Malignancies	Without NMSC	%	0.3	0	0.2		

Abbreviations: EL= Eyelashes; EB = Eyebrows; TEAE = treatment-emergent Adverse Events; SAE = treatment-emergent Serious Adverse Event; VTE = Venous thrombotic event.Notes:

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Favourable effects

There are limited treatment options available for the management of severe AA. No centrally approved medication is authorized in the EU.

Baricitinib is the first JAK inhibitor to be considered for an AA indication. The primary outcome (SALT ≤ 20 at week 36) was met ($p<0.001$) in both baricitinib treatment groups (both 4-mg and 2-mg dosing regimens). A higher clinically relevant and statistically more robust treatment effect was observed in baricitinib 4-mg as compared to baricitinib 2-mg, supported by key secondary endpoints.

The onset of treatment effect was between 8-24 weeks and continues to improve.

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. A minimum of 30% of hair growth was needed to meet the primary endpoint in each patient. This outcome was considered to be clinically relevant in severe AA by patients and physicians who were panellists in the development of SALT. Patient satisfaction with the treatment result was not directly assessed in the pivotal trials but is supported to some extent by the changes in emotional and functional subscales of Skindex and the anxiety and depression subscales of the HADS.

Hair loss is generally more important in women (they need a denser hair growth for cosmetically acceptable hair than men). In subgroup analysis, the primary endpoint (SALT scores under 20) was met for both men and women. Skindex and HADS measures showed comparable results for female subjects and in some domains such as depression, better outcomes were observed in women.

Long-term efficacy has been established as the response rate improves to 39% for 4-mg doses at week 52. Predictor analysis shows that 21% of patients are late responders. 74% of the responders in 4-mg group still showed response after down titration to 2-mg. 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.

Unfavourable effects

From the description of baseline characteristics of patients with severe AA included in the trials (JAHO and JAIR), it appears that these are relatively younger patients than patients with RA. Although the occurrence of SAEs was low, these play a major role in the appraisal of Benefit/Risk in this patient group. The 52-week safety data for baricitinib 2-mg and 4-mg were updated during the procedure; the safety results were in line with the results of the placebo-controlled phase.

AEs and SAEs were only slightly higher for baricitinib 2-mg and 4-mg compared to placebo; SAEs and discontinuations due to an AE were infrequent. Few patients discontinued study drug or study due to AEs, suggesting good tolerability of baricitinib in people with AA. The safety data are consistent with the known safety profile of baricitinib for the approved indications, including infections, headache, nausea, acne, increased CPK, increased ALT/AST, increased blood lipids. VTE did not occur, malignancies and MACE occurred in single cases. These data overall are indicative of an acceptable safety profile.

However, the safety profile of baricitinib is complicated and includes several ADRs concerning laboratory values, most notably of blood lipids, CPK, ALT/AST, of which the long-term results are not exactly clear. It is of relevance from the safety perspective (malignancy, MACE, VTE, infections, …) to

avoid unnecessary long-term exposure in relatively young people. During the procedure therefore, proposals for the SmPC regarding when to stop treatment in case of non-response and when to reduce the dose in case of good response were included at the CHMP's request, similar to what was done for RA and AD.

Folliculitis appears to be a condition-specific ADR for AA. As folliculitis usually occurs in areas of growing hair, maybe due to mechanical irritation at the follicle-site. At the CHMP's request, it was added to the table of adverse reactions in Section 4.8 of the SmPC.

3.7.2. Balance of benefits and risks

The primary endpoint was met in both pivotal studies, which was supported by key secondary endpoints. The 4-mg dose was more effective than the 2-mg dose, but also, the lower dose can be considered more effective than placebo. Primary and secondary outcomes support the clinical relevance of the treatment effect. The long-term efficacy of baricitinib until week 52 data has been demonstrated.

Dosing recommendations for stopping in case of non-response and down-titration in maintaining a good response were included in the SmPC at the CHMP's request. However, a treatment stop in case of maintained good response will lead to a loss of response in a considerable portion of patients. Therefore, the SmPC recommendation for regular benefit-risk assessment for stopping treatment on an individual basis by the treating physician is endorsed.

The safety profile of baricitinib is overall positive. AEs and SAEs were only slightly higher for baricitinib 2-mg and 4-mg compared to placebo. SAEs and discontinuations due to an AE were infrequent. The safety data are consistent with the known safety profile of baricitinib for the already approved indications including infections, headache, nausea, acne, increased CPK, increased ALT/AST, increased blood lipids. VTE, malignancies, and MACE occurred in single cases. No new safety signals that impact Benefit/Risk were identified in the treatment of adult patients with severe AA.

3.7.3. Additional considerations on the benefit-risk balance

EMA's safety committee, PRAC, has started a review of the safety of Janus kinase (JAK) inhibitors used to treat several chronic inflammatory disorders (rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, ulcerative colitis and atopic dermatitis). Olumiant is part of the products reviewed in the on-going referral. The review of JAK inhibitors in the treatment of inflammatory disorders has been initiated at the request of the European Commission (EC) under Article 20 of Regulation (EC) No 726/2004.

The recommendation on the present application is without prejudice to the final conclusions of the ongoing referral procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data.

3.8. Conclusions

The overall B/R of Olumiant is positive in the following indication:

"Alopecia areata: Baricitinib is indicated for the treatment of severe alopecia areata in adult patients (see section 5.1)."

4. Recommendations

Outcome

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

Variations accepted		**Type**	**Annexes affected**
C.I.11.z	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	Type IB	None
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Grouping of the following variations:
C.I.6 - Extension of indication to include treatment of severe alopecia areata in adult patients for Olumiant; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Changes were also made to the PI to bring it in line with the current Agency/QRD template. Version 12.3 of the RMP has been adopted.
C.I.11.z - Update of RMP (version 12.1) to change the category 3 study PASS I4V-MC-B011 end of data collection for the Atopic Dermatitis cohort from 'December 2026' to 'December 2027' and the subsequent final study report milestone from 'December 2027' to 'December 2028'.

This recommendation is without prejudice to the final conclusions of the ongoing referral procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data.

Amendments to the marketing authorisation

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

5. EPAR changes

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

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion "Olumiant EMEA/H/C/004085/II/0029/G".

Attachments

1. SmPC and Package Leaflet (changes highlighted) as adopted by the CHMP on 19 May 2022.