17 September 2020
EMA/520470/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Olumiant

International non-proprietary name: baricitinib

Procedure No. EMEA/H/C/004085/II/0016

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

Acronym or Term	Definition
1-mg	the baricitinib 1-mg group
2-mg	the baricitinib 2-mg group
4-mg	the baricitinib 4-mg group
AD	atopic dermatitis
ADR	adverse drug reaction
ADSS	Atopic Dermatitis Sleep Scale
AE	adverse event
All BARI AD	Safety analysis set that includes all AD patients exposed to any dose of baricitinib
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BARI 2-mg AD PC	Safety analysis set comparing baricitinib 2-mg and placebo
BARI 4-mg AD PC	Safety analysis set comparing baricitinib 4-mg and placebo
BARI 2-mg AD PC vs. 4-mg AD PC	Safety analysis set comparing baricitinib 2-mg and 4-mg
BSV	between-subject variability
CHMP	Committee for Medicinal Products for Human Use
CL/F	apparent total clearance of the drug from plasma after oral administration
Cmax	maximum (or peak) serum concentration
CPK	creatinine phosphokinase
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DLQI	Dermatology Life Quality Index
DVT	deep vein thrombosis
EASI	Eczema Area and Severity Index
EASIXX	an XX% reduction from baseline in EASI score
EMA	European Medicines Agency
EU	European Union
Ext BARI 2-mg and 4-mg AD	Safety analysis set comparing baricitinib 2-mg and 4-mg for the Extended Period, data censored at dose change in Study JAHN

HADS	Hospital Anxiety Depression Scale
HDL	high-density lipoprotein
HOME	Harmonising Outcomes Measures in Eczema
IGA	Investigator's Global Assessment. In the baricitinib AD clinical programme, this is the vIGA-ADTM.
IL	interleukin
IR	incidence rate
ITT	intent-to-treat
JAHG	Study I4V-MC-JAHG
JAHL	Study I4V-MC-JAHL
JAHM	Study I4V-MC-JAHM
JAHN	Study I4V-MC-JAHN
JAIN	Study I4V-MC-JAIN
JAIW	Study I4V-MC-JAIW
JAIX	Study I4V-MC-JAIX
JAIY	Study I4V-MC-JAIY
JAK	Janus kinase
LDL	low-density lipoprotein
MACE	major adverse cardiovascular events
MCID	minimal clinically important difference
NMSC	non-melanoma skin cancer
NRS	numeric rating scale
PBI	Patient Benefit Index
PE	pulmonary embolism
PK	pharmacokinetics
Pooled Phase 3 monotherapy population	Efficacy analysis set that included pooled data from the monotherapy Studies JAHL and JAHM. Primarily used for subgroup analyses.
pooled RA/AD	Safety dataset which includes all RA and AD patients treated with baricitinib in a 16-week placebo-controlled period. This dataset was used for the frequency of ADRs.
PRO	patient-reported outcomes
PROMIS	Patient-Reported Outcomes Measurement Information System
pSTAT	phosphorylated signal transducer and activator of transcription

pSTAT3	phosphorylated signal transducer and activator of transcription 3
PSUR	periodic safety update report
QoL	quality of life
RA	rheumatoid arthritis
RMP	risk management plan
SAE	serious adverse event
SCE	Summary of Clinical Efficacy Module 2.7.3
SCORAD	SCORing Atopic Dermatitis
SCORAD75	a 75% reduction from baseline in SCORAD score
SCS	Summary of Clinical Safety Module 2.7.4
SmPC	Summary of Product Characteristics
SOC	system organ class
STAT	signal transducer and activator of transcription
t1/2	elimination half life
TCI	topical calcineurin inhibitors
TCS	topical corticosteroids
TE	treatment-emergent
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
URTI	upper respiratory tract infection
V/F	apparent volume of distribution
VTE	venous thromboembolism

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eli Lilly Nederland B.V. submitted to the European Medicines Agency on 25 November 2019 an application for a variation.

The following variation was requested:

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

Extension of Indication to include a new indication in the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy for Olumiant; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 of the SmPC are updated.
The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.
Minor editorial changes were brought to the Labelling. Furthermore, the Annex II is brought in line with the latest QRD template version 10.1.
The RMP version 8.1 has also been submitted.

The variation requested amendments to the Summary of Product Characteristics, Annex II, Labelling 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/0239/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0239/2019 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 received Scientific Advice from the CHMP on 15 December 2016 (EMA/CHMP/SAWP/811151/2016). The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Bart Van der Schueren

Timetable	Actual dates
Submission date	25 November 2019
Start of procedure:	28 December 2019
CHMP Co-Rapporteur Assessment Report	21 February 2020
CHMP Rapporteur Assessment Report	21 February 2020
PRAC Rapporteur Assessment Report	2 March 2020
PRAC members comments	4 March 2020
PRAC Outcome	12 March 2020
CHMP members comments	16 March 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	19 March 2020
Request for supplementary information (RSI)	26 March 2020
MAH submission of responses	27 April 2020
CHMP Rapporteur Assessment Report	13 May 2020
CHMP members comments	18 May 2020
2nd Request for supplementary information (RSI)	28 May 2020
MAH submission of responses	22 June 2020
CHMP Rapporteur's preliminary assessment report circulated on	7 July 2020
CHMP members comments	13 July 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	17 July 2020
3rd Request for supplementary information (RSI)	23 July 2020
MAH submission of responses	17 August 2020
CHMP Rapporteur's preliminary assessment report circulated on	02 September 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	11 September 2020
Opinion	17 September 2020

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Atopic Dermatitis (AD) (eczema) is a chronic relapsing, pruritic, inflammatory skin disease that occurs most frequently in children but also occurs in adults. While in children, most cases of AD spontaneously resolve, AD can persist or start in adulthood (Thomsen 2014). It is estimated that in Europe, 2% to 7% of adults have AD and the proportion of adults with moderate to severe AD is estimated at 30%, with 1 in 4 adults with AD reporting adult-onset of the disease (Sacotte and Silverberg 2018; Diepgen et al. 2016; Bieber and Straeter 2015). The pathomechanism of AD includes skin barrier defects, immune dysregulation, and genetic predisposition (Boguniewicz and Leung 2011). The main manifestations of AD are eczematous skin lesions, itch, skin pain, sleep disturbances, and other atopic conditions such as asthma and allergic rhinitis (Silverberg 2018). Itch is the central and debilitating manifestation. AD may lead to difficult to control scratching and superimposed skin inflammation and infections, sleep disturbances, functional impairment and mental distress, feelings of anxiety and depression (Jeon et al. 2017, Yu et al. 2016, Thyssen et al. 2019, Boguniewicz et al. 2017, Thyssen et al. 2018, Ronnstad et al. 2018).

Management

The aim of medical treatment of AD is symptomatic, to bring signs and symptoms of AD under control (Wollenberg et al. 2018). Patients with mild disease are generally managed with emollients and mild- to moderate-potency topical corticosteroids (TCS). Topical calcineurin inhibitors are considered as an alternative or adjunct treatment to TCS, especially when treatment with TCS is either inadvisable or not possible and when steroid-sparing treatment is needed in sensitive areas, such as face and skin folds. However, patients with moderate to severe AD require additional therapies to control their skin inflammation and alleviate the most bothersome symptoms. These additional therapies include phototherapy, high-potency TCS, and, eventually when topical options fail to control the disease, systemic treatments.

Currently, 2 systemic therapies are approved for patients with moderate to severe AD:

- ciclosporin (an oral systemic agent approved only for severe patients), and
- dupilumab (SC injection).

Ciclosporin is only approved for patients with severe AD and due to its safety profile, it is recommended for intermittent use (Ciclosporin SmPC). Dupilumab is approved for patients with moderate and severe AD; the most common side effects, when used in treatment of AD, are injection-site reactions (≥10%), conjunctivitis and blepharitis (Dupixent EPAR).

Staquis (an ointment with a PDE-4 inhibitor) was recently approved for treatment of mild to moderate atopic dermatitis in adults and paediatric patients from 2 years of age with ≤ 40% body surface area (BSA) affected.

Other therapies are not centrally authorised but are approved in individual member states and recommended by AD treatment guidelines (Wollenberg et al. 2018):

- Oral glucocorticosteroids are intended for severe AD (Wollenberg et al. 2018).
- PUVA is intended for severe AD (Wollenberg et al. 2018).

Non pharmacological approaches are recommended in moderate to severe AD according to AD treatment guidelines (Wollenberg et al. 2018).

In addition to approved therapies, current AD guidelines and expert advice recommend off-label use of other oral therapies, such as systemic corticosteroids, methotrexate, azathioprine, and mycophenolate mofetil (Wollenberg et al. 2018b).

The MAH submitted an application for a new indication in "the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy".

2.1.2. About the product

Baricitinib (Olumiant) is a Janus Kinase inhibitor with selectivity for JAK2 and JAK1, and less potency for JAK3 or TYK2. The JAKs and their associated signal transducers and activators of transcription (STATs) are the major intracellular pathway that controls the magnitude and duration of signalling for cytokines that bind to Type I and Type II cytokine receptors. These receptors lack intrinsic enzymatic activity capable of mediating signal transduction; so receptor-associated STATs are instead phosphorylated by JAKs, resulting in STAT activation. Activated STATs are active transcription factors and drive the expression of multiple genes important for cell activation, localisation, survival, and proliferation.

Baricitinib has a low potency for JAK3. JAK3 may be more associated with the common gamma chain receptor, than the other JAKS. The common gamma chain cytokines include IL-15 and IL-21, which regulate lymphocyte activation, function, and proliferation.

For patients with moderate to severe AD for whom treatment with TCS and or TCIs and/or systemic therapies is insufficient, treatment options are limited and therefore there is a need for new treatment options. An advantage for patients with moderate to severe AD may be that baricitinib is taken orally once daily, where dupilumab is administered by sc injection every-other-week.

The JAK-STAT pathway is a major signal transduction pathway for several pro-inflammatory cytokines involved in the pathogenesis of AD, such as thymic stromal lymphopoietin, IL-4, IL 5, IL 13, IL-22, and IL-31 (Brunner et al. 2017). Thus, interruption of JAK1 and JAK2 pathways by baricitinib could have therapeutic effects on signs and symptoms of AD.

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

The MAH received Scientific advice from the CHMP on 15 December 2016 (EMA/CHMP/SAWP/811151/2016). The Scientific advice pertained to non-clinical and clinical aspects of the dossier.

The main clinical points of the advice were:

- The strategy for dose-finding including the ongoing phase 2 study (JAHG) with 2 mg and 4 mg was agreed.
- Besides studying baricitinib as monotherapy, it should also be studied in combination with TCS

and with TCI, as otherwise it will be difficult to judge the potential benefit of baricitinib in clinical practice.
- The appropriate target population is patients with an insufficient response to topical treatments, which should be well documented. Inclusion of patients with moderate and severe AD is acceptable.
- Rescue treatment should be provided in the pivotal studies and indication for rescue should be appropriately standardised.
- The sub-studies in the maintenance study, on randomised withdrawal and on lower-dose maintenance treatment, are welcomed, and also the possibility to assess late (after 16 weeks) response in initial non-responders.
- IGA score 0 or 1 with a ≥2 point improvement from baseline is acceptable as the primary endpoint, while it would be expected that EASI 75 or SCORAD is a co-primary or key secondary endpoint.
- The use of PROs is welcomed. If they are not validated, the Applicant is encouraged to use this development program to validate the proposed PRO.

The MAH implemented nearly all recommendations from the scientific advice.

Notably, use of baricitinib with TCS while allowing for concomitant TCIs was evaluated in an additional study (JAIY).

While the inclusion of an active comparator (e.g. ciclosporin) was suggested in the advice, the MAH chose not to. The reasoning by the MAH was mainly that the only widely approved systemic treatment is ciclosporin, which is indicated for severe AD only while baricitinib is intended for moderate and severe AD. Further, it was put forward that ciclosporin has side effects making dose adaptations/intermittent use necessary [ciclosporin SmPC]. This can be understood. Meanwhile, dupilumab had been approved for moderate to severe AD, and the MAH provided an indirect comparison with dupilumab clinical trials in the submission. Further, a study in AD patients with insufficient response to ciclosporin was added to the clinical programme in response to advice by HTA agencies. This study has meanwhile been finalised and was submitted upon CHMP request during this application.

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

Summary of Environmental Risk Assessment for the Use of Baricitinib in Europe

Baricitinib was approved in the European Union in 2017 for the treatment of moderate to severe rheumatoid arthritis. An environmental risk assessment was submitted as part of the initial marketing authorisation application. The current Type II variation application is for a proposed new indication (atopic dermatitis). An updated environmental risk assessment has been provided that considers environmental exposure due to both the original and proposed indications. The environmental data previously submitted with the initial dossier serves as the basis for the updated environmental risk assessment.

Data from environmental chemistry, fate and toxicity studies and predictions of concentrations in the environment were considered to evaluate the risk to the environment from the therapeutic use of baricitinib in humans in Europe. Physical-chemical properties and fate characteristics indicate that

baricitinib will not persist in the aqueous environmental compartment since it undergoes some removal by binding to sludge biosolids during sewage treatment and by partitioning to sediment once in the water column. The concentrations of baricitinib in sediment would be very low. Baricitinib is subject to some removal from the sediment compartment through biodegradation and irreversible binding to sediment particles. The rate of removal is slow and, therefore, there is some potential for persistence of low concentrations in aquatic sediment. Using assumptions of no metabolism, no removal during sewage treatment, and 1% of the European population taking the maximum dose, the maximum predicted environmental concentration of total baricitinib residue in surface water is 0.04 µg/L and in sediment is 152 µg/kg (dry weight). Studies to evaluate both acute and chronic effects on environmental species have been conducted with baricitinib. Fish was the most sensitive species tested. The predicted no-effect concentrations (PNECs) of baricitinib for surface water, groundwater, and sewage microorganisms were 60, 210, and 100000 µg/L, respectively. The PNEC for sediment was 27150 µg/kg. The predicted environmental concentrations of total residues of baricitinib are significantly lower than the PNEC values. Therefore, excretion by humans of baricitinib and its metabolites is not expected to result in a significant environmental risk to aquatic organisms. Baricitinib is not expected to bioaccumulate in aquatic organisms and it does not meet the criteria for classification as a toxic to aquatic organisms. Therefore, baricitinib is not classified as a PBT molecule.

Summary of main ERA study results (including updated values)

Table 1 ***Summary of main ERA study results (including updated values)***

Substance (INN/Invented Name): baricitinib			
CAS-number (if available): 1187594-09-7			
PBT-screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	1.4 (pH 5) 1.4 (pH 7) 1.5 (pH 9)	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	1.4 (pH 5) 1.4 (pH 7) 1.5 (pH 9)	not B
Persistence	DT50	DT_{50} water: 22.8/50.7 d DT_{50} system 349/279 d	Results obtained in two river systems; DT_{50} values corrected to 12°C. Conclusion: vP
Toxicity	NOEC algae NOEC crustacea NOEC fish	3.1 mg/L 2.1 mg/L 0.6 mg/L	not T
	CMR	toxicity to reproduction observed	potentially T
PBT-statement:	baricitinib is not PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surface\ water}$, default F_{pen}	0.04	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)

Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 16 952 L/kg (soil) K_{oc} = 13 250 L/kg (soil) K_{oc} = 36 083 L/kg (soil) K_{oc} = 371 L/kg (sludge) K_{oc} = 276 L/kg (sludge)			Geomean used in risk assessment: $K_{oc,soil}$ of 20 087 L/kg, and $K_{oc,sludge}$ of 320 L/kg.
Ready Biodegradability Test	OECD 301				Not available, but can be waived because OECD 308 is submitted.
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT_{50} water: 10.8/24.0 d DT_{50} system 165/132 d Compound (including NER) shifts to sediment, 80.6 to 88.8% over the duration of the test			Results obtained in two river systems; sediment risk assessment triggered
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Pseudokirchneriella subcapitata*	OECD 201	NOEC	3100	µg/L	growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	2100	µg/L	mortality and reproduction
Fish, Early Life Stage Toxicity Test/*Pimephales promelas*	OECD 210	NOEC	600	µg/L	growth
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	$\geq 10^6$	µg/L	respiration
Phase IIb Studies					
Sediment dwelling organism/*Chironomus riparius*	OECD 218	NOEC	≥2570	mg/kg	normalised to 10% o.c.

2.2.2. Discussion on non-clinical aspects

During the initial procedure at MAA, a full ERA of baricitinib was submitted, including the determination of physical-chemical properties, Phase I and II fate studies. The MAH has now, based on the new indication, recalculated the PECsw, which increased from 0.02 µg/L to 0.04 µg/L. The new PECsw exceeds the Phase I action limit of 0.01 µg/L. However, as this was already the case at the initial (first) indication at MAA, no additional ERA studies have to be performed. In addition, other PEC parameters, like groundwater, sediment and sewage treatment plant, changed, but this did not lead to a different conclusion on the low environmental risk of the use of baricitinib. Therefore, the initial conclusion as stated below, is maintained.

Baricitinib is neither PBT nor vPvB. Considering the above data and the environmental risk assessment, baricitinib is not expected to pose a risk to the surface water and groundwater compartment and the sewage treatment plant. The revised values in the above table "Main ERA study results" have been endorsed by the CHMP.

2.2.3. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of baricitinib. Considering the above data, baricitinib is not expected to pose a risk to the environment.

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

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

Table 2 ***Overview of Study Designs for Studies JAHG, JAHL, JAHM, JAIY, and JAHN***

	Study JAHG	Study JAHL	Study JAHM	Study JAIY	Study JAHN
N	124	624	615	329	1081, plus 211 patients from 2-mg OL addendum
Phase	2	3	3	3	3
Treatment	• Placebo (N=49) • BARI 2-mg (N=37) • BARI 4-mg (N=38)	• Placebo (N=249) • BARI 1-mg (N=127) • BARI 2-mg (N=123) • BARI 4-mg (N=125)	• Placebo (N=244) • BARI 1-mg (N=125) • BARI 2-mg (N=123) • BARI 4-mg (N=123)	• Placebo (N=109) • BARI 2-mg (N=109) • BARI 4-mg (N=111)	• Placebo (N=52) • BARI 1-mg (N=45) • BARI 2-mg (N=616[a]) • BARI 4-mg (N=579)
Baseline Randomization Ratio	4:3:3	2:1:1:1	2:1:1:1	1:1:1	1:1[b]
Background TCS[c]	Moderate-potency: Triamcinolone 0.1%	No	No	Moderate- and low-potency	Moderate- and low-potency provided; Other higher potency TCS allowed.
AD Treatment History	IR to TCS	IR or IT to moderate- or higher potency TCS	IR or IT to moderate- or higher potency TCS	IR to moderate- or higher potency TCS	IR or IT to moderate- or higher potency TCS
Treatment Period	16 weeks	16 weeks	16 weeks	16 weeks	104 weeks
Primary Endpoint	Proportion of patients achieving EASI50 at Week 16	Proportion of patients achieving IGA of 0 or 1 with a ≥2-point improvement at Week 16	Proportion of patients achieving IGA of 0 or 1 with a ≥2-point improvement at Week 16	Proportion of patients achieving IGA of 0 or 1 with a ≥2-point improvement at Week 16	Proportion of patients achieving IGA of 0 or 1 assessed at Weeks 16, 36 and 52
LTE	NA	Study JAHN	Study JAHN	Study JAHN	NA
Status	Complete	Complete	Complete	Complete	Ongoing
Study Location	US and Japan	EU, Japan, ROW	EU, Japan, ROW	EU, Japan, ROW	EU, Japan, ROW

Abbreviations: AD = atopic dermatitis; BARI = baricitinib; EASI = Eczema Area and Severity Index; EU = European Union; IGA = Investigator's Global Assessment; IR = inadequate response; IT = intolerance; LTE = long-term extension; N = number of patients randomized in the study, or for whom data were available as of the data cut-off date; NA = not applicable; OL = open label; ROW = rest of world; TCI = topical calcineurin inhibitor; TCS = topical corticosteroids; US = United States.

[a] Includes patients in the 2-mg open-label addendum.

[b] Nonresponders who received placebo, baricitinib 1-mg or 2-mg in the originating study were randomized 1:1 to baricitinib 2-mg or 4-mg.

[c] TCIs or the topical phosphodiesterase 4 inhibitor crisaborole, where approved, were permitted in place of TCS. More details are provided in SCE Section 2.7.3.1.3.3.

In addition, Study JAIN is a Phase 3 study investigating the efficacy and safety of baricitinib in patients who experienced failure with ciclosporin or are intolerant to or have a contraindication to ciclosporin.

Similar to Study JAIY, patients in Study JAIN are permitted to use low- and moderate-potency TCS as concomitant therapy throughout the study.

2.3.2. Pharmacokinetics

At time of MAA for rheumatoid arthritis, the pharmacokinetics of baricitinib were investigated in 27 clinical *in vivo* PK studies after single (1-40 mg) and repeated dosing (up to 20 mg once daily for 10 days, up to 15 mg once daily for 28 days, and up to 10 mg daily for 28 days). In addition, several *in vitro* studies with human biomaterials were performed to determine protein binding, metabolism, and the potential for baricitinib to cause DDIs.

Three additional pharmacokinetics studies (studies JAHG, JAHL and JAHM) were performed in patients with atopic dermatitis. Dosages of 1 mg, 2 mg and 4 mg once daily were investigated.

Analytical method

The analytical methodology employed liquid chromatography with tandem mass spectrometric detection (LC/MSMS) for analyses of baricitinib concentrations in plasma (method 8232103). The plasma samples were analysed at Covance Laboratories, Inc (Indianapolis, IN) which also measured plasma samples for the MAA of baricitinib for rheumatoid arthritis.

Table 3 Analytical method used for the analysis of baricitinib in patients with atopic dermatitis

method	linear range	accuracy	precision	dilution integrity	stability
8232103	0.20-2000 ng/mL	100.7-103.3%	2.0-3.8%	10×	RT = 48 h -20°C = 380 d -70°C = 583 d freeze-thaw-cycles = 5

Absorption

In the current application, the pharmacokinetics of baricitinib 1 mg, 2 mg, and 4 mg once daily have been investigated in patients with atopic dermatitis in three clinical studies (studies JAHG, JAHL and JAHM). The demographics are summarised in Table 4.

Table 4 Demographics of the patients with atopic dermatitis in studies JAHG, JAHL and JAHM

study	dose (mg)	gender	race	age (year)	body weight (kg)	BMI (kg/m^2)	eGFR ($ml/min/1.73m^2$)
JAHG	2 (n=37)	F=41%	22% Asian 24% African-American 54% Caucasian	40±14 (18-63)	78.8 (43.7-142)	27.9 (19.4-61.1)	106 (58.4-154)
	4 (n=38)	F=42%	5% other 24% Asian 24% African-American 47% Caucasian	36±15 (18-71)	78.8 (52.1-151)	27.1 (18.5-60.5)	110 (53.0-146)
JAHL	1 (n=127)	F=39%	11% other 31% Asian 58% Caucasian	36±12 (17-64)	74±17.2 (46.0-117)	25±4.6 (17.7-42.3)	106 (56.4-137)
	2 (n=123)	F=33%	11% other 28% Asian 61% Caucasian	35±14 (18-77)	75±17.7 (47.0-136)	25±5.1 (18.5-48.9)	108 (66.5-139)
	4 (n=125)	F=34%	11% other 33% Asian 56% Caucasian	37±13 (18-71)	74±17.2 (42.9-148)	25±4.3 (16.9-41.5)	106 (69.0-139)
JAHM	1	F=36%	3% other	33±10	75±17	26±5.2	110

(n=124)		29% Asian 68% Caucasian	(18-56)	(45.3-136)	(17.1-45.8)	(52.3-140)
2 (n=122)	F=47%	1% other 30% Asian 69% Caucasian	36±13 (18-77)	72±15 (45.0-120)	25±5.0 (17.1-48.9)	109 (62.4-138)
4 (n=123)	F=33%	2% other 31% Asian 67% Caucasian	34±14 (18-84)	73±15 (45.0-120)	25±4.2 (16.8-35.1)	107 (46.2-146)

Study JAHG is a Phase II randomised, double blind study to evaluate the efficacy and safety of baricitinib (2 mg and 4 mg once daily) versus placebo in combination with moderate potency topical corticoid steroid in patients with moderate to severe atopic dermatitis for a treatment period of 16 weeks. Baricitinib plasma concentrations were evaluated with sparse sampling approach (using a model previously validated for rheumatoid arthritis) and samples were obtained at Week 0 (pre-dose and 15-30 minutes after dosing), Week 4 (1.5-4 h after dosing), Week 8 (4-8 h after dosing), Week 12 (pre-dose), and Week 16 (30-90 minutes after dosing). A total of 311 PK samples from 75 patients characterised the PK in patients with moderate to severe atopic dermatitis. Only the AUC and C_{max} at steady state following a dose of 4 mg were provided. No information was provided following a dose of 2 mg. Furthermore, no information was provided on the clearance and half-life.

Study JAHL is a Phase III randomised, double blind study to evaluate the efficacy and safety of baricitinib (1 mg, 2 mg and 4 mg once daily) versus placebo in patients with moderate to severe atopic dermatitis for a treatment period of 16 weeks. Baricitinib plasma concentrations were evaluated with sparse sampling approach (using a model previously validated for rheumatoid arthritis) and samples were obtained at Week 0 (15 minutes and 1 hour post-dose), Week 4 (2 to 4 hour post-dose), Week 8 (pre-dose), Week12 (pre-dose), and Week 16 (4 to 6 hours post-dose). A total of 1956 PK samples from 375 patients characterised the PK in patient with moderate to severe atopic dermatitis.

Study JAHM is a Phase III randomised, double blind study to evaluate the efficacy and safety of baricitinib (1 mg, 2 mg and 4 mg once daily) versus placebo in patients with moderate to severe atopic dermatitis for a treatment period of 16 weeks. Baricitinib plasma concentrations were evaluated with sparse sampling approach (using a model previously validated for rheumatoid arthritis) and samples were obtained at Week 0 (15 minutes and 1 hour post-dose), Week 4 (2 to 4 hour post-dose), Week 8 (pre-dose), Week 12 (pre-dose), and Week 16 (4 to 6 hours post-dose). A total of 1855 PK samples from 369 patients characterised the PK in patients with moderate to severe atopic dermatitis.

The PK data from studies JAHG, JAHL and JAHM were used as input for the PopPK model for patients with atopic dermatitis to estimate the PK parameters of baricitinib in patients with atopic dermatitis. The PopPK analysis for patients with AD used the same PopPK model developed for the rheumatoid arthritis. A 2-compartment model with zero-order absorption and a partitioning of total CL/F into CL_r/F and CL_{nr}/F well described the PK of baricitinib in patients with atopic dermatitis. The model structure for CL/F was set up in this manner based on the knowledge that renal excretion represents the primary elimination route for baricitinib. The covariate retained in the final PopPK model was body weight on the volume term. The PK parameters obtained with the PopPK model are summarised in Table 5. Steady state $C_{max,ss}$ and $AUC_{\tau,ss}$ in patients with atopic dermatitis were 0.86-fold of those seen in patients with rheumatoid arthritis at the same dose based on PopPK modelling.

Table 5 PopPK parameter estimates in atopic dermatitis patients based on studies JAHG, JAHL and JAHM

dose (mg)	**$C_{max,ss}$ (ng/ml)**	**$C_{max,ss}$ (nM)**	**$AUC_{\tau,ss}$ (ng × h/mL)**	**$AUC_{\tau,ss}$ (nM × h)**	**V/F (L)**	**$t_{½}$ (h)**	**CL/F (L/h)**
4	45.9 (CV%=21)	124 (CV%=21)	415 (CV%=50)	1117 (CV%=50)	126 (CV%=17)	12.9 (CV%=36)	11.2 (CV%=33)

Previously, the pharmacokinetics of 2 mg and 5 mg baricitinib after repeated-dose once daily have been investigated in healthy subjects and patients with rheumatoid arthritis. In healthy volunteers, the absolute bioavailability after oral administration of baricitinib from the commercial tablet was ~79%.

The pharmacokinetics are summarised in Table 6 for healthy volunteers, Table 7 for patients with rheumatoid arthritis and Table 8 for patients with atopic dermatitis (per study).

Table 6 PK parameters of baricitinib after repeated oral dosing in healthy volunteers

dose (mg)	$C_{max,ss}$ (nM)	$AUC_{0-24,ss}$ (nM × h)	t_{max} (h)	$t_{½}$ (h)	study
2	46.3 (CV%=17)	318 (CV%=19)	1.4 ± 0.4	8.5 (CV%=21)	JADE
5	141 (CV%=27)	842 (CV%=17)	1.2 ± 0.5	7.4 (CV%=18)	JADE

Table 7 PK parameters of baricitinib after repeated oral dose in rheumatoid arthritis patients

dose (mg)	$C_{max,ss}$ (nM)	$AUC_{τ,ss}$ (nM × h)	study
2	65.6 (CV%=21)	615 (CV%=43)	JADW
2	70.2 (CV%=26	637 (CV%=45)	JADX
4	143 (CV%=20)	1220 (CV=46)	JADV
4	130 (CV%=19)	1140 (CV%=39)	JADW
4	138 (CV%=26)	1210 (CV%=47)	JADX
4	135 (CV%=23)	1280 (CV%=47)	JADZ

Table 8 PK parameters of baricitinib after repeated oral dosing in atopic dermatitis patients

dose (mg)	$C_{max,ss}$ (ng/ml)	$C_{max,ss}$ (nM)	$AUC_{τ,ss}$ (ng × h/mL)	$AUC_{τ,ss}$ (nM × h)	study
1	11.3 (CV%=21)	30.4 (CV%=21)	95.4 (CV%=36)	257 (CV%=36)	JAHL
1	11.3 (CV%=19)	30.4 (CV%=19)	99.1 (CV%=40)	267 (CV%=40)	JAHM
2	20.8 (CV%=27)	56.0 (CV%=27)	191 (CV%=48)	514 (CV%=48)	JAHG
2	21.9 (CV%=20)	59.0 (CV%=20)	175 (CV%=35)	471 (CV%=35)	JAHL
2	21.9 (CV%=19)	59.0 (CV%=20)	197 (CV%=43)	530 (CV%=43)	JAHM
4	42.0 (CV%=24)	113.1 (CV%=24)	366 (CV%=52)	985.4 (CV%=52)	JAHG
4	46.3 (CV%=20)	124.7 (CV%=20)	401 (CV%=46)	1080 (CV%=46)	JAHL
4	46.3 (CV%=18)	124.7 (CV%=18)	364 (CV%=37)	980 (CV%=37)	JAHM

Distribution

Based on previous data, baricitinib is a low-to-moderate permeable drug. The plasma protein binding of baricitinib is ~50% and was independent of the concentration. The blood-to-plasma ratio is 1.14, indicating weak/moderate association with the blood cell compartment. In healthy volunteers the volume of distribution is ~1.1 L/kg, indicating that baricitinib distributes from the plasma compartment into tissues. The V/F was 108 L (CV%=19) in patients with rheumatoid dermatitis.

In patients with atopic dermatitis, the V/F was 126 L (CV%=17) based on data from the three clinical PK studies.

Elimination

Based on previous data, absorbed baricitinib is mainly excreted via urine and predominately as parent compound. Baricitinib is metabolised to a limited extent both in vitro and in vivo. In vivo, only baricitinib was detected circulating in plasma. Total metabolites accounted for 4-7% of the dose in urine and ~1% in faeces. Overall, these data indicate that metabolism does not significantly contribute to the clearance of baricitinib. In healthy subjects, the total clearance ranged from 15-17 L/h and the renal clearance is ~13.4 L/h. The elimination half-life of baricitinib is ~10 h in healthy volunteers and

12.5 h in patients with rheumatoid arthritis. The elimination data indicate that baricitinib is actively excreted into urine. This is supported by the transporter studies where baricitinib was identified as a substrate for the transporters P-glycoprotein, OAT3 and MATE2-K which are involved in the active excretion into urine.

In patients with atopic dermatitis, the elimination half-life was 12.9 h based on the three clinical PK studies. Furthermore, the CL/F was 11.2 L/h and the renal clearance 8.02 L/h based on popPK.

Dose proportionality and time dependencies

Based on previous data, C_{max} and $AUC_{0-\infty}$ increased dose-proportional over a single dose range of 1 to 30 mg and a slightly more than dose-proportional increase is observed over the dose range 30 to 40 mg in healthy subjects. In rheumatoid arthritis patients, the C_{max} is dose proportional over a dose range of 2 to 15 mg baricitinib administered once daily. AUC is slightly less then dose proportional over a dose range of 2 to 15 mg baricitinib administered once daily, but dose proportional over the clinical dose range of 2 to 4 mg. Following multiple once-daily dosing over the range of 2 to 20 mg, baricitinib exposure at steady state increases slightly less than dose-proportional. After multiple once-daily dosing, steady state was reached between the second and third dose. Accumulation after repeated-dose administration of baricitinib is minimal; the accumulation ratio ranged from 0.89-1.25-fold and 1.02-1.24-fold based on C_{max} and AUC, respectively.

No new data was provided on the dose proportionality in patients with atopic dermatitis over the dose range of 1 mg to 4 mg.

Intra- and inter-individual variability

Based on previous data, the intra-individual variability in healthy subjects is low (<14%) and the inter-individual variability moderate (17-26%) in healthy subjects. In patients with rheumatoid arthritis, the inter-individual variability is 41% for the AUC and 22% for the C_{max}.

Based on the clinical PK data in patients with atopic dermatitis, the inter-individual variability was 50% for the AUC and 21% for the C_{max} in patients with atopic dermatitis.

Special populations

Previously, a reduction in baricitinib renal clearance and an increase in the AUC was observed with increased severity of renal impairment in healthy subjects. In patients with rheumatoid arthritis, a less pronounced effect of the renal function on the exposure of baricitinib was observed. This is consistent with a reduced fraction of excretion out of the total elimination pathways of baricitinib in patients with rheumatoid arthritis compared to healthy subjects. The systemic exposure to baricitinib in subjects with moderate hepatic impairment were comparable with subjects with normal hepatic function. The observed lack of hepatic function on the clearance of baricitinib is in-line with the renal clearance as the parent compound and that <10% of the dose is excreted as metabolite. In rheumatoid arthritis, body weight affects the PK of baricitinib; C_{max} decreased with increasing body weight. However, the effect of body weight on baricitinib PK is not considered clinically relevant and a higher dose is not recommended. Gender and race (American versus Japanese) were shown to have an effect (not clinically relevant) on the PK of baricitinib inpatients with rheumatoid arthritis. However, this is most likely caused by differences in body weight between the groups. The PK of baricitinib is similar across the age range of 19 to 83 years in patients with rheumatoid arthritis. The Erythrocyte Sedimentation

Rate (measure of disease state in rheumatoid arthritis patients) had an effect on the renal clearance of baricitinib but did not have a clinically significant effect on the exposure to baricitinib.

In patients with atopic dermatitis, body weight and renal function were also significant covariates for the PK. Age and race did not have an effect on the PK of baricitinib.

Pharmacokinetic interaction studies

No new DDI studies have been performed in patients with atopic dermatitis which was considered acceptable to CHMP. At the time of MAA for patients with rheumatoid arthritis, several DDI studies have been performed to identify clinically relevant DDIs with baricitinib as perpetrator and as victim.

Baricitinib as perpetrator

Based on *in vitro* data, it can be concluded that baricitinib is not a CYP inhibitor or inducer at clinically relevant concentrations. Furthermore, baricitinib is not an inhibitor of the transporters P-glycoprotein, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, OAT2, OAT3, MATE-1 and MATE2-K at clinically relevant concentrations. Baricitinib may be an inhibitor of OCT1 at maximal portal vein concentrations. Concomitant administration of baricitinib with drugs for which the rate limiting step is hepatic uptake by OCT1, may lead to an increase in C_{max}. In clinical DDI studies, the potential of baricitinib to affect the PK of oral contraceptives (via CYP3A), simvastatin (via CYP3A and OATP1B1), and digoxin (via P-glycoprotein) was investigated. The clinical DDI studies confirm the *in vitro* data that baricitinib is not an inhibitor or inducer of CYP3A and not an inhibitor of P-glycoprotein. Concomitant administration of baricitinib with simvastatin led to a (not clinically significant) decrease in AUC and C_{max} of simvastatin. The mechanism of action causing the observed decrease after concomitant administration of baricitinib (multiple dosing) with simvastatin is unknown.

In the clinical safety studies, an effect on the creatinine clearance was observed (decrease in creatinine clearance). Creatinine is cleared by the following transporters OCT2, OAT2, MATE1 and MATE2-K. Baricitinib was not an inhibitor of these transporters at clinically relevant concentrations. Therefore, the mechanism of action causing the observed decrease after concomitant administration of baricitinib on the creatinine clearance is unknown.

Baricitinib as victim

Baricitinib does not have an effect on the PK of methotrexate, a commonly concomitant prescribed drug, in Rheumatoid Arthritis patients.

In vitro and *in vivo* data indicate that less then 10% of the baricitinib dose is metabolised. Baricitinib is actively excreted by the transporters P-glycoprotein, BCRP, OAT3 and MATE2-K. In clinical DDI studies, the potential of other drugs to affect the PK of baricitinib was investigated. Co-administration of ketoconazole (strong CYP3A inhibition), fluconazole (strong CYP2C19 inhibition and moderate CYP2C9 and 3A inhibition), rifampicin (inducer via CAR/PXR of among others CYP3A and P-glycoprotein) and ciclosporin (P-glycoprotein inhibition) with baricitinib did not have a clinically relevant effect on the pharmacokinetics of baricitinib. A clinically significant interaction was observed when baricitinib was co-administered with probenecid (an OAT3 inhibitor). No other clinical DDI studies have been conducted with OAT3 inhibitors with less inhibition potential. The prodrug leflunomide rapidly converts to teriflunomide and teriflunomide is an inhibitor of OAT3 (furosemide exposure was increased in patients concomitantly taking teriflunomide and furosemide). Therefore, concomitant administration of baricitinib with leflunomide or teriflunomide may lead to an increase in baricitinib exposure. Concomitant use of ibuprofen and diclofenac will most likely have no clinically meaningful effect on the PK of baricitinib, since their inhibition potential for OAT3 is too weak. No studies were performed for inhibition of BCRP and MATE2-K. Complete inhibition of BCRP in the intestine may lead to a

bioavailability 100% which may result in an AUC increase of 1.25. This is considered clinically not relevant. Furthermore, the clinical significance of an interaction at MATE2-K would be minimised given the multiple exit routes of baricitinib from the proximal tubule cell. Maximal inhibition of MATE-2K will lead to a less than 2-fold increase in AUC of baricitinib, because other transporters can compensate for the lack of function. Therefore, inhibition of MATE-2K is likely not clinically relevant. Increase in gastric pH does not affect the overall exposure to baricitinib. Therefore, baricitinib may be co-administered with drugs that are gastric pH modifying agents.

2.3.3. Pharmacodynamics

Mechanism of Action

Baricitinib is an orally available JAK inhibitor with potency and selectivity for JAK1 and JAK2 and less potency for tyrosine kinase 2 or JAK3 (Fridman et al. 2010). The JAK-STAT pathway is a major signal transduction pathway for numerous pro-inflammatory cytokines involved in AD pathogenesis, such as thymic stromal lymphopoietin (TSLP), IL-4, IL 5, IL 13, IL-22, and IL-31 (Brunner et al. 2017). The cytokines signaling through the JAK-STAT pathway play a role in regulating many immune system responses that influence AD (Nomura and Kabashima 2016) such as:

- immune response, including exaggeration of T-helper 2 cell response (Boguniewicz and Leung 2011)
- activation of eosinophils
- epidermal chemokines
- proinflammatory cytokines
- mediators of itch (Bao et al. 2013)
- increased keratinocyte pSTAT3 levels (Lee et al. 2016; Mitamura et al. 2018), and
- barrier function abnormalities, such as decreased filaggrin levels (Thyssen and Kezic 2014).

Considering the numerous cytokines associated with AD pathogenesis, it is hypothesised that the interruption of JAK1 and JAK2 pathways by baricitinib would have significant therapeutic effects for both signs and symptoms of AD.

Primary Pharmacodynamics in AD

The overall pharmacodynamic properties and mechanism of action of baricitinib based on blood-based pharmacodynamics studies was described in the marketing authorisation application for RA. These studies show that baricitinib inhibits JAK1 and JAK2 activity thereby, interfering with the cytokine-mediated signaling through JAK1 and JAK2 phosphorylation, and the subsequent activation of STAT proteins. Upon phosphorylation, pSTAT translocates from the cytoplasm to the nucleus and activates transcription in many cells.

In order to evaluate the use of baricitinib in AD, 2 approaches were pursued to specifically assess the activity of baricitinib in the skin of AD patients and explore the mechanism of action of baricitinib in AD, namely:

- Skin biopsies: Elevated pSTAT3 levels are associated with increased inflammation in AD (Lee et al. 2012; Lee et al. 2016; Mitamura et al. 2018). pSTAT3 levels were assessed in skin biopsies from the lesional skin of patients in the AD Phase 2 Study JAHG at baseline and Week 4. Treatment with baricitinib reduced pSTAT3 levels at Week 4. The reduction in pSTAT3 levels were greater amongst patients achieving EASI50 improvements compared to patients that did

not achieve EASI50 improvement, confirming the pharmacodynamics effect of baricitinib and pSTAT3 levels in patients with AD.

- *Ex-vivo* skin model: A 3-dimensional AD-like human skin model was generated by exposing human skin equivalents to a combination of IL-4, IL-13, and IL-31.
    - In this model, pathological changes consistent with AD, and elevated levels of epidermal keratinocyte pSTAT3 were reduced with the presence of baricitinib.
    - Filaggrin is a protein that plays a role in skin barrier function and in the pathogenesis of AD (Thyssen et al. 2014). The presence of baricitinib in the human skin model enhanced constitutive filaggrin expression as detected by immunohistochemical staining and quantitative microscopic evaluation. While the addition of the aforementioned cytokine cocktail reduced filaggrin expression, treatment with baricitinib produced a filaggrin increase by epidermal keratinocytes.

Taken together, these results support the conclusion that baricitinib, via inhibition of JAK/STAT signalling, reduces pathological changes induced by numerous cytokines that contribute to AD inflammation.

2.3.4. PK/PD modelling

The PK data from studies JAHG, JAHL and JAHM were used as input for the PopPK model for patients with atopic dermatitis to estimate the PK parameters of baricitinib in patients with atopic dermatitis. The PopPK analysis for patients with atopic dermatitis used the same PopPK model developed for rheumatoid arthritis. A 2-compartment model with zero-order absorption and a partitioning of total CL/F into CLr/F and CLnr/F well described the PK of baricitinib in patients with atopic dermatitis. In patients with atopic dermatitis, the Cmax and AUC at steady state are 124 nM and 1117 nM × h, respectively, at the clinically relevant dose of 4 mg.

2.3.5. Discussion on clinical pharmacology

Pharmacokinetics

The analytical method used to measure baricitinib in plasma samples from patients with atopic dermatitis was the same used for the original MAA for rheumatoid arthritis. The LC-MS/MS methods used for the analysis of baricitinib in plasma was considered sufficiently validated by the CHMP.

PK data from patients with atopic dermatitis was only obtained through sparse sampling. Therefore, information on t_{max} is not available and can, therefore not be compared between the different groups. However, based on the physiology and disease, no difference in t_{max} is expected between the different groups. After oral administration of baricitinib to healthy subjects, maximal plasma levels were reached ~1 h after dosing (range = 0.5-3.0 h).

The MAH included subjects with moderate renal impairment (eGFR <60 mL/min/1.73m2) and normal renal function in the estimation of the PK parameters from studies JAHG, JAHL and JAHM. Since renal impairment previously was identified as having a clinically significant effect on the PK, the Applicant was requested to recalculate the PK parameters for subjects with normal renal function and exclude subjects with moderate renal impairment. Only 6 subjects with moderate renal impairment were included (<1% of the total population) in the response. The impact of these few subjects was too limited to affect the calculated PK parameters. This issue was therefore no longer pursue by the CHMP. However, renal function and body weight had an effect on the PK of baricitinib in patients with

rheumatoid arthritis and atopic dermatitis. For both patient groups, the effect of body weight on the PK is not considered clinically relevant. Renal function has a clinically significant effect on the PK, and for both patient groups, a dose reduction is advised if a patient has a moderate renal function (GFR between 30 and 60 mL/min/1.73m2) in line with the existing recommendation for RA in Section 4.2 of the SmPC. As for RA, baricitinib is not recommended for use in patients with creatinine clearance < 30 mL/min (see section 5.2). This proposal is acceptable to CHMP.

At the MAA for rheumatoid arthritis, the developed PopPK model was suitable to predict the PK in healthy subjects and patients with rheumatoid arthritis. Also, the model is suitable to predict the effect of renal function, hepatic function, race, age, weight, gender and Baseline Erythrocyte Sedimentation Rate on the PK of baricitinib. The same PopPK model was used for atopic dermatitis which is acceptable to the CHMP. Based on the PopPK model the following PK parameters were estimated for subjects with normal renal function:

- After oral administration of baricitinib to healthy subjects, the Cmax is 53 and ~112 nM, respectively and the AUC0-∞ is 342 and 740 nM × h, respectively, at the proposed dose of 2 and 4 mg. The elimination half-life of baricitinib is ~8 h.
- In rheumatoid arthritis patients, the Cmax and AUC at steady state are ~135 nM and 1200 nM × h, respectively, at the clinically relevant dose of 4 mg.
- In patients with atopic dermatitis, the Cmax and AUC at steady state are 124 nM and 1117 nM × h, respectively, at the clinically relevant dose of 4 mg.

The CHMP concluded that the $C_{max, ss}$ and $AUC_{\tau, ss}$ tend to be lower in patients with atopic dermatitis compared to patients with rheumatoid arthritis (factor 0.8) and higher compared to healthy volunteers (not assessed by the MAH) at the clinically relevant dose of 4 mg. The Section 5.2 of the SmPC was updated accordingly.

Baricitinib can be taken independent of food. A low-fat meal led to a 14% decrease in AUC0-∞ and a 12% decrease in Cmax. The 90% CIs were entirely contained within the 0.8 to 1.25 limits for bioequivalence, indicating that a low-fat meal has no significant effect in the pharmacokinetics of baricitinib. A high-fat meal decreased the AUC by 11% and the Cmax by 18%. The 90% CIs of the AUC were within the 0.8 to 1.25 limits for bioequivalence. The 90% CIs of the Cmax were outside the limits for bioequivalence; below the 0.8 limit. However, considering that the proposed product is designed for chronic treatment and the AUCs are within the 0.8 to 1.25 limits for bioequivalence, the CHMP agreed that this will most likely not lead to a clinically relevant effect on the exposure. Therefore, in line with RA patients, food is not expected to significantly affect the PK of baricitinib in patients with atopic dermatitis.

PopPK resulted in a Vd/F of 126 L in patients with atopic dermatitis. The Vd is ~159 L in patients with atopic dermatitis when correcting for the absolute bioavailability and assuming similar bioavailability in the different populations (~79%). The Vd in patients with rheumatoid arthritis (137 L) is smaller than that in patients with atopic dermatitis. When assuming an average body weight of 70 kg, the Vd is 2.3 L/kg in patients with atopic dermatitis and 2.0 L/kg in patients with rheumatoid arthritis. The volume of distribution is lowest in healthy volunteers (~1.1 L/kg) and highest in patients with atopic dermatitis.

PopPK resulted in a CL/F of 11.2 L/h in patients with atopic dermatitis (typical patient with normal renal function and body weight of 73 kg). The CL/Fin patients with rheumatoid arthritis (9.42 L/h) is slower than that in patients with atopic dermatitis (~19% difference). This is reflected in Section 5.2 of the SmPC. When correcting for the absolute bioavailability (~79%), the CL is ~8.8 L/h, which is lower than the clearance in healthy subjects (15 L/h).

Renal clearance (when correcting for the absolute bioavailability) is 10.5 L/h in healthy subjects, 6.4 L/h in patients with atopic dermatitis and 5.4 L/h in patients with rheumatoid arthritis. This difference can be explained due to the difference in renal function, which was decreased in subjects with rheumatoid arthritis.

The elimination half-life of baricitinib is ~10 h in healthy volunteers and 12.5 h in patients with rheumatoid arthritis and 12.9 h in patients with atopic dermatitis based on PopPK modelling. This indicates that the elimination is more rapid in healthy volunteers compared to the patient population.

Baricitinib increases dose-proportional over the clinical dose range of 2 to 4 mg. Following once-daily dosing, steady-state is reached between the 2nd and 3rd dose and accumulation is negligible.

Data in atopic dermatitis patients confirm the dose proportionality shown in healthy subjects and patients with rheumatoid arthritis.

The inter-individual variability in exposure in the patient population (rheumatoid arthritis and atopic dermatitis) is higher compared to healthy volunteers (17-26% versus 41-50%).

In general, the CHMP assumes that the DDI risk with baricitinib as victim and as perpetrator is independent of the disease since similar dosages were administered.

Baricitinib is not a CYP inhibitor or inducer at clinically relevant concentrations. Furthermore, baricitinib is not an inhibitor of the transporters P-glycoprotein, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, OAT2, OAT3, MATE-1 and MATE2-K at clinically relevant concentrations. Baricitinib may be an inhibitor of OCT1 at maximal portal vein concentrations. However, the frequently concomitant oral drugs in patients with atopic dermatitis are not OCT1 substrates, and therefore no DDIs are expected with frequently concomitant medication in patients with atopic dermatitis.

Baricitinib is actively excreted by the transporters P-glycoprotein, BCRP, OAT3 and MATE2-K. A clinically significant interaction was observed when baricitinib was co-administered with an OAT3 inhibitor, but not with inhibitors of CYP2C9, CYP2C19, CYP3A and P-glycoprotein inhibition and inducers via CAR/PXR. Furthermore, inhibition of BCRP and MATE-2K is considered clinically not relevant. The frequently concomitant oral drugs in patients with atopic dermatitis are not inhibitors of OAT3 and therefore no DDIs are expected with frequently concomitant medication in patients with atopic dermatitis.

Pharmacodynamics

Baricitinib inhibits JAK1 and JAK2 kinase activity thereby interfering with the cytokine-mediated signalling through JAK1 and JAK2 phosphorylation, leading to an inhibition of phosphorylation of transcription factor STAT3 (pSTAT3) and subsequent inactivation pSTAT3. Pro-inflammatory cytokines, that signal via the JAK-STAT pathway, are implicated in the pathogenesis of RA. This inhibition of pSTAT3 has been shown in blood cells, suggesting a role in reducing inflammation, cellular activation, and proliferation of key immune cells as described in the marketing authorisation application for RA.

The JAK-STAT pathway is also implicated as a major signal transduction pathway for numerous pro-inflammatory cytokines involved in AD pathogenesis, such as thymic stromal lymphopoietin (TSLP), IL-4, IL-5, IL-13, IL-22, and IL-31 and elevated levels of pSTAT3 are found in keratinocytes from lesional AD skin and in cytokine-treated keratinocytes monolayer cultures.

In a three-dimensional human skin model using neonatal human skin keratinocytes overlaid on a collagen matrix embedded with fibroblasts, a cocktail of pro-inflammatory cytokines (IL-4, IL-13, IL-31) induced Atopic Dermatitis-like effects, such as diminished keratinocyte pSTAT3 expression, granular cell layer and increased spongiosis. Baricitinib, both without and with these cytokines, was

found to inhibit pSTAT3 formation, which is indicative of JAK inhibition, and to increase filaggrin expression, which is suggested to play a role in skin barrier function and in the pathogenesis of atopic dermatitis. Baricitinib was without significant effects on the skin (granular or spongiosis) layer thickness.

The effect of baricitinib on the skin after 4 and 16 weeks of treatment was studied in lesional and non-lesional skin biopsies from TCS non-responding AD patients, given TCS combined with placebo, 2 mg or with 4 mg baricitinib (Phase 2 Study JAHG). Baricitinib treatment was found to decrease the pSTAT3 expression in skin biopsies as compared to baseline but no statistical significance was reached as compared to placebo after 4 or 16 weeks treatment although the decrease in pSTAT3 staining seemed to be stronger in the EASI-50 responders correlating with clinical response.

These *in vitro* data indicate that in human skin (keratinocytes) baricitinib inhibits the JAK/STAT pathway leading to increases in filaggrin expression, which may be beneficial for AD patients given its presumed role in AD pathogenesis.

2.3.6. Conclusions on clinical pharmacology

In patients with atopic dermatitis, the Cmax and AUC at steady state are 124 nM and 1117 nM × h, respectively, at the clinically relevant dose of 4 mg. The $C_{max,ss}$ and $AUC_{\tau,ss}$ tend to be lower in patients with atopic dermatitis compared to patients with rheumatoid arthritis (factor 0.8) and higher compared to healthy volunteers at the clinically relevant dose of 4 mg. In addition, mean apparent clearance (CL/F) and half-life in patients with atopic dermatitis was 11.2 L/hr (CV = 33.0%) and 12.9 hrs (CV = 36.0%), respectively. Section 5.2 of the SmPC was updated accordingly.

Baricitinib may be an inhibitor of OCT1 at maximal portal vein concentrations and may lead to clinically relevant DDIS. The frequently concomitant oral drugs in patients with atopic dermatitis are not OCT1 substrates, and therefore no DDIs are expected with frequently concomitant medication in patients with atopic dermatitis. Furthermore, baricitinib is actively excreted by OAT3, and a clinically relevant DDI was observed with probenecid. The frequently concomitant oral drugs in patients with atopic dermatitis are not inhibitors of OAT3, and therefore no DDIs are expected with frequently concomitant medication in patients with atopic dermatitis. However, combination with ciclosporin or other potent immunosuppressants has not been studied and is not recommended. This is adequately reflected in the Section 4.4 and 4.5 of the SmPC.

In an in-vitro human skin model treated with pro-inflammatory cytokines (i.e., IL-4, IL-13, IL-31), baricitinib reduced epidermal keratinocyte pSTAT3 expression, and increased the expression of filaggrin, a protein that plays a role in skin barrier function and in the pathogenesis of atopic dermatitis. Section 5.1 of the SmPC was updated accordingly.

The CHMP considered that the application was acceptable from a clinical pharmacology perspective.

2.4. Clinical efficacy

2.4.1. Dose response study

The MAH performed a single 'phase 2' dose-finding and proof-of-concept study, comparing baricitinib 2 mg and 4 mg once daily against placebo.

"A Randomised, Double-Blind, Placebo-Controlled, Phase 2 Study to Evaluate the Safety and Efficacy of Baricitinib in Patients with Moderate-to-Severe Atopic Dermatitis (JAHG)"

Dose selection

Dose selection for this study was based on the results of 'phase 2' and 'phase 3' studies in RA (JADA, JADW, JADX) and a 'phase 2' study in psoriasis (JADP). It was considered by the MAH that the 2 mg and 4 mg doses have shown efficacy in RA with an acceptable safety profile, while there was no additional efficacy associated with an 8-mg dose in the 'phase 2' RA study. In patients with psoriasis, doses of 4 mg to 10 mg showed reductions in Psoriasis Area and Severity Index (PASI) score, with greater efficacy at the higher doses. The dose of 2 mg was not effective on PASI but was effective on itch. Doses of 8 mg and 10 mg were associated with a higher rate of AEs related to laboratory abnormalities.

Methods

Design

Study JAHG was a randomised, double-blind, parallel, placebo-controlled, multicentre, 16-week study to evaluate the efficacy and safety of baricitinib 2 mg and baricitinib 4mg versus placebo, in combination with moderate-potency TCS. Primary outcome was EASI50 at week 16; secondary outcomes were EASI75, IGA 0 or 1, itch NRS and DLQI.

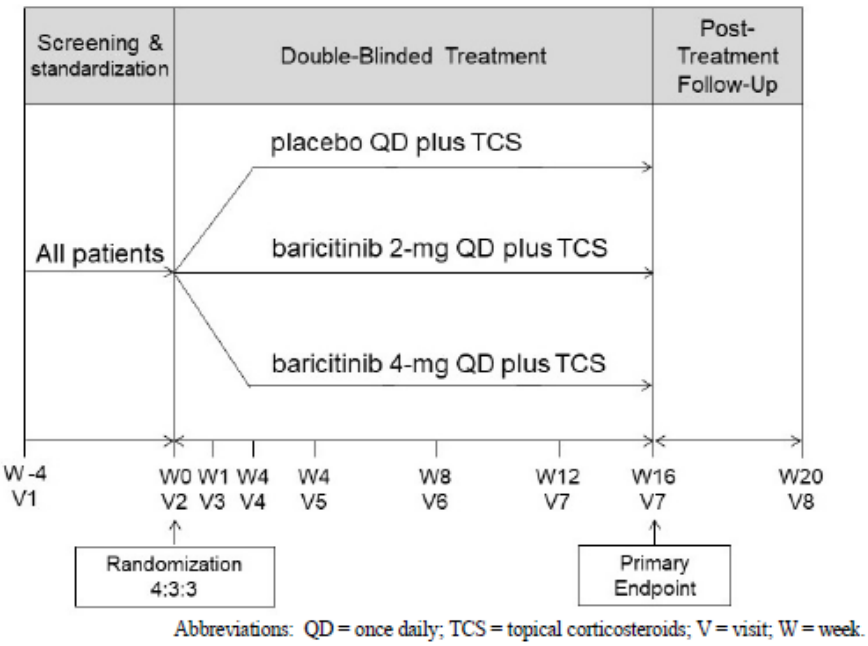


Figure 1 ***Design of study JAHG***

Study participants

Patients were included if they were 18 years or older and had AD for at least 2 years. They should have moderate to severe AD, as defined by an EASI score ≥12 and a BSA ≥10%, while having had an

inadequate response to previous AD therapies. This was defined as a history of inadequate response to at least 1 of the following 3 categories of AD treatments, after at least 4 weeks of use:

1) Emollient plus TCS, or antibiotics, or topical immune modulators such as TCIs
2) Systemic steroids or phototherapy
3) Ciclosporin or other systemic immunomodulators.

Treatments

Patients received baricitinib 2 mg QD, baricitinib 4 mg QD, or placebo QD, for 16 weeks. Blinding was maintained using double-dummies.

In the 4 weeks prior to randomisation, patients had to use triamcinolone 0.1% cream (moderate potency TCS) as supplied by the investigator, and continue this use throughout the 16 weeks of study. (Patients were not included if they improved in those 4 weeks and at time of randomisation did not meet the inclusion criteria anymore.) Other AD treatments were to be stopped at least 4 weeks before randomisation: potent TCS or TCIs; systemic therapies; phototherapy. Patients had to apply emollients throughout the study.

It was not foreseen in rescue treatment.

Outcomes

Primary outcome was the proportion of patients with at least a 50% change from baseline to week 16 in Eczema Area and Severity Index (EASI) score (EASI50).

Secondary outcomes were amongst others: EASI75; the proportion of patients with an Investigator's Global Assessment (IGA) score of 0 or 1; mean change in itch severity on a NRS; mean change from baseline in Dermatology Life Quality Index (DLQI). (*See the main studies for further explanation of outcomes.*)

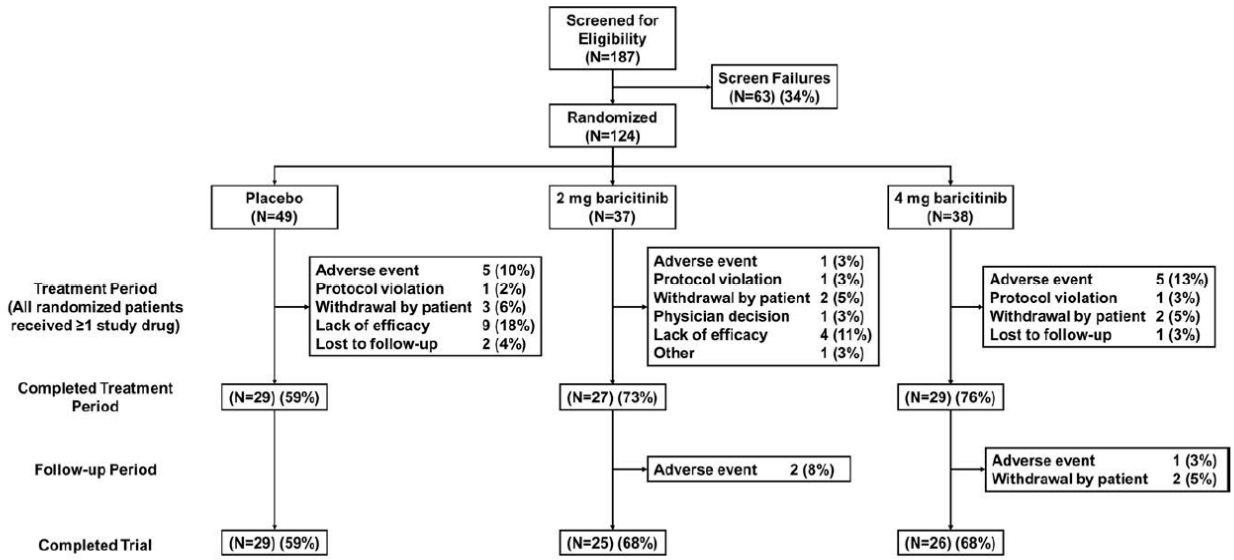
Statistical methods

The analyses for efficacy were based on the ITT population. NRI was applied to missing values of the primary outcome and other categorical outcomes. A step-wise testing strategy was employed for testing the primary outcome (EASI50) of the two dose groups against placebo at an α of 5%.

Results

Participant flow

There were 187 patients screened and 124 patients were randomised to one of the three treatment groups (Figure 2). All randomised patients had received at least 1 dose of study drug. In total, 85 (69%) patients completed the 16 week study period. Most patients discontinued in the placebo and 2 mg groups, with lack of efficacy as a frequent reason. Of the 5 patients in the placebo group who discontinued due to an AE, 2 of the 5 AEs were aggravated AD. The most frequent reason for discontinuation for baricitinib 4-mg was an AE, usually laboratory abnormalities.



Abbreviation: N = number of patients.

Figure 2 ***Patient disposition in study JAHG***

Baseline data

At baseline, there were numerical between-group differences in age, disease duration and gender; disease severity (EASI, itch NRS, POEM) and use of prior therapies were numerically similar (Table 9).

Table 9 ***Baseline data of all randomised patients in study JAHG***

	Placebo (n=49)	Bari 2-mg (n=37)	Bari 4-mg (n=38)
Age, median (yrs)	35.0	42.0	32.5
Female (%)	51	41	42
Male (%)	49	59	58
Asian (%)	33	22	24
African-American (%)	14	24	24
Multiple (%)	4	0	0
Native Hawaiian/Pacific Islander	2	0	5
White	47	54	47
EASI total score, median (min-max)	22.1 (12.0-70.3)	22.1 (12.2-72.0)	19.5 (12.2-71.4)
Worst Itch NRS, median (min-max)	7.0 (1-10)	6.0 (2-10)	6.5 (2-10)
POEM total score, median (min-max)	20 (3-28)	17 (3-28)	20.5 (5-28)
Time since AD diagnosis, median (yrs)	17.7	26.4	22.0
Prior therapies			
Systemic corticosteroids (%)	53	62	47
Cyclosporine and/or other immunosuppressants (%)	33	19	26

Abbreviations: AD = atopic dermatitis; Bari = baricitinib; EASI = Eczema Area and Severity Index; n = number of patients in the analysis set; NRS = Numerical Rating Scale; POEM = Patient-Oriented Eczema Measure.

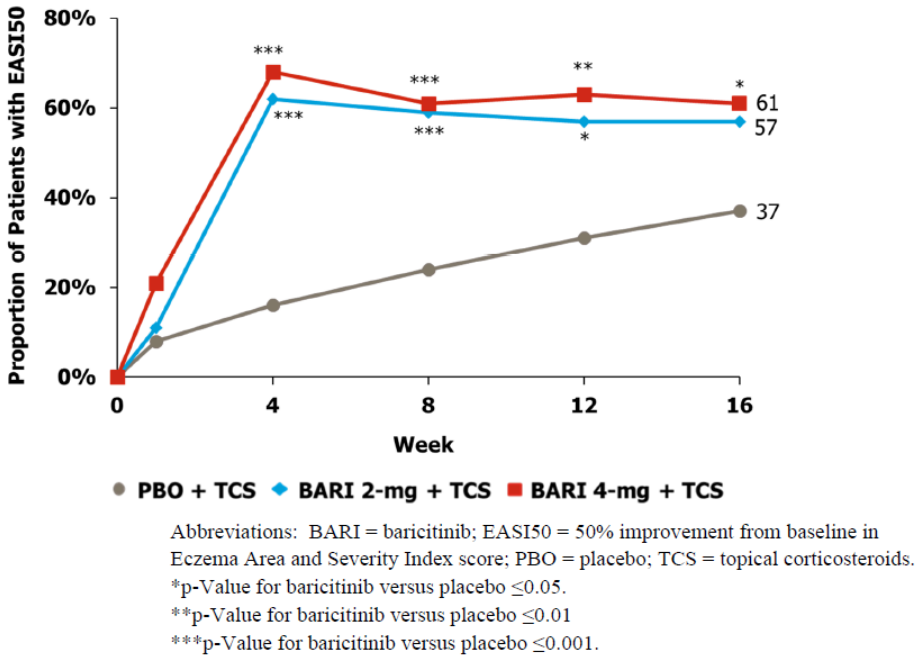
Outcomes and estimation

All 124 randomised patients were included in the efficacy analyses (ITT). In the baricitinib groups, nearly all patients were ≥80% compliant with study medication; in the placebo group 90% of patients were compliant.

The proportion of patients reaching EASI50 at week 16 (primary outcome) was 61% in the baricitinib 4 mg group, 57% in the baricitinib 2 mg group, and 37% in the placebo group (Figure 3). The difference between baricitinib 4 mg and placebo was statistically significant (p=0.027) and the difference between baricitinib 2 mg and placebo was not statistically significant (p=0.065).

At weeks 4, 8 and 12, the differences in EASI50 of 2 mg and 4 mg versus placebo (secondary outcomes) were statistically significant (without application of correction for multiplicity). The placebo response increased numerically over time, the responses in the baricitinib groups remained numerically stable after week 4 (Figure 3).

At week 16, the responses in EASI75, IGA 0 or 1, and itch NRS were numerically larger in the baricitinib treated groups as compared to the responses in the placebo group, but the differences were not statistically significant (Table 10). Statistically significant differences at week 16 appeared for the change in the continuous EASI score, SCORAD75 and DLQI 0 or 1. The responses in the baricitinib groups were numerically similar (Table 10). Numerical differences in IGA 0 or 1 (the CHMP noted that it was similar to the primary outcome in the following pivotal studies) of baricitinib 4 mg compared to placebo appeared from week 4.



Abbreviations: BARI = baricitinib; EASI50 = 50% improvement from baseline in Eczema Area and Severity Index score; PBO = placebo; TCS = topical corticosteroids.
*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 3 *EASI50 response (ITT) over time in study JAHG*

Table 10 ***Efficacy results at week 16 of study JAHG***

	PBO + TCS N=49	BARI 2-mg + TCS N=37	BARI 4-mg + TCS N=38
Primary Endpoint			
Proportion of patients with EASI50, % (n)	37 (18)	57 (21)	61* (23)
Secondary Endpoints			
Proportion of patients with EASI75, % (n)	20 (10)	30 (11)	34 (13)
Proportion of patients with EASI90, % (n)	6 (3)	19 (7)	21 (8)
Percent change from baseline in EASI score (SE)	-45.87 (5.85)	-64.19* (6.20)	-64.69* (6.21)
Proportion of patients with IGA[a] 0 or 1, % (n)	8 (4)	22 (8)	21 (8)
Proportion of patients with SCORAD75, % (n)	0	11* (4)	11* (4)
Mean change from baseline in Itch NRS (SE)	-1.72 (0.44)	-2.61 (0.47)	-2.22 (0.46)
Proportion of patients with DLQI 0 or 1, % (n)	4 (2)	32** (12)	18* (7)
Change from baseline in DLQI (SE)	-6.27 (0.82)	-6.89 (0.89)	-7.96 (0.86)

Abbreviations: BARI = baricitinib; DLQI = Dermatology Life Quality Index; EASI50/75/90 =50%/75%/90% improvement in Eczema Area and Severity Index; IGA = Investigator's Global Assessment; N = number of patients in the analysis population; n = number of patients in the specified category; NRS = Numeric Rating Scale; PBO= placebo; SCORAD75 = 75% improvement in SCORing Atopic Dermatitis; SE = standard error.

Note: Section 2.7.3.1.5 describes the method of controlling Type I error rate for the primary endpoint. No adjustments for multiplicity were made for the secondary endpoints.

[a] The IGA scale used in Study JAHG consisted of a 6-point severity scale.

*p-Value for baricitinib versus placebo ≤0.05.

**p-Value for baricitinib versus placebo ≤0.01.

2.4.2. Main studies

In the three 16-week 'phase 3' studies (JAHL, JAHM, JAIY), three oral doses of baricitinib were evaluated against placebo: 1-mg, 2-mg, and 4-mg once daily (also see Table 2). These doses were primarily chosen based on the results of 'phase 2' study JAHG. In the first 52-week period of the long-term extension study (JAHN) all three doses of baricitinib were evaluated (Table 2). Patients were mainly recruited from JAHL, JAHM and JAIY.

"A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Baricitinib in Adult Patients with Moderate to Severe Atopic Dermatitis (JAHL and JAHM)"

"A Multicenter, Randomised, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Baricitinib in Combination with Topical Corticosteroids in Adult Patients with Moderate to Severe Atopic Dermatitis (JAIY)"

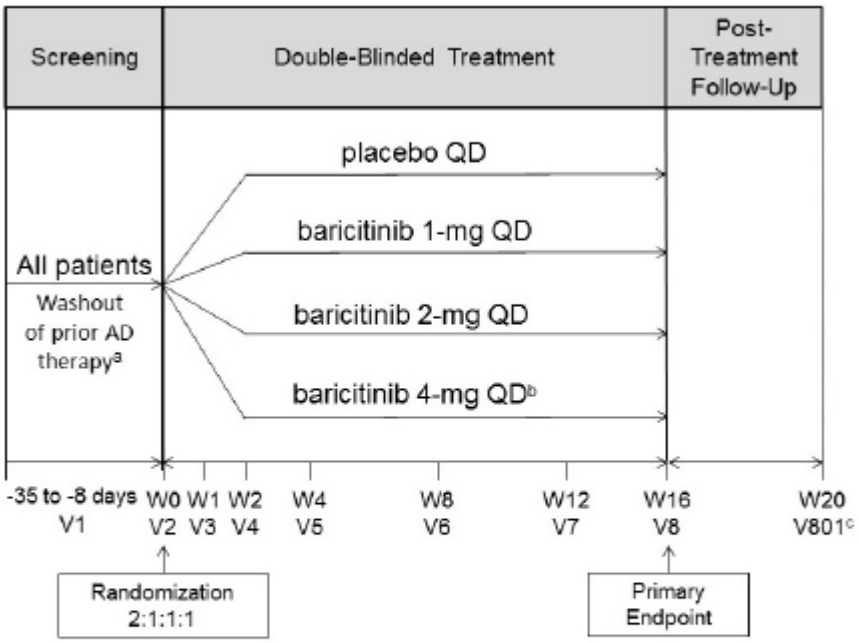
Design and objectives

Studies JAHL and JAHM were identically designed as a 16-week, multicenter, randomised, double-blind, placebo-controlled, parallel-group, outpatient study evaluating the efficacy and safety of baricitinib 1-mg QD, 2-mg QD, and 4-mg QD as compared to placebo (1:1:1:2) in adult patients with moderate to severe AD and a history of inadequate response or intolerance to available topical AD therapies (Figure 4).

The primary objective was to test the hypothesis that baricitinib 4-mg once daily or baricitinib 2-mg once daily is superior to placebo in the treatment of patients with moderate to severe AD. The primary endpoint was the proportion of patients achieving IGA of 0 or 1 with a 2 or more point improvement at Week 16. A key secondary objective was to test the hypothesis that baricitinib 1-mg once daily is superior to placebo in the treatment of patients with moderate to severe AD.

Study JAIY is a 16-week multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient study evaluating the efficacy and safety of baricitinib 2-mg QD + TCS, and 4-mg QD + TCS as compared to placebo + TCS (1:1:1) in adult patients with moderate to severe AD and a history of inadequate response to available topical therapies (Figure 5).

The primary objective of study JAIY was to test the hypothesis that baricitinib 4-mg once daily plus TCS or baricitinib 2-mg once daily plus TCS is superior to placebo plus TCS in the treatment of patients with moderate to severe AD. The primary endpoint was the proportion of patients achieving IGA of 0 or 1 with a 2 or more point improvement at Week 16.



Abbreviations: AD = atopic dermatitis; eGFR = estimated glomerular filtration rate; LTE = long-term extension; QD = once daily; V = visit; W = week.

[a] Applicable to patients taking topical or systemic treatments for AD at the time of screening, except for emollients.

[b] For patients randomised to the 4-mg QD dose who have renal impairment, defined as eGFR <60 mL/min/1.73 m², the baricitinib dose was 2-mg QD.

[c] Occurred approximately 28 days after the last dose of investigational product. Not required for those patients entering the LTE study JAHN.

Figure 4 ***Design of studies JAHL and JAHM***

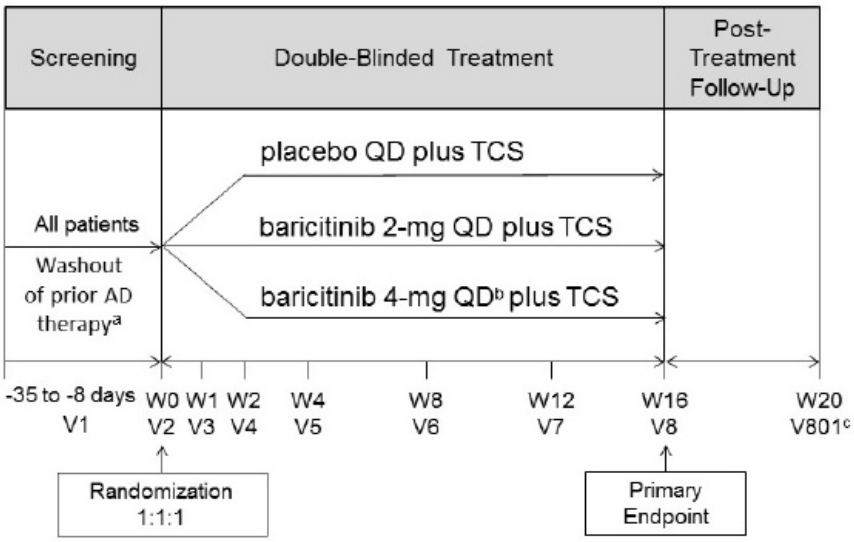


Figure 5 ***Design of study JAIY***

Methods

Study participants

Studies JAHL and JAHM had identical inclusion and exclusion criteria, aiming at an adult population with moderate to severe AD and a recent history of inadequate response/intolerance to topical AD therapies. The inclusion and exclusion criteria for study JAIY were very similar, with the exception that patients with intolerance to TCS were excluded while TCS was to be used concomitantly.

Key inclusion criteria were:

- Age of 18 years or older with a diagnosis of AD [Eichenfield et al. 2014] for at least 12 months prior to screening.
- Moderate to severe AD with an EASI score ≥16, an IGA ≥3 and a BSA involvement ≥10%.
- Have a history of inadequate response to/intolerance to topical AD therapies within 6 months prior to screening, defined by at least 1 of the following:
  - Not having achieved at least mild disease with TCS of at least moderate potency for at least 4 weeks.
  - Failure of systemic AD therapies, such as: ciclosporin, methotrexate, azathioprine, or mycophenolate mofetil.
  - Clinically significant adverse reactions with the use of TCS, such as: skin atrophy, allergic reactions, or systemic effects (JAHL, JAHM).

Key exclusion criteria were:

- Previous or concomitant conditions that may have confounded efficacy and safety assessments or increased the risks to patients. This included: psoriasis, SLE, active skin infection, history of eczema herpeticum, recurrent or recent VTE, current or recent serous infection.

Treatments

Investigational treatments

Patients could receive baricitinib 1 mg QD, 2 mg QD, baricitinib 4 mg QD, or placebo QD, for 16 weeks. The investigational treatment was packed in blisters. Blinding was maintained using double dummies. In studies JAHL and JAHM patients therefore had to take 3 tablets daily (e.g. one 4 mg baricitinib tablet and matching placebo of the 2 mg and 1 mg baricitinib tablets).

Compliance

Patient compliance with investigational treatment was assessed by pill count at each visit. If a patient at his/her own intention had missed more than 20% of doses of study drug, or had taken more than 20% of study drug, he/she was considered significantly noncompliant.

Concomitant treatments

Other AD treatments were to be stopped between 2 or 4 weeks before randomisation: topical therapies except emollients, systemic therapies, phototherapy and sedating antihistamines. In the 2 weeks prior to randomisation, patients had to use emollients daily and continue this use throughout the study (but not on the day of a study visit).

In combination study JAIY, patients were instructed to start with the use of a moderate-potency TCS (such as triamcinolone 0.1% cream) once daily until lesions were clear or almost clear. Then, patients should switch to a low potency TCS (hydrocortisone 2.5% ointment) and treat previously affected areas for another 7 days and then stop. If lesions reappeared, treatment with the moderate- or low-potency TCS was to be resumed. In addition, the use of TCI's (or Crisaborole, a topical PDE-4 inhibitor) was permitted to treat areas with sensitive skin (e.g. face, neck, skin folds, genital areas).

Rescue treatments

Rescue treatment was allowed for patients who were experiencing unacceptable or worsening AD symptoms at any time (JAHL, JAHM) or after 2 weeks from baseline (JAIY).

In studies JAHL and JAHM, first-line rescue treatment was topical treatment with a moderate-potency TCS (triamcinolone 0.1% cream) and/or a low-potency TCS (hydrocortisone 2.5%). If patients did not improve sufficiently after 7 days of use, they could switch to a higher potency TCS.

In combination study JAIY, high- or ultra-high potency TCS could be used as first-line rescue treatment.

In all three studies, second-line rescue treatment was oral systemic treatment, such as oral corticosteroids or ciclosporin. Then, investigational treatment was discontinued for the remainder of the study (but patients remained eligible for the long term extension study JAHN).

Outcomes

The primary outcome for the three 16-week 'phase 3' studies (JAHL, JAHM, JAIY) was the proportion of patients achieving an Investigator's Global Assessment (IGA) score of 0 or 1, with at least a 2-point improvement from baseline at Week 16 (here referred to as IGA 0 or 1). IGA assesses the clinician's impression of overall disease severity at a single time point. It does not specifically measure the extent of AD, although for patients to be considered severe, they must have widespread disease. An IGA score of 0 or 1 equates to skin that is 'clear' or 'almost clear' from AD signs (Figure 6).

IGA is a commonly used scale in AD clinical studies (Futamura et al. 2016). For the 'phase 3' trials a common validated version was used (vIGA-AD™; International Eczema Council 2017) and all investigators underwent training and certification with this version.

Instructions:

The IGA score is selected using the descriptors below that best describe the overall appearance of the lesions at a given time point. It is not necessary that all characteristics under Morphological Description be present.

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

Figure 6 ***Description of the Investigator's Global Assessment (IGA) score.***

The key secondary outcomes were: Eczema Area and Severity Index (EASI); Itch NRS; Atopic Dermatitis Sleep Scale (ADSS); Skin pain NRS; SCORing Atopic Dermatitis (SCORAD). Additional secondary outcomes were amongst others: Dermatology Life Quality Index (DLQI); body surface area affected (BSA); Patient Oriented Eczema Measure (POEM); and Hospital Anxiety and Depression Scale (HADS).

The EASI is a validated, investigator-assessed, composite scale that assesses the extent and severity of AD at 4 body regions: head and neck, trunk, upper extremities, and lower extremities. The EASI is a reliable and comprehensive assessment for AD (Hanifin et al. 2001). The proportion of affected skin is assessed in each region and the extent of 4 clinical signs (erythema, induration/papulation, excoriation, lichenification) is assessed, each on a scale of 0 (none) to 3 (severe). The EASI score ranges from 0 to 72, an EASI score of 7.1 to 21 is equated with 'moderate severity' (Leshem et al. 2015). EASI75 and EASI90 correspond to a 75% and 90% improvement in EASI score from baseline, respectively. All patients were required to have a baseline EASI score ≥16 to enrol in the 'phase 3' studies. The minimal clinically important difference (MCID) for EASI is 6.6 (Schram et al. 2012). Therefore, all patients who achieved EASI75 or EASI90 would also have achieved an improvement in EASI that exceeds the MCID.

The Itch Numeric Rating Scale (NRS) is a validated, patient-assessed, 11-point horizontal scale anchored at 0 and 10, with 0 representing 'no itch' and 10 representing 'worst itch imaginable', used to assess itch over the past 24 hours. Itch NRS is considered a relevant, reliable, valid, sensitive to change, and comprehensive assessment of itch severity in AD (Newton et al. 2019; Yosipovitch et al. 2019). An improvement from baseline of 4 points is considered clinically meaningful (Kimball et al. 2016; Yosipovitch et al. 2019).

The ADSS is a 3-item, patient-administered daily questionnaire to assess the impact of itch on sleep last night, developed and validated by the Applicant. The ADSS items are: difficulty falling asleep (Item 1); frequency of waking last night (Item 2); and difficulty getting back to sleep (Item 3). Patients rate Items 1 and 3 using a 5-point Likert-like scale ranging from 0 'not at all' to 4 'very difficult'. Patients report Item 2 by indicating the number of times they woke up at night. Improvement of 1.5 or more points in item 2 is considered clinically meaningful (ADSS validation report, 2019).

The Skin Pain NRS is a patient-administered, 11-point horizontal scale anchored at 0 and 10, with 0 representing 'no pain' and 10 representing 'worst pain imaginable' in the past 24 hours, developed and validated by the Applicant. Skin Pain NRS is considered a valid, reliable, and appropriate assessment of skin pain severity (Newton et al. 2019). An improvement of 4 or more points is considered clinically meaningful (Skin pain NRS validation report, 2019).

The SCORAD is a validated and well established composite scoring system for AD combining the extent in BSA (20% of the score) with the severity of 6 signs: erythema, oedema/papules, scratching, oozing/crust formation, lichenification, dryness, each scored from 0 'absent' to 3 'severe' (60% of the score), and 2 symptoms (itch, sleeplessness) of the previous 3 days scored on a VAS from 0 representing no symptom and 10 represents the worst imaginable itch or sleeplessness (20% of the score). The maximum score of SCORAD is 103, scores between 25 and 50 indicate moderate AD, while scores greater than 50 indicate severe AD (Oranje et al. 2007). SCORAD75 corresponds to an improvement of 75% from baseline, which is considered clinically meaningful, given that the MCID for SCORAD is 8.7 (Schram et al. 2012). Any patient who had moderate to severe AD at baseline, that is, a SCORAD score of 25 or greater, and who achieved SCORAD75 will have exceeded the MCID.

The DLQI is a patient-administered, 10-item, validated, questionnaire on the impact of skin disease on 6 domains over the last week:

- symptoms and feelings
- daily activities
- leisure
- work and school
- personal relationships, and
- treatment.

Response categories range from 0 'not at all' to 3 'very much'. The total score ranges from 0 to 30, with higher scores indicating greater impact on QoL. The MCID for DLQI is 4 (Khilji et al. 2002; Basra et al. 2015), and a DLQI score of 0 to 1 equates to no or minimal impact on a patient's QoL (Hongbo et al. 2005).

The POEM is a 7-item, validated, patient-administered scale that assesses disease severity in AD patients. The patients assess the frequency of 7 symptoms over the last week (itching, sleep disturbance, bleeding, weeping/oozing, cracking, flaking, dryness/roughness). The total score ranges from 0 to 28, with higher total scores indicating greater disease severity (Charman et al. 2004). An improvement in POEM of 3.4 is considered clinically meaningful (Schram et al. 2012).

The HADS is a widely-used 14-item self-assessment scale to determine the levels of anxiety and depression symptoms that a patient experienced over the past week. Scores for each domain, that is, anxiety and depression, can range from 0 to 21, with higher scores indicating greater symptoms of anxiety or depression (Zigmond and Snaith 1983; Snaith 2003). An Anxiety Score or a Depression Score of 8 or greater indicates that a patient is suffering from anxiety or depression, respectively (Bjelland et al. 2002).

Sample size

Study JAHL aimed to enroll approximately 600 patients ≥18 years of age. The study was designed with a 90% power to detect an absolute difference of 20% in IGA between the baricitinib 4-mg and placebo treatment groups and the baricitinib 2-mg and placebo treatment groups, each using a 2-sided alpha of 0.025, assuming a 10% placebo response rate for the primary endpoint. Study JAHM will aim to enroll approximately 600 patients ≥18 years of age. The proposed sample size will ensure a >90% power to detect an absolute difference of 20% between the baricitinib 4-mg and placebo treatment groups, assuming a 10% placebo response rate for the primary endpoint using a 2-sided alpha of 0.25. Study

JAIY aimed to enroll approximately 300 patients ≥18 years of age. The study was designed with a 89% power to detect an absolute difference of 20% in IGA between the baricitinib 4-mg and placebo treatment groups and the baricitinib 2-mg and placebo treatment groups, each using a 2-sided alpha of 0.025, assuming a 10% placebo response rate for the primary endpoint. For all three studies, the assumptions were based on the results of the Phase 2 study (JAHG) and on the discussion with therapeutic experts.

In all studies the primary endpoint of IGA 0 or 1 represented patients whose AD was clear or almost clear from a baseline of moderate or severe disease.

Assignment to treatment groups was determined by a computer-generated random sequence using an interactive web-based response system. Using the system, numbered blister packs with blinded investigational treatment are assigned to patients. Emergency unblinding for AEs was also performed through the interactive web-based response system.

In studies JAHL and JAHM, patients were randomly allocated in a 2:1:1:1 ratio to placebo, baricitinib 1-mg, 2-mg, or 4-mg, stratified by geographic region (EU, Japan, rest-of-the-world) and baseline disease severity (IGA 3 versus 4).

In study JAIY, patients were randomly allocated in a 1:1:1 ratio to placebo, baricitinib 2-mg, or 4-mg, stratified by geographic region (EU, Japan, rest-of-the-world) and baseline disease severity (IGA 3 versus 4).

Blinding

A double-dummy design was used for blinding (see Treatments section). All study drugs used were identical in color, shape, smell, and taste to their respective placebo. Study drugs were packed in blisters.

Patients, investigators, and all other personnel involved in the conduct of the studies were blinded to individual treatment assignments for the duration of the studies.

In studies JAHL and JAHM, unblinding occurred only after the reporting database was validated and locked for final statistical analysis. Unblinding of study JAHL occurred on 17 January 2019. Unblinding of study JAHM occurred on 23 January 2019.

In study JAIY, an interim database lock was performed after all patients had completed the 16-week double-blind treatment period of the study. At that time (13 August 2019) a limited number of pre-identified individuals in the submission team accessed limited unblinded data prior to the final database lock. The final database lock was performed 2 weeks later after all patients completed the post-treatment follow-up period.

Statistical methods

Populations and treatment groups

Unless otherwise specified, efficacy analyses in Studies JAHL, JAHM and JAHY were conducted on the ITT population, which includes all patients who were randomised. A per protocol sensitivity analysis was also performed.

For Studies JAHL, JAHM and JAIY, patients were analysed according to the treatment group to which they were randomised.

The following table defines the efficacy analysis populations for the completed Phase 3 studies:

Table 11 Efficacy analysis populations for the completed Phase 3 studies

Efficacy analysis population	Definition	Analyses performed
Studies JAHL, JAHM, and JAIY		
Intent-to-treat (ITT)	All randomised patients, even if the patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Patients were analysed according to the treatment to which they were assigned.	All efficacy analyses
Per Protocol Set (PPS)	All randomised patients who did not have any significant or important protocol deviations, as defined in the individual CSRs.	Primary and key secondary endpoints
Follow-up	All patients who entered the follow-up period	Descriptive summaries for primary and key secondary endpoints

Analyses performed

The primary analysis method for treatment comparisons of dichotomous categorical outcome variables was logistic regression analysis with the following covariates:

- Region
- baseline disease severity (IGA)
- baseline value (if the endpoint studied is not IGA), and
- treatment group.

Firth's correction was used in order to accommodate potential sparse response rates. The p-value for the odds ratio from the logistic regression model was used for statistical inference, unless Firth's correction still resulted in quasi-separation. In that case, Fisher's exact test was used for statistical inference. The difference in percentages and 100(1-alpha)% confidence interval of the difference in percentages were calculated using the Newcombe-Wilson method without continuity correction. The p-value from the Fisher exact test was also produced.

A post hoc analysis investigated the time to IGA 0 or 1, EASI75, and Itch NRS 4 or more point improvement response in Studies JAHL, JAHM, and JAIY using Kaplan Meier methods and nonresponder imputation (NRI).

The relative risk comparing responses was estimated for the primary endpoint and each of the key categorical secondary endpoints. The relative risk compared the response rate of each dose of baricitinib to that of placebo, and the response rate of baricitinib 4-mg to that of baricitinib 2-mg using non-modelled methods. As none of the studies were powered to detect baricitinib 4-mg to baricitinib 2-mg differences, Wald's 95% Confidence Limits were used for this comparison. Statistical significance for categorical endpoints is based only on the odds ratio.

The primary analysis method for treatment comparisons of continuous outcomes variables was a restricted maximum likelihood-based mixed-effects model of repeated measures (MMRM). The model included the following elements as fixed categorical effects:

- treatment
- region
- baseline disease severity (IGA)
- visit, and
- treatment-by-visit interaction.

The model included the following elements as fixed continuous effects:

- baseline value, and
- baseline score-by-visit interaction.

Continuous data were summarised in terms of the number of observations, mean, standard deviation, median, quartiles, minimum and maximum.

The test statistic was the F value derived within the MMRM framework.

Handling of dropouts and missing data

Intercurrent events were defined as:

- application of 1 of the censoring rules (including after permanent study drug discontinuation or after rescue therapy)
- discontinuation
- missing an intermediate visit prior to discontinuation or rescue
- lost to follow-up.

Censoring rules were defined for efficacy and health outcome data collected after a patient permanently discontinued study drug or began rescue therapy:

- The primary censoring rule censored efficacy and health outcome data after permanent study drug discontinuation or after rescue therapy. When the primary censoring rule was applied, all data up to rescue were used.
- The secondary censoring rule censored only efficacy and health outcome data after permanent study drug discontinuation. This rule was applied in the sensitivity analysis and included all observed values up to study drug discontinuation.

In each study, imputation rules were applied after the application of the censoring rules. In Studies JAHL, JAHM, and JAIY the efficacy analyses used 2 pre-specified censoring rules:

Table 12 Studies JAHL, JAHM, and JAIY: pre-specified censoring rules in the efficacy analyses

Primary Censoring Rule	Secondary Censoring Rule
Censored data after permanent study drug discontinuation or use of rescue therapy	Censored data after permanent study drug discontinuation.
In Studies JAHL and JAHM, the primary censoring rule answers the "monotherapy" estimand, that is, estimating the effects of treatments in a monotherapy setting. In Study JAIY, the primary censoring rule answers the "TCS background" estimand, that is, estimating the effects of treatments in a TCS background setting.	In Studies JAHL and JAHM, the secondary censoring rule answers the "TCS rescue" estimand, that is, estimating the effects of treatments if patients followed the treatment policy that includes TCS rescue therapy for patients who experienced unacceptable or worsening symptoms of AD. In Study JAIY, the secondary censoring rule answers the "TCS background plus rescue" estimand, that is, estimating the effects of treatments if patients followed the treatment policy that includes TCS background and additional topical rescue therapy for patients who experienced unacceptable or worsening symptoms of AD.
The primary censoring rule is justified through the composite strategy, that is, NRI after rescue, treatment discontinuation, or study discontinuation (ICH E9 R1).	The secondary censoring rule is justified through the treatment policy estimand (ICH E9 R1).

After applying the censoring rules, different imputation methods were applied for categorical and continuous endpoints.

For categorical endpoints, nonresponder imputation imputed missing values as nonresponses and could be justified based on the composite strategy for handling intercurrent events (ICH E9 R1). This imputation procedure assumed the effects of treatments disappeared after the occurrence of an intercurrent event defined by the associated censoring rule.

For continues endpoints, mixed-effects model of repeated measures analyses were performed on continuous endpoints to mitigate the impact of missing data. This approach assumed that missing observations were missing at random and borrowed information from patients in the same treatment arm, taking into account both the missingness of data through the correlation of the repeated measurements. Essentially, MMRM estimates the treatment effects had all patients remained on their initial treatment throughout the study. For this reason, the MMRM imputation implies a different estimand (hypothetical strategy [ICH E9 R1]) than the one used for NRI on categorical outcomes.

Sensitivity analyses

Sensitivity analyses using different missing data imputation methods ensured that efficacy results were invariant to the primary method of handling missing data. In Studies JAHL, JAHM, and JAIY, sensitivity analyses used placebo multiple imputation (pMI) for categorical and continuous endpoints, Modified last observation carried forward (mLOCF) for continuous endpoints, and tipping point analyses for IGA 0 or 1, EASI75, and Itch NRS 4 or more point improvement.

Multiplicity adjustment

The primary and key secondary endpoints were adjusted for multiplicity to control the overall family-wise Type I error rate through a graphical testing approach. described by Bretz et al. (2011). The studies did not implement adjustments for multiplicity for analyses of any additional efficacy endpoints.

The graphical multiple testing procedure controlled the overall Type I error rate at a 2-sided alpha level of 0.05 within each study. The alpha was split between the 3 doses of baricitinib tested in Studies JAHL and JAHM. To apply the multiplicity adjustment approach, the adjusted significance (alpha) levels were calculated for each hypothesis test.

Results

Participant flow

Patient flow was similar in studies JAHL, JAHM, and JAIY (Table 13). In all three studies, more than 90% of patients completed the 16-weeks study, about 88% of the patients continued in the long term follow-up study JAHN. Discontinuations were lowest in the baricitinib 4 mg treated groups and were similar in the other treatment groups. In the placebo groups, the most frequent reasons for discontinuation were 'lack of efficacy' and 'withdrawal by patient'. Few patients discontinued due to adverse events, usually from the baricitinib treated groups.

Table 13 Patient flow of studies JAHL, JAHM and JAIY

	Study JAHL					Study JAHM					Study JAIY			
	PBO N=249	BARI 1-mg N=127	BARI 2-mg N=123	BARI 4-mg N=125	Total N=624	PBO N=244	BARI 1-mg N=125	BARI 2-mg N=123	BARI 4-mg N=123	Total N=615	PBO +TCS N=109	BARI 2-mg +TCS N=109	BARI 4-mg +TCS N=111	Total N=329
Completed, % (n)	90.8 (226)	91.3 (116)	91.9 (113)	96.0 (120)	92.1 (575)	92.2 (225)	92.0 (115)	91.9 (113)	95.1 (117)	92.7 (570)	92.7 (101)[a]	91.7 (100)	96.4 (107)	93.6 (308)
Entered LTE Study JAHN, % (n)	85.5 (213)	83.5 (106)	87.8 (108)	92.0 (115)	86.9 (542)	87.7 (214)	85.6 (107)	88.6 (109)	90.2 (111)	88.0 (541)	88.1 (96)	86.2 (94)	91.9 (102)	88.8 (292)
Discontinued, % (n)	9.2 (23)	8.7 (11)	8.1 (10)	4.0 (5)	7.9 (49)	7.8 (19)	8.0 (10)	8.1 (10)	4.9 (6)	7.3 (45)	6.4 (7)	8.3 (9)	3.6 (4)	6.1 (20)
Reasons for discontinuation, % (n)														
Adverse event	0.4 (1)	0	0.8 (1)	0	0.3 (2)	0.4 (1)	2.4 (3)	1.6 (2)	1.6 (2)	1.3 (8)	0	0.9 (1)	2.7 (3)	1.2 (4)
Lack of efficacy	4.0 (10)	3.1 (4)	0.8 (1)	2.4 (3)	2.9 (18)	4.1 (10)	1.6 (2)	5.7 (7)	2.4 (3)	3.6 (22)	1.8 (2)	2.8 (3)	0	1.5 (5)
Lost to follow-up	0	0	0.8 (1)	0	0.2 (1)	0	0	0	0.8 (1)	0.2 (1)	0	0	0	0
Withdrawal by patient	4.0 (10)	3.9 (5)	5.7 (7)	1.6 (2)	3.8 (24)	3.3 (8)	2.4 (3)	0.8 (1)	0	2.0 (12)	2.8 (3)	4.6 (5)	0.9 (1)	2.7 (9)
Other	0.8 (2)	1.6 (2)	0	0	0.6 (4)	0	1.6 (2)	0	0	0.3 (2)	1.8 (2)	0	0	0.6 (2)

Abbreviations: BARI = baricitinib; LTE = long-term extension; n = number of patients in the specified category; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo; TCS = topical corticosteroids.

[a] At the time of the interim lock for Study JAIY, 1 patient had completed the Week 16 visit, but was still ongoing in the study. This patient completed the post-treatment follow-up visit (Visit 801) at the time of final database lock.

Source: t_sdydisp_itt.rtf.

For study JAHL, 757 patients were screened and 624 (82%) patients were randomised. For study JAHM, 728 patients were screened and 615 (84%) were randomised. For study JAIY, 378 patients were screened and 329 (87%) were randomised.

Virtually all patients randomly assigned to a treatment group received the correct dose (except for 1 patient in study JAHM randomised to placebo, who got and took baricitinib 1 mg on the day of randomisation only). All randomised patients were included in the ITT population.

In Studies JAHL, JAHM, and JAIY, the PP population consisted of 95% and 100% of the ITT population for all treatment groups.

Recruitment

Studies JAHL and JAHM both ran from November 2017 (first patient first visit) to December 2018 (last patient last visit). Study JAIY ran from November 2018 to August 2019.

For study JAHL, patients were enrolled from sites in 9 countries, European sites from CZ, FR, GE, IT enrolled 337 (54%) of the included patients. For study JAHM, patients were enrolled from sites in 10 countries, European sites from AT, HU, PL, ES, CH enrolled 280 (46%) of the included patients.

For study JAIY, sites from 10 countries enrolled patients; the European sites from AT, GE, IT, PL, ES enrolled 115 (35%) of the included patients.

Conduct of the study

In study JAHL, there had been a single amendment that was performed about 3 weeks after the first patient visit. In study JAHM, there had been two amendments that were performed about 3 weeks and 7 weeks after the first patient visit. The changes in the amendment of study JAHL and the first amendment of study JAHM were based on regulatory feedback (not CHMP), the main change was that the 2 mg dose was added to the primary objective. The second amendment in study JAHM concerned the study title.

In study JAIY, there had been a single amendment that was performed about 4 weeks after the first patient visit. The main changes were that: leukotriene inhibitors were removed from the list of prohibited medications with the rationale that evidence suggested they have limited impact on AD; eosinophilia was removed from the criteria for discontinuation with the rationale that elevated levels of eosinophils are common in AD and do not reflect an increased risk for liver adverse events.

Important protocol deviations were considered to included issues concerning: informed consent; eligibility; study treatment; study procedures. In studies JAHL and JAHM, 21 (3%) and 24 (4%) of patients had at least 1 important protocol deviation and as a consequence, 13 and 12 patients were excluded from the respective PP populations. In study JAIY, 12 (4%) of patients had at least 1 important protocol deviation and as a consequence, 8 patients were excluded from the PP population. The jointly most common important protocol deviations concerned violations of in/exclusion criteria and significant non-compliance to study treatment. There was one patient with a missing informed consent.

Baseline data

Baseline demographical data (age, sex, weight, race) were similar across trials and treatment groups. On average, patients were about 35 years old and nearly all (97%) patients were <65 years of age. About 34%-37% of patients were female and 63%-66% were male. The mean body mass index was about 25. The proportion of patients from the EU in studies JAHL and JAHM was 54% and 46%, which was 35% in study JAIY. Over all three studies, about 18% of patients were from Japan, 28% to 46% were from the rest-of-the-world.

Baseline disease characteristics were similar across trials and treatment groups (Table 14). Disease duration was on average about 25 years (while mean age was 35). Overall most patients had moderate disease severity (IGA of 3) but a large proportion of patients with severe disease (IGA of 4) was included. Baseline variables of main outcomes (IGA, EASI, Itch, sleep disturbance (ADSS item 2), skin pain) and patient reported outcomes (POEM, DLQI, HADS) were equally distributed across treatment groups (Table 14).

Table 14 ***Baseline disease characteristics in studies JAHL, JAHM and JAIY***

	JAHL					JAHM					JAIY			
	PBO N=249	BARI 1-mg N=127	BARI 2-mg N=123	BARI 4-mg N=125	Total N=624	PBO N=244	BARI 1-mg N=125	BARI 2-mg N=123	BARI 4-mg N=123	Total N=615	PBO +TCS N=109	BARI 2-mg +TCS N=109	BARI 4-mg +TCS N=111	Total N=329
Duration since AD diagnosis (years), mean (SD)	25.9 (15.5)	26.7 (14.9)	25.2 (14.6)	24.7 (14.9)	25.7 (15.1)	25.4 (13.9)	23.7 (12.7)	23.9 (13.8)	22.7 (14.8)	24.2 (13.9)	22.0 (12.2)	24.6 (14.8)	25.5 (13.2)	24.0 (13.5)
IGA of 4, %	42.2	41.7	42.3	40.8	41.8	49.6	50.8	50.4	51.2	50.3	44.4	45.9	45.0	45.1
EASI, mean (SD)	31.5 (13.0)	29.1 (11.8)	30.8 (11.7)	31.6 (12.7)	30.9 (12.4)	33.1 (12.8)	33.1 (12.7)	34.7 (16.0)	33.4 (12.7)	33.5 (13.4)	28.5 (12.3)	29.3 (11.9)	30.9 (12.6)	29.6 (12.3)
SCORAD, mean (SD)	67.6 (14.0)	65.9 (14.4)	67.9 (13.0)	67.9 (12.9)	67.4 (13.6)	68.2 (12.7)	67.2 (12.9)	69.2 (13.3)	68.0 (13.6)	68.2 (13.0)	66.6 (13.8)	66.8 (14.1)	68.3 (13.2)	67.2 (13.7)
BSA, mean (SD)	52.8 (23.1)	47.3 (21.2)	49.9 (22.1)	52.2 (21.8)	51.0 (22.3)	52.2 (21.7)	54.7 (21.9)	54.7 (26.1)	53.7 (21.5)	53.5 (22.6)	48.1 (24.4)	50.6 (21.6)	52.1 (23.3)	50.3 (23.1)
POEM, mean (SD)	21.0 (5.6)	20.1 (5.6)	20.7 (5.6)	20.8 (5.6)	20.7 (5.6)	20.5 (6.3)	19.9 (6.5)	20.6 (6.0)	20.4 (6.3)	20.4 6.3	20.9 (6.74)	21.0 (6.32)	21.4 (6.03)	21.1 (6.35)
ADSS Item 2, mean (SD)	3.4 (5.2)	2.5 (3.4)	2.3 (4.1)	3.3 (5.2)	3.0 (4.7)	1.8 (2.1)	1.6 (1.8)	2.1 (2.9)	1.9 (2.5)	1.8 (2.3)	1.8 (2.0)	1.9 (2.3)	1.8 (2.3)	1.8 (2.2)
DLQI, mean (SD)	14.3 (7.4)	12.8 (6.8)	13.1 (7.7)	13.6 (7.1)	13.6 (7.3)	14.6 (8.1)	14.7 (8.1)	14.4 (7.7)	13.8 (8.4)	14.4 (8.1)	15.0 (7.9)	15.0 (7.7)	14.7 (7.9)	14.9 (7.8)
Itch NRS, mean (SD)	6.7 (2.0)	6.1 (2.1)	6.4 (2.2)	6.5 (2.0)	6.5 (2.1)	6.8 (2.2)	6.4 (2.2)	6.6 (2.2)	6.6 (2.2)	6.6 (2.2)	7.4 (1.7)	7.0 (2.1)	7.0 (2.0)	7.1 (2.0)
Skin Pain NRS, mean (SD)	6.1 (2.5)	5.5 (2.4)	5.7 (2.6)	5.7 (2.4)	5.8 (2.5)	6.2 (2.5)	5.7 (2.7)	6.2 (2.5)	6.0 (2.6)	6.1 (2.5)	6.8 (2.3)	6.3 (2.6)	6.0 (2.5)	6.4 (2.5)
PGI-S-AD, mean (SD)	3.9 (0.8)	3.7 (0.8)	3.8 (0.8)	3.9 (0.8)	3.9 (0.8)	3.9 (0.9)	3.9 (0.8)	3.9 (0.8)	3.9 (0.8)	3.9 (0.8)	4.2 (0.8)	3.9 (0.8)	4.0 (0.8)	4.0 (0.8)
HADS anxiety, mean (SD)	6.1 (4.1)	6.2 (4.1)	6.1 (4.3)	5.7 (4.1)	6.1 (4.1)	6.1 (4.2)	6.6 (4.2)	6.1 (4.3)	6.1 (4.6)	6.2 (4.3)	6.8 (4.3)	6.4 (4.0)	6.7 (4.4)	6.6 (4.2)
HADS depression, mean (SD)	4.9 (4.0)	4.9 (4.0)	4.7 (4.2)	4.5 (3.7)	4.8 (4.0)	5.2 (4.2)	5.4 (4.4)	5.1 (4.6)	4.8 (4.2)	5.1 (4.3)	5.8 (4.3)	5.3 (3.7)	5.5 (4.1)	5.5 (4.0)

Baseline Disease Characteristics

Abbreviations: AD = atopic dermatitis; ADSS = Atopic Dermatitis Sleep Scale; BARI = baricitinib; BSA = body surface area affected by AD; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; HADS = Hospital Anxiety Depression Scale; IGA = Investigator's Global Assessment; N = number of patients in the analysis population; NRS = Numeric Rating Scale; PBO = placebo; PGI-S-AD = Patient Global Impression of Severity–Atopic Dermatitis; POEM = Patient Oriented Eczema Measure; SCORAD = SCORing Atopic Dermatitis; SD = standard deviation; TCS = topical corticosteroids.

Source: t_adcc_itt.rtf.

All patients who were included in the three studies reported prior use of TCS and/or systemic therapies (Table 15). TCS was used by 89% to 94% of included patients, TCI was used by 50% to 63% of included patients. Systemic therapy for AD, including corticosteroids, immunosuppressants, biologicals, was used by 52% to 71% of included patients. Most patients for whom systemic therapy failed also had received topical treatment. The most common systemic treatments used were corticosteroids and ciclosporin; dupilumab had been used by few patients (Table 15). The most common reason for treatment failure with ciclosporin was an insufficient response. Of those patients who had not previously used ciclosporin, ciclosporin was contraindicated for 2 to 3% of patients, and medically inadvisable for 45 to 50% of patients. Ciclosporin was considered 'medically inadvisable' if the patient had: a previous inadequate response or intolerance to ciclosporin; a contraindication to ciclosporin; or if there were specific concerns about side effects by the treating physician.

Table 15 ***Prior treatment for AD in studies JAHL, JAHM and JAIY***

	Study JAHL					Study JAHM					Study JAIY			
	PBO N=249	BARI 1-mg N=127	BARI 2-mg N=123	BARI 4-mg N=125	Total N=624	PBO N=244	BARI 1-mg N=125	BARI 2-mg N=123	BARI 4-mg N=123	Total N=615	PBO +TCS N=109	BARI 2-mg +TCS N=109	BARI 4-mg +TCS N=111	Total N=329
Topical therapy[a], % (n)	93.6 (233)	94.5 (120)	96.7 (119)	97.6 (122)	95.2 (594)	95.1 (232)	93.6 (117)	93.5 (115)	94.3 (116)	94.3 (580)	98.2 (107)	97.2 (106)	97.3 (108)-	97.6 (321)
TCS, % (n)	90.8 (226)	90.6 (115)	91.9 (113)	93.6 (117)	91.5 (571)	90.6 (221)	88.8 (111)	90.2 (111)	92.7 (114)	90.6 (557)	92.7 (101)	91.7 (100)	92.8 (103)	92.4 (304)
TCI, % (n)	53.8 (134)	56.7 (72)	55.3 (68)	55.2 (69)	55.0 (343)	59.0 (144)	58.4 (73)	49.6 (61)	62.6 (77)	57.7 (355)	57.8 (63)	55.0 (60)	57.7 (64)	56.8 (187)
TCI inadequate response[b], % (n/N2)	39.6 (53/134)	52.8 (38/72)	60.3 (41/68)	33.8 (23/68)	45.3 (155/342)	46.5 (66/142)	47.9 (35/73)	44.3 (27/61)	41.6 (32/77)	45.3 (160/353)	33.3 (21/63)	26.7 (16/60)	43.8 (28/64)	34.8 (65/187)
TCI intolerance[b], % (n/N2)	7.5 (10/134)	6.9 (5/72)	8.8 (6/68)	10.3 (7/68)	8.2 (28/342)	4.9 (7/142)	6.8 (5/73)	13.1 (8/61)	2.6 (2/77)	6.2 (22/353)	4.8 (3/63)	6.7 (4/60)	6.3 (4/64)	5.9 (11/187)
TCI Ci[c], % (n/N2)	1.8 (2/114)	1.8 (1/55)	0	1.8 (1/56)	1.4 (4/280)	1.0 (1/100)	0	0	0	0.4 (1/260)	7.1 (3/42)	2.1 (1/47)	0	3.0 (4/134)
TCI Inadvisable, % (n/N2)	38.7 (96/248)	45.7 (58/127)	47.2 (58/123)	41.6 (52/125)	42.4 (264/623)	43.9 (107/244)	40.8 (51/125)	39.0 (48/123)	42.3 (52/123)	42.0 (258/615)	40.0 (42/105)	33.6 (36/107)	48.6 (53/109)	40.8 (131/321)
Systemic therapy, % (n)	53.8 (134)	54.3 (69)	54.5 (67)	52.0 (65)	53.7 (335)	68.9 (168)	61.6 (77)	70.7 (87)	59.3 (73)	65.9 (405)	68.8 (75)	63.3 (69)	61.3 (68)	64.4 (212)
Corticosteroid, 1`% (n)	39.4 (98)	40.2 (51)	31.7 (39)	37.6 (47)	37.7 (235)	50.0 (122)	37.6 (47)	48.8 (60)	39.8 (49)	45.2 (278)	54.1 (59)	45.9 (50)	42.3 (47)	47.4 (156)
Immunosuppressant, % (n)	26.5 (66)	25.2 (32)	30.9 (38)	27.2 (34)	27.2 (170)	45.9 (112)	39.2 (49)	52.0 (64)	40.7 (50)	44.7 (275)	39.4 (43)	36.7 (40)	33.3 (37)	36.5 (120)
Ciclosporin, % (n)	21.7 (54)	23.6 (30)	25.2 (31)	24.0 (30)	23.2 (145)	40.6 (99)	32.0 (40)	48.0 (59)	37.4 (46)	39.7 (244)	35.8 (39)	32.1 (35)	29.7 (33)	32.5 (107)
Ciclosporin inadequate response[b], % (n/N2)	57.4 (31/54)	56.7 (17/30)	61.3 (19/31)	56.7 (17/30)	57.9 (84/145)	55.6 (55/99)	55.0 (22/40)	50.8 (30/59)	50.0 (23/46)	53.3 (130/244)	38.5 (15/39)	51.4 (18/35)	39.4 (13/33)	43.0 (46/107)
Ciclosporin intolerance[b], % (n/N2)	16.7 (9/54)	23.3 (7/30)	9.7 (3/31)	20.0 (6/30)	17.2 (25/145)	24.2 (24/99)	15.0 (6/40)	8.5 (5/59)	19.6 (9/46)	18.0 (44/244)	20.5 (8/39)	14.3 (5/35)	15.2 (5/33)	16.8 (18/107)
Ciclosporin Ci[c], % (n/N2)	1.0 (2/194)	2.1 (2/97)	2.2 (2/92)	3.2 (3/95)	1.9 (9/478)	2.8 (4/145)	2.4 (2/85)	0	1.3 (1/77)	1.9 (7/371)	7.8 (5/64)	0	1.3 (1/75)	2.8 (6/211)
Ciclosporin Inadvisable, % (n/N2)	41.1 (102/248)	49.6 (63/127)	47.2 (58/123)	44.8 (56/125)	44.8 (279/623)	54.9 (134/244)	39.2 (49/125)	41.5 (51/123)	41.5 (51/123)	46.3 (285/615)	49.5 (51/103)	49.5 (53/107)	52.8 (57/108)	50.6 (161/318)
Biologic[d], % (n)	5.2 (13)	12.6 (16)	13.0 (16)	5.6 (7)	8.3 (52)	3.3 (8)	4.0 (5)	4.9 (6)	4.1 (5)	3.9 (24)	5.5 (6)	9.2 (10)	6.3 (7)	7.0 (23)

Dupilumab, % (n)	2.4 (6)	8.7 (11)	8.9 (11)	5.6 (7)	5.6 (35)	1.6 (4)	2.4 (3)	4.1 (5)	0	2.0 (12)	4.6 (5)	3.7 (4)	0.9 (1)	3.0 (10)

Abbreviations: CI = contraindication; N = number of patients in the analysis population; n = number of patients in the specified category; N2 = number of patients in the analysis; TCI = topical calcineurin inhibitor; TCS = topical corticosteroids.

a Patients with documented systemic treatment for AD in the past 6 months were also considered inadequate responders to topical treatments and were eligible to enrol in the studies.

b Percentages shown were calculated using the number of patients who had previously used the therapy as the denominator.

c Percentages shown were calculated using the number of patients who had not previously used the therapy as the denominator.

d Prior biologic therapies that were reported included etanercept, lebrikizumab, nemolizumab, omalizumab, reslizumab, tralokinumab, and ustekinumab.

Sources: t_premedad, t_premedad_v2, and t_adcc_itt.rtf.

Numbers analysed

In studies JAHL, JAHM and JAIY, all patients randomised were included in the ITT population. The PP populations consisted of 95% and 100% of the ITT population for all treatment groups.

Compliance and rescue

In each of the studies JAHL, JAHM and JAIY, few patients were classified as non-compliant and compliance was ≥98%. Patient compliance with study treatment had been assessed by pill count at each visit. If a patient at his/her own intention had missed more than 20% of doses of study drug, or had taken more than 20% of study drug, he/she was considered significantly noncompliant.

In studies JAHL and JAHM, 56% and 69% of the patients received rescue treatment (Table 16). The largest proportions of patients needing rescue treatment were in the placebo groups and the smallest proportions were in the baricitinib 4 mg treated groups. In the 4 mg treated groups, 41% and 59% of patients needed rescue during the 16 weeks of study, with few exceptions always TCS (Table 16). In the placebo and 1 mg and 2 mg groups, rescue treatment with TCS was more frequently used as compared to the 4 mg group. TCI and systemic treatments were not frequently used as rescue treatment, when then in the placebo, 1 mg and 2 mg groups (with few exceptions). Rescue treatment was initiated earlier in the placebo and lower-dose groups as compared to the baricitinib 4 mg treated group (Figure 7).

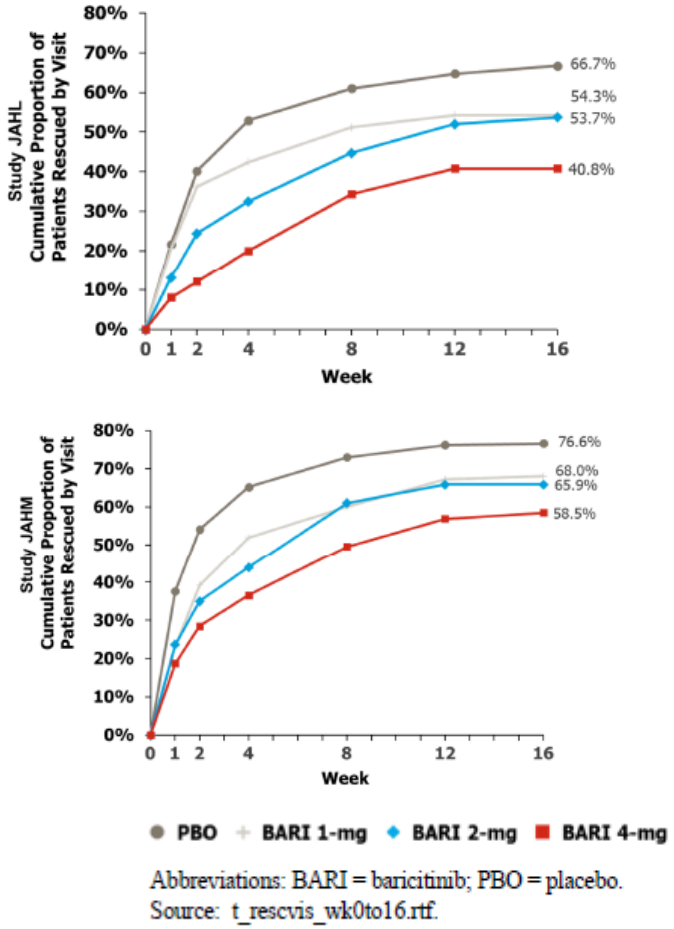
Table 16 ***Use of rescue medication in studies JAHL and JAHM***

	Study JAHL					Study JAHM				
Rescue Therapy, % (n)	PBO N=249	BARI 1-mg N=127	BARI 2-mg N=123	BARI 4-mg N=125	Total N=624	PBO N=244	BARI 1-mg N=125	BARI 2-mg N=123	BARI 4-mg N=123	Total N=615
Any rescue	66.7 (166)	54.3 (69)	53.7 (66)	40.8 (51)	56.4 (352)	76.6 (187)	68.0 (85)	65.9 (81)	58.5 (72)	69.1 (425)
Topical medications	65.1 (162)	52.8 (67)	52.8 (65)	40.8 (51)	55.3 (345)	76.2 (186)	68.0 (85)	65.9 (81)	58.5 (72)	68.9 (424)
TCS	65.1 (162)	52.8 (67)	52.8 (65)	40.8 (51)	55.3 (345)	76.2 (186)	68.0 (85)	65.9 (81)	58.5 (72)	68.9 (424)
TCI	1.2 (3)	1.6 (2)	0.8 (1)	0	1.0 (6)	3.7 (9)	1.6 (2)	2.4 (3)	0.8 (1)	2.4 (15)
Systemic medications	2.4 (6)	2.4 (3)	1.6 (2)	0.8 (1)	1.9 (12)	2.0 (5)	2.4 (3)	2.4 (3)	0	1.8 (11)
Corticosteroids	0.8 (2)	2.4 (3)	0.8 (1)	0.8 (1)	1.1 (7)	2.0 (5)	2.4 (3)	1.6 (2)	0	1.6 (10)
Ciclosporin	1.6 (4)	0	0.8 (1)	0	0.8 (5)	0	0	0.8 (1)	0	0.2 (1)

Abbreviations: BARI = baricitinib; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo; TCI = topical calcineurin inhibitor; TCS = topical corticosteroids.

Note: Rescue using TCS did not require study drug discontinuation. Rescue using systemic medications did require study drug discontinuation.

Source: t_cmrs.rtf.



Abbreviations: BARI = baricitinib; PBO = placebo.
Source: t_rescvis_wk0to16.rtf.

Figure 7 ***Cumulative proportion of patients having received rescue treatment in studies JAHL and JAHM***

In add-on study JAIY, study treatment was added to existing treatment with low- or moderate potency TCS (*described in the Treatments section above*). In total, 6% of the patients received rescue treatment, most frequently in the placebo group (9%) and less (5%) in the baricitinib treated groups (Table 17). Rescue treatment usually was a high-potency TCS (study drug was continued) and less frequently systemic treatment (study drug discontinued).

Table 17 ***Use of rescue medication in study JAIY***

Rescue Therapy, % (n)	PBO +TCS N=109	BARI 2-mg +TCS N=109	BARI 4-mg +TCS N=111	Total N=329
Any rescue	9.2 (10)	4.6 (5)	5.4 (6)	6.4 (21)
TCS	9.2 (10)	3.7 (4)	3.6 (4)	5.5 (18)
Systemic medications	0.9 (1)	0.9 (1)	1.8 (2)	1.2 (4)
Corticosteroids	0	0.9 (1)	1.8 (2)	0.9 (3)
Ciclosporin	0.9 (1)	0	0	0.3 (1)

Abbreviations: BARI = baricitinib; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo; TCS = topical corticosteroids.
Note: Rescue using TCS did not require study drug discontinuation. Rescue using systemic medications did require study drug discontinuation.

Outcomes and estimation

IGA 0 or 1 (primary outcome)

In all three studies (JAHL, JAHM, JAIY), baricitinib 4 mg was statistically significant more effective than placebo in reaching IGA 0 or 1 at week 16 (with a ≥2 points improvement from baseline), while adjusting for multiplicity (Table 18). Baricitinib 2 mg was more effective than placebo in reaching IGA 0 or 1 at week 16 in studies JAHL and JAHM, but not in study JAIY. The 1 mg dose was not more effective than placebo.

In study JAHL, IGA 0 or 1 was reached by 17% of patients in the baricitinib 4 mg group, 11% in the 2 mg group, 12% in the 1 mg group, and 5% in the placebo group. The difference (95%CI) with placebo was 12.0% (5.5% – 19.8%) for the 4 mg group and 6.6 (0.9% – 13.7%) for the 2 mg group, which was significant after adjustment for multiplicity for both comparisons.

In study JAHM, IGA 0 or 1 was reached by 14% of patients in the baricitinib 4 mg group, 11% in the 2 mg group, 9% in the 1 mg group, and 5% in the placebo group. The difference (95%CI) with placebo was 9.3% (3.3% – 16.8%) for the 4 mg group and 6.1 (0.6% – 13.0%) for the 2 mg group, which was significant after adjustment for multiplicity for both comparisons.

In study JAIY, IGA 0 or 1 was reached by 31% of patients in the baricitinib 4 mg group, 24% in the 2 mg group, and 15% in the placebo group. The difference (95%CI) with placebo was 16.0% (4.9% – 26.6%) for the 4 mg group and 9.2 (-1.4% – 19.5%) for the 2 mg group, which was significant after adjustment for multiplicity for the 4 mg dose group.

Table 18 ***Proportions of patients reaching IGA 0 or 1 at week 16, in studies JAHL, JAHM and JAIY (ITT).***

	Study JAHL				Study JAHM				Study JAIY		
	PBO N=249	BARI 1-mg N=127	BARI 2-mg N=123	BARI 4-mg N=125	PBO N=244	BARI 1-mg N=125	BARI 2-mg N=123	BARI 4-mg N=123	PBO +TCS N=109	BARI 2-mg +TCS N=109	BARI 4-mg +TCS N=111
Response, % (n) 95% CI	4.8 (12) (2.8, 8.2)	11.8 (15) (7.3, 18.6)	11.4 (14) (6.9, 18.2)	16.8 (21) (11.3, 24.3)	4.5 (11) (2.5, 7.9)	8.8 (11) (5.0, 15.1)	10.6 (13) (6.3, 17.2)	13.8 (17) (8.8, 21.0)	14.7 (16) (9.2, 22.5)	23.9 (26) (16.8, 32.7)	30.6 (34) (22.8, 39.7)
Difference vs placebo, % (95% CI)		7.0 (1.3, 14.1)	6.6 (0.9, 13.7)	12.0 (5.5, 19.8)		4.3 (-0.8, 10.9)	6.1 (0.6, 13.0)	9.3 (3.3, 16.8)		9.2 (-1.4, 19.5)	16.0 (4.9, 26.6)
p-Value[a] vs placebo		0.014	**0.020**	**<0.001**		0.085	**0.026**	**0.001**		0.082	**0.004**
Relative risk vs placebo at Week 4		1.31	3.71	4.32		0.87	2.20	4.19		3.17	3.60
Relative risk vs placebo at Week 16		2.45	2.36	3.49		1.95	2.34	3.07		1.63	2.09

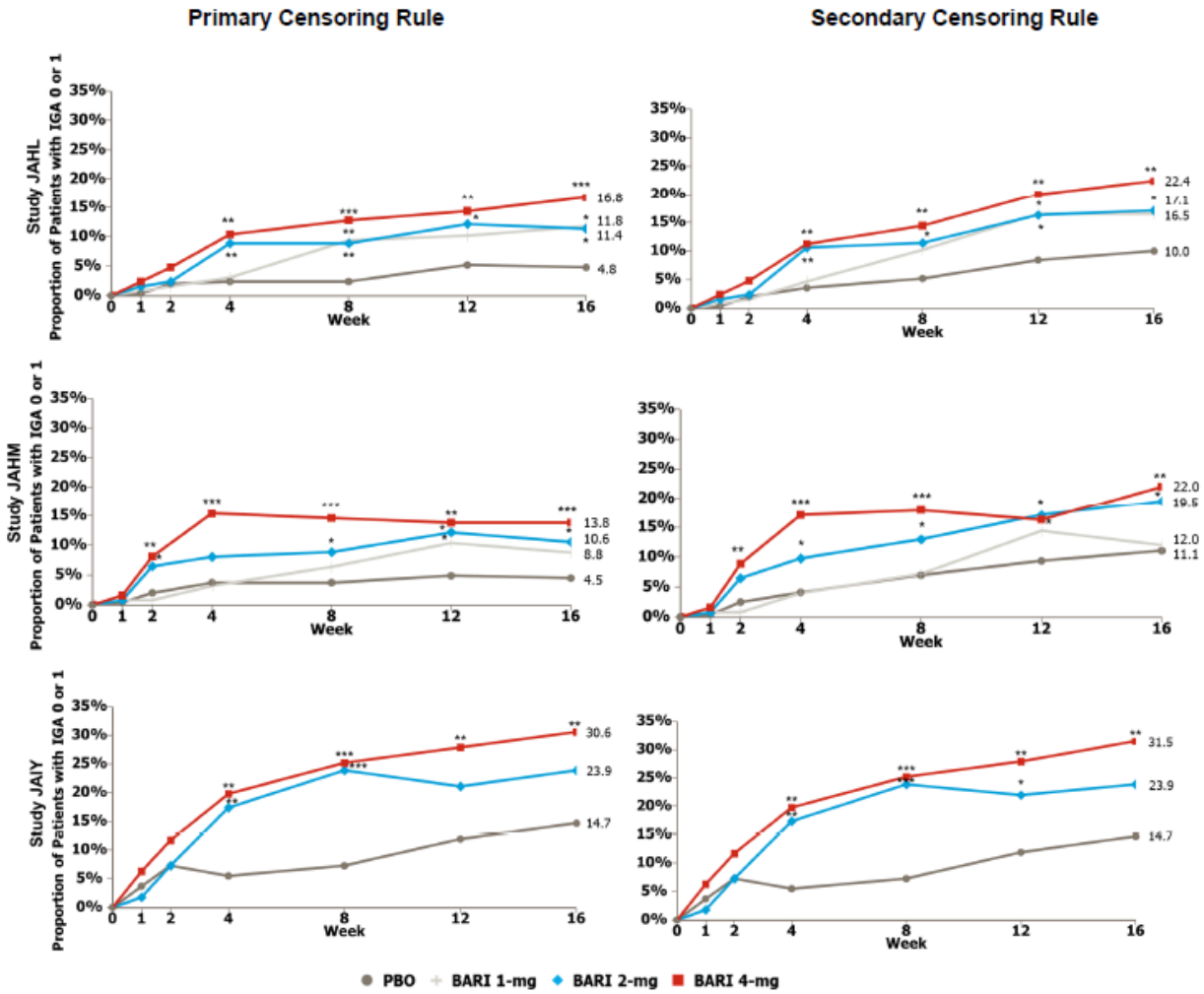
Abbreviations: BARI = baricitinib; CI = confidence interval; IGA = Investigator's Global Assessment; ITT = intent-to-treat; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo; TCS = topical corticosteroids.

[a] Odds ratio p-value from logistic regression.

Note: Results in **bold** were statistically significant after adjustment for multiplicity.

Source: t_igaresp_nri_itt_wk0to16r.rtf.

The effect of baricitinib 4 mg and 2 mg on IGA 0 or 1 appeared after 2-4 weeks of treatment in studies JAHL, JAHM and JAIY (Figure 8). By means of sensitivity analysis, the efficacy data were also analysed with data that were obtained after rescue treatment ('secondary censoring'). In studies JAHL and JAHM, responses in IGA 0 or 1 became somewhat higher after secondary censoring, but the time course and between-group differences were similar (Figure 8). In study JAIY rescue treatment was not frequently applied and results of primary and secondary censoring were about the same (Figure 8).



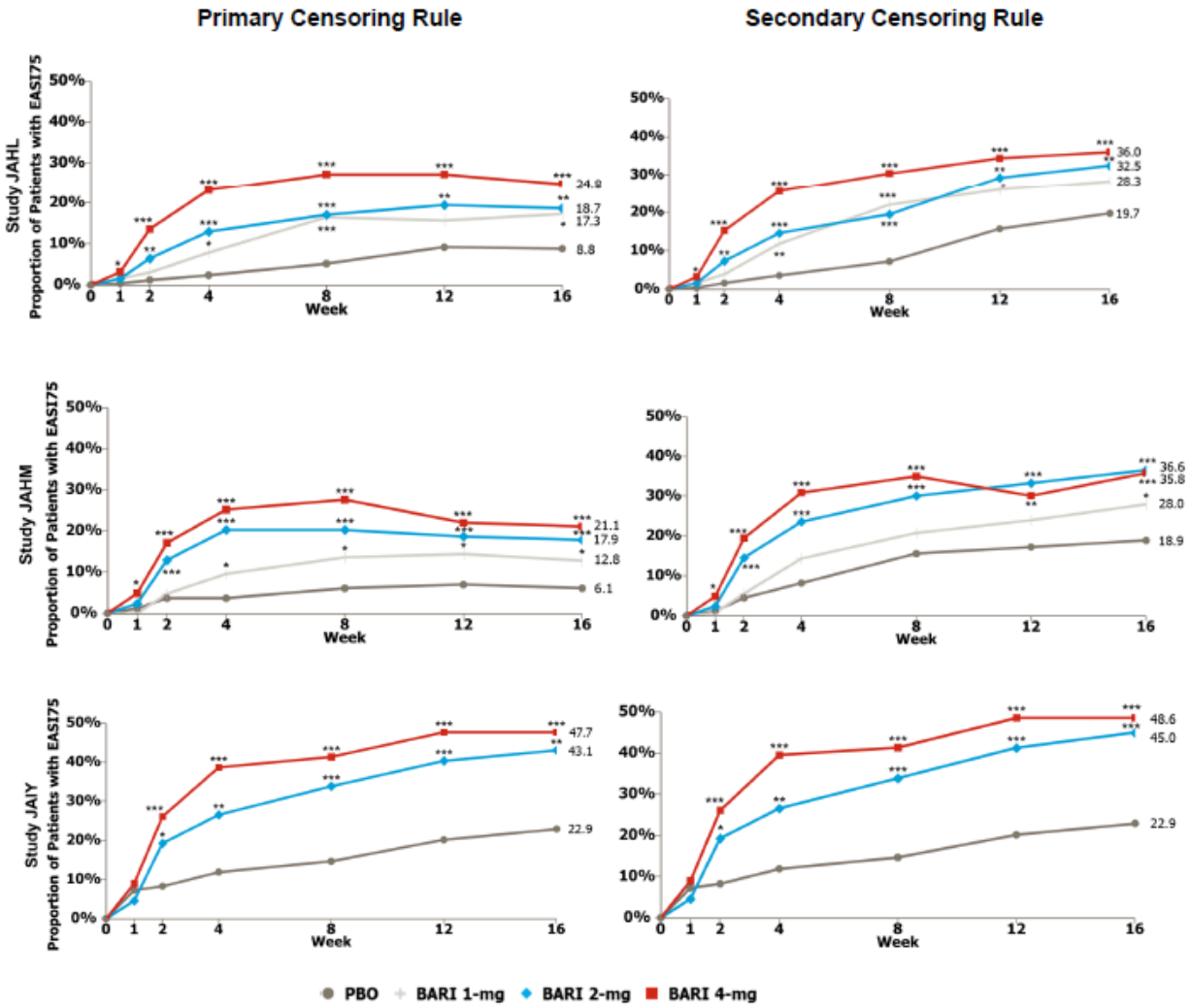
Abbreviations: BARI = baricitinib; IGA = Investigator's Global Assessment; ITT = intent-to-treat; PBO = placebo.
*p-Value for baricitinib versus placebo ≤0.05.
**p-Value for baricitinib versus placebo ≤0.01.
***p-Value for baricitinib versus placebo ≤0.001.
Sources: t_igaresp_nri_itt_wk0to16r.rtf and t_igaresp_nri_itt_wk0to16.rtf.

Figure 8 Proportions of patients with IGA 0 or 1 over time in studies JAHL, JAHM, JAIY, with (primary censoring) and without censoring after rescue (secondary censoring).

Eczema Area and Severity Index (EASI)

For baricitinib 4 mg, the percentage of patients with EASI75 response at week 16 was statistically significant larger as compared to placebo, in all three studies. For baricitinib 2 mg, this was reached in studies JAHL and JAHM, but not in study JAIY.

In study JAHL, EASI75 at week 16 was reached by 25% of patients on baricitinib 4 mg, 19% on 2 mg, 17% on 1 mg and 9% on placebo, which was statistically significant versus placebo for the 4 mg and 2 mg groups (Table 19). In study JAHM, EASI75 at week 16 was reached by 21% of patients on baricitinib 4 mg, 18% on 2 mg, 13% on 1 mg and 6% on placebo, which was statistically significant versus placebo for the 4 mg and 2 mg groups (Table 20). In study JAIY, EASI75 at week 16 was reached by 48% of patients on baricitinib 4 mg + TCS, 43% on 2 mg + TCS, and 23% on placebo + TCS, which was statistically significant for 4 mg only (Table 21).



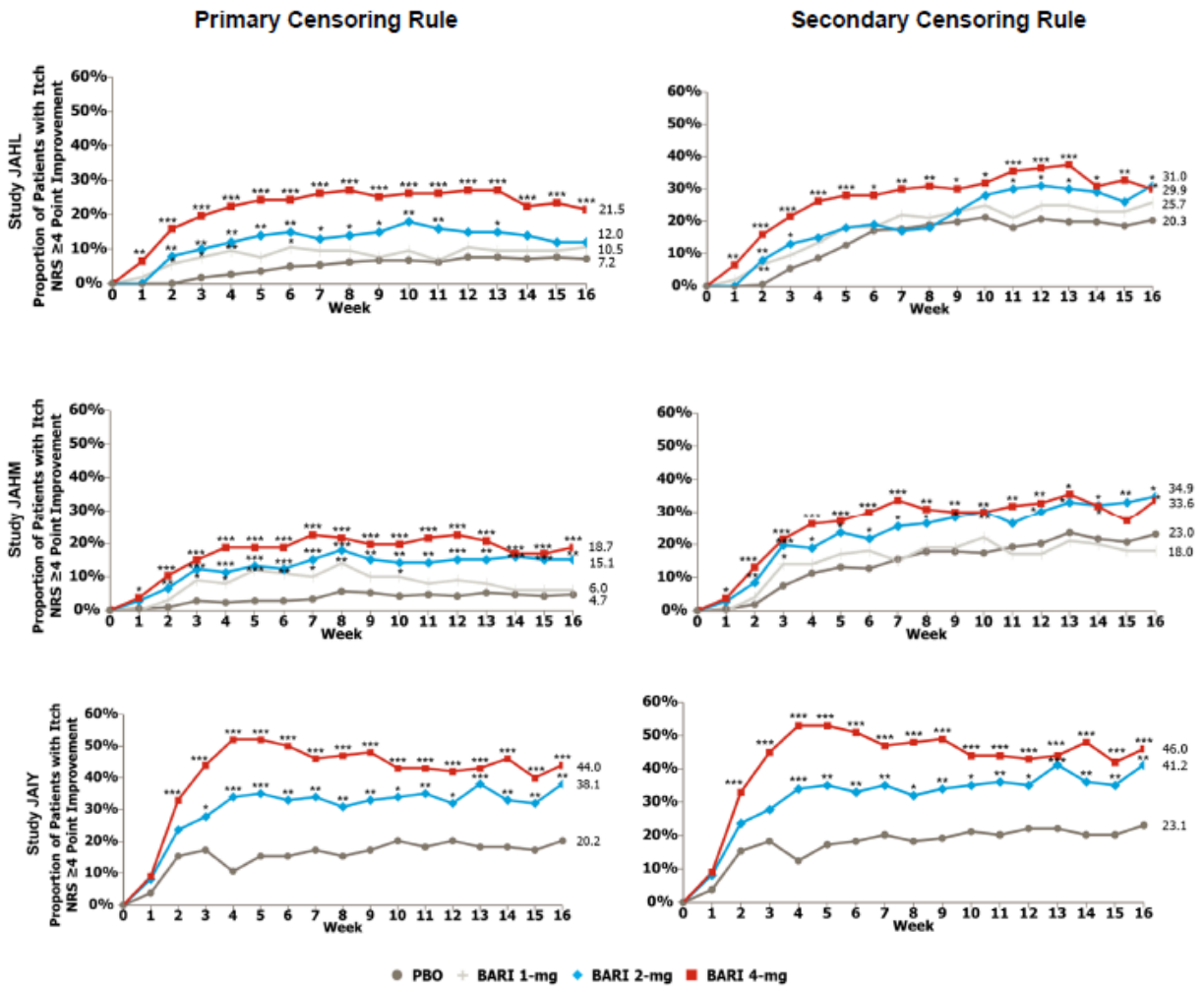
Abbreviations: BARI = baricitinib; EASI75 = 75% improvement in Eczema Area and Severity Index; ITT = intent-to-treat; PBO = placebo.
*p-Value for baricitinib versus placebo ≤0.05.
**p-Value for baricitinib versus placebo ≤0.01
***p-Value for baricitinib versus placebo ≤0.001.
Sources: t_easi507590_nri_itt_wk0to16r.rtf and t_easi507590_nri_itt_wk0to16.rtf.

Figure 9 Proportions of patients with EASI75 over time in studies JAHL, JAHM, JAIY, with (primary censoring) and without censoring after rescue (secondary censoring).

Itch NRS

For baricitinib 4 mg, the percentage of patients with an improvement ≥4 points in the Itch NRS at week 16 was statistically significant larger as compared to placebo, in all three studies (Table 19 to Table 21). For baricitinib 2 mg, this was reached in study JAHM, but not in studies JAHL and JAIY.

In studies JAHL and JAHM an improvement ≥4 points in the Itch NRS at week 16 was reached by 22% and 19% of patients treated with baricitinib 4 mg, 12% and 15% in patients treated with 2 mg, and 7% and 5% in the placebo groups. In study JAIY, an improvement in Itch NRS≥4 points was reached by 44% of patients treated with 4 mg, 38% of patients on 2 mg, and 20% of patients on placebo.



Abbreviations: BARI = baricitinib; ITT = intent-to-treat; NRS = Numeric Rating Scale; PBO = placebo.
*p-Value for baricitinib versus placebo ≤0.05.
**p-Value for baricitinib versus placebo ≤0.01
***p-Value for baricitinib versus placebo ≤0.001
Sources: t_itchresp_nri_itt_wk0to16r.rtf and t_itchresp_nri_itt_wk0to16.rtf.

Figure 10 Proportions of patients with an improvement in Itch ⩾4 points over time, in studies JAHL, JAHM, JAIY, with (primary censoring) and without censoring after rescue (secondary censoring).

Atopic Dermatitis Sleep Scale (ADSS)

ADSS sleep item 2 concerns the number of times a patient woke up at night. For baricitinib 4 mg, the change in this item at week 16 was statistically significant larger as compared to placebo, in studies JAHL and JAHM, but not in study JAIY (Tables Table 19 to Table 21). For baricitinib 2 mg, the change in the ADSS sleep item 2 was statistically significant in study JAHM, but not in studies JAHL and JAIY.

In study JAHL, the mean change in number of times a patient woke up (ADSS item 2) at week 16 as compared to baseline was -1.4 for baricitinib 4 mg, -1.0 for 2 mg, -1.2 for 1 mg and -0.8 for placebo. In study JAHM, the mean change in number of times a patient woke up at week 16 as compared to baseline was -1.1 for baricitinib 4 mg, -1.0 for 2 mg, -0.8 for 1 mg and -0.5 for placebo. In study JAIY, the mean change in number of times a patient woke up at week 16 as compared to baseline was -1.4 for baricitinib 4 mg, -1.3 for 2 mg, and -0.5 for placebo. This transformed in a larger average proportion of nights without awakenings on higher doses of baricitinib as compared to placebo (Figure 11; post-hoc analysis).

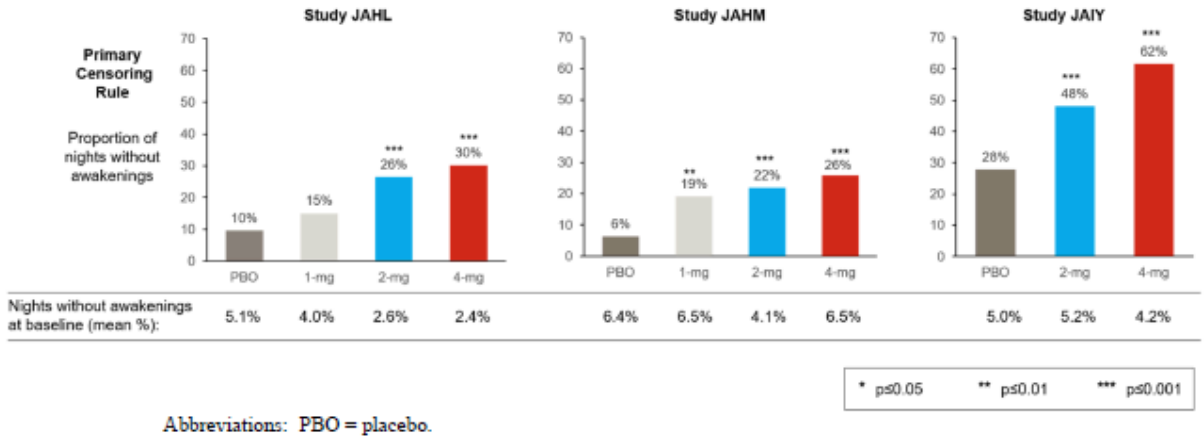


Figure 11 ***Proportion of nights without awakenings in studies JAHL, JAHM and JAIY***

Results in the SCORAD sleep loss item and ADSS item 1 on 'difficulty falling asleep' in studies JAHL, JAHM and JAIY showed numerically larger effects in baricitinib 4 mg, and to a less extent 2 mg, versus placebo, not corrected for multiplicity. In ADSS item 3 on 'difficulty getting back to sleep' the effects compared to placebo were small and not statistically significant.

SCORing Atopic Dermatitis (SCORAD)

For baricitinib 4 mg, the percentage of patients having reached SCORAD75 at week 16 was statistically significant larger as compared to placebo, in studies JAHL and JAHM, but not in study JAIY (Table 19 to Table 21). For baricitinib 2 mg, this was reached in study JAHM, but not in studies JAHL and JAIY.

The proportions of patients reaching SCORAD75 on baricitinib 4 mg were 10% and 11% versus 1% and 2% on placebo in studies JAHL and JAHM. In study JAIY, SCORAD75 at week 16 was reached by 18% of patients on 4 mg and 7% on placebo.

Skin pain NRS

For baricitinib 4 mg, the change in the Skin Pain NRS at week 16 was statistically significant larger as compared to placebo, in studies JAHL and JAHM, but not in study JAIY (Table 19 to Table 21). For baricitinib 2 mg, the change in Skin Pain NRS was statistically significant in study JAHM, but not in studies JAHL and JAIY.

In studies JAHL and JAHM, the mean change in the skin pain NRS for patients treated with baricitinib 4 mg was -1.9 and -2.5 compared to -0.8 and -0.9 in the placebo groups. In study JAIY, the mean change in the skin pain NRS for patients treated with baricitinib 4 mg was -3.7 compared to -2.1 in the placebo group.

Dermatology Life Quality Index (DLQI)

For baricitinib 4 mg and 2 mg, the change in the DLQI at week 16 was larger ($p<0.05$, without adjustment for multiplicity) as compared to placebo, in studies JAHL, JAHM and JAIY. The response of the 4 mg dose was numerically better than the response of the 2 mg dose group. Similar results for the two doses were found with improvement in DLQI ≥4 points (considered as MCID) as outcome.

Patient Oriented Eczema Measure (POEM)

For baricitinib 4 mg and 2 mg, the change in the POEM at week 16 was larger ($p<0.05$, without adjustment for multiplicity) as compared to placebo, in studies JAHL, JAHM and JAIY. The response of the 4 mg dose was numerically better than the response of the 2 mg dose group. Similar results for the two doses were found with improvement in POEM ≥4 points (larger than the MCID) as outcome.

Hospital Anxiety and Depression Scale (HADS)

For baricitinib 4 mg, the change in the HADS total score at week 16 was larger ($p<0.05$, without adjustment for multiplicity) as compared to placebo, in studies JAHL, JAHM and JAIY. For baricitinib 2 mg this was the case in studies JAHL and JAIY, but not in JAHM. The response of the 4 mg dose was numerically better than the response of the 2 mg dose group. For HADS anxiety score <8 points and HADS depression score <8 points results were less clear.

Sensitivity analyses

Analysis of the PPS population in studies JAHL, JAHM and JAIY, gave comparable results and the same conclusions as the ITT population for the primary and key secondary endpoints, notably for IGA 0 or 1, EASI75 and Itch NRS≥4.

The efficacy results, notably for IGA 0 or 1, EASI75 and Itch NRS≥4, obtained using secondary censoring, which included data after rescue treatment (usually TCS) were largely consistent (JAHL and JAHM) or practically identical (JAIY) with those of primary censoring that included only data on monotherapy.

The results analysed using 'placebo' Multiple Imputation (with the assumption that the investigational product provides no pharmacological benefit over placebo following an intercurrent event) supported the effect of baricitinib 4 mg over placebo (notably in IGA 0 or 1, EASI75 and Itch NRS≥4) in studies JAHL, JAHM and JAIY. In these analyses, the effects of the 2 mg dose were not consistently statistically significant different from placebo.

Table 19 ***Results for primary and key secondary outcomes in study JAHL (ITT)***

	PBO N=249	BARI 1-mg N=127	BARI 2-mg N=123	BARI 4-mg N=125
Primary Endpoint				
IGA				
Proportion of patients with IGA 0 or 1 at W16, % (n)	4.8 (12)	11.8* (15)	**11.4*** (14)	**16.8***** (21)
Key Secondary Endpoints				
EASI				
Proportion of patients with EASI75 at W16, % (n)	8.8 (22)	17.3* (22)	**18.7**** (23)	**24.8***** (31)
Proportion of patients with EASI90 at W16, % (n)	4.8 (12)	8.7 (11)	10.6* (13)	**16.0***** (20)
LSM percent change from baseline in EASI at W16 (SE)	-34.82 (3.64)	-48.22* (4.52)	-51.89** (4.29)	**-59.36***** (3.84)
Itch NRS				
Proportion of patients with Itch NRS ≥4-point improvement				
at W16, % (n/N2)	7.2 (16/222)	10.5 (11/105)	12.0 (12/100)	**21.5***** (23/107)
at W4, % (n/N2)	2.7 (6/222)	9.5** (10/105)	12.0** (12/100)	**22.4***** (24/107)
at W2, % (n/N2)	0.0 (0/222)	5.7* (6/105)	8.0** (8/100)	**15.9***** (17/107)
at W1, % (n/N2)	0.0 (0/222)	1.9 (2/105)	0.0 (0/100)	**6.5**** (7/107)
SCORAD				
Proportion of patients with SCORAD75 at W16, % (n)	1.2 (3)	5.5* (7)	7.3** (9)	**10.4***** (13)
ADSS				
LSM change from baseline in ADSS Item 2				
at W16 (SE)	-0.84 (0.15)	-1.21 (0.18)	-1.04 (0.17)	**-1.42**** (0.16)
at W1 (SE)	0.11 (0.11)	-0.32* (0.15)	-0.30* (0.15)	**-0.91***** (0.15)
Skin Pain NRS				
LSM change from baseline in Skin Pain NRS at W16 (SE)	-0.84 (0.24)	-1.92** (0.30)	-1.58 (0.29)	**-1.93**** (0.26)

Abbreviations: ADSS = Atopic Dermatitis Sleep Scale; BARI = baricitinib; EASI75/90 = 75%/90% improvement from baseline in Eczema Area and Severity Index; IGA = Investigator's Global Assessment; ITT = intent-to-treat; LSM = least squares mean; N = number of patients in the analysis population; n = number of patients in the specified category; N2 = number of eligible patients for categorical assessment. For Itch NRS improvement, only patients with baseline severity of 4 or more points were included in the analysis; NRS = Numeric Rating Scale; PBO = placebo; SCORAD75 = 75% improvement in SCORing Atopic Dermatitis; SE = standard error; W = week.

Note: Results in **bold** were statistically significant after adjustment for multiplicity. Other results designated with asterisks were statistically significant, without adjustment for multiplicity.

*p-Value for baricitinib versus placebo ≤0.05.

**p-Value for baricitinib versus placebo ≤0.01.

***p-Value for baricitinib versus placebo ≤0.001.

Sources: t_igaresp_nri_itt_wk0to16r.rtf, t_easi507590_nri_itt_wk0to16r.rtf, t_easipchg_mmrm_itt_wk0to16r.rtf, t_itchresp_nri_itt_wk0to16r.rtf, t_scorad7590_nri_itt_wk0to16r.rtf, t_adsschg_mmrm_itt_wk0to16r.rtf, and t_skinchg_mmrm_itt_wk0to16r.rtf.

Table 20 ***Results for primary and key secondary outcomes in study JAHM (ITT)***

	PBO N=244	BARI 1-mg N=125	BARI 2-mg N=123	BARI 4-mg N=123
Primary Endpoint				
IGA				
Proportion of patients with IGA 0 or 1 at W16, % (n)	4.5 (11)	8.8 (11)	**10.6*** (13)	**13.8***** (17)
Key Secondary Endpoints				
EASI				
Proportion of patients with EASI75 at W16, % (n)	6.1 (15)	12.8* (16)	**17.9***** (22)	**21.1***** (26)
Proportion of patients with EASI90 at W16, % (n)	2.5 (6)	6.4 (8)	**8.9**** (11)	**13.0***** (16)
LSM percent change from baseline in EASI score at W16 (SE)	-28.91 (4.32)	-41.68 (5.33)	**-54.80***** (4.99)	**-54.88***** (4.56)
Itch NRS				
Proportion of patients with Itch NRS ≥4-point improvement				
at W16, % (n/N2)	4.7 (10/213)	6.0 (6/100)	**15.1**** (16/106)	**18.7***** (20/107)
at W4, % (n/N2)	2.3 (5/213)	8.0* (8/100)	**11.3***** (12/106)	**18.7***** (20/107)
at W2, % (n/N2)	0.9 (2/213)	3.0 (3/100)	**6.6**** (7/106)	**10.3***** (11/107)
at W1, % (n/N2)	0.5 (1/213)	0.0 (0/100)	2.8 (3/106)	**3.7*** (4/107)
SCORAD				
Proportion of patients with SCORAD75 at W16, % (n)	1.6 (4)	4.8 (6)	**7.3**** (9)	**11.4***** (14)
ADSS				
LSM change from baseline in Item 2 of ADSS				
at W16 (SE)	-0.50 (0.12)	-0.78 (0.14)	**-1.03**** (0.13)	**-1.13***** (0.13)
at W1 (SE)	-0.02 (0.07)	**-0.37**** (0.10)	**-0.37**** (0.10)	**-0.58***** (0.10)
Skin Pain NRS				
LSM change from baseline in Skin Pain NRS at W16 (SE)	-0.86 (0.26)	-1.09 (0.32)	**-2.61***** (0.30)	**-2.49***** (0.28)

Abbreviations: ADSS = Atopic Dermatitis Sleep Scale; BARI = baricitinib; EASI75/90 = 75%/90% improvement from baseline in Eczema Area and Severity Index; IGA = Investigator's Global Assessment; ITT = intent-to-treat; LSM = least squares mean; N = number of patients in the analysis population; n = number of patients in the specified category; N2 = number of eligible patients for categorical assessment. For Itch NRS improvement, only patients with baseline severity of 4 or more points were included in the analysis; NRS = Numeric Rating Scale; PBO = placebo; SCORAD75 = 75% improvement in SCORing Atopic Dermatitis; SE = standard error; W = week.

Note: Results in **bold** were statistically significant after adjustment for multiplicity. Other results designated with asterisks were statistically significant, without adjustment for multiplicity.

*p-Value for baricitinib versus placebo ≤0.05.

**p-Value for baricitinib versus placebo ≤0.01.

***p-Value for baricitinib versus placebo ≤0.001.

Sources: t_igaresp_nri_itt_wk0to16r.rtf, t_easi507590_nri_itt_wk0to16r.rtf, t_easipchg_mmrm_itt_wk0to16r.rtf, t_itchresp_nri_itt_wk0to16r.rtf, t_scorad7590_nri_itt_wk0to16r.rtf, t_adsschg_mmrm_itt_wk0to16r.rtf, and t_skinchg_mmrm_itt_wk0to16r.rtf.

Table 21 ***Results for primary and key secondary outcomes in study JAIY (ITT)***

	PBO + TCS N=109	BARI 2-mg + TCS N=109	BARI 4-mg + TCS N=111
Primary Endpoint			
IGA			
IGA 0 or 1 response rate at W16, % (n)	14.7 (16)	23.9 (26)	**30.6**** (34)
EASI			
Proportion of patients with EASI75 at W16, % (n)	22.9 (25)	43.1** (47)	**47.7***** (53)
Proportion of patients with EASI90 at W16, % (n)	13.8 (15)	16.5 (18)	24.3* (27)
LSM percent change from baseline in EASI score at W16 (SE)	-45.08 (3.83)	-58.16* (3.69)	**-67.21***** (3.68)
Itch NRS			
Proportion of patients with Itch NRS ≥4-point improvement			
at W16, % (n/N2)	20.2 (21/104)	38.1** (37/97)	**44.0***** (44/100)
at W4, % (n/N2)	10.6 (11/104)	34.0***** (33/97)	**52.0***** (52/100)
at W2, % (n/N2)	15.4 (16/104)	23.7 (23/97)	33.0***** (33/100)
at W1, % (n/N2)	3.8 (4/104)	8.2 (8/97)	9.0 (9/100)
at Day 2[a], % (n/N2)	1.9 (2/104)	5.2 (5/97)	8.0 (8/100)
SCORAD			
Proportion of patients with SCORAD75 at W16, % (n)	7.3 (8)	11.0 (12)	18.0* (20)
ADSS			
LSM change from baseline in ADSS Item 2			
at W16 (SE)	-0.51 (0.15)	-1.33***** (0.15)	-1.42***** (0.15)
at W1 (SE)	-0.50 (0.10)	-0.73 (0.10)	-0.93** (0.10)
Skin Pain NRS			
LSM change from baseline in Skin Pain NRS at W16 (SE)	-2.06 (0.23)	-3.22***** (0.22)	-3.73***** (0.23)

Abbreviations: BARI = baricitinib; EASI75/90 = 75%/90% improvement from baseline in Eczema Area and Severity Index; IGA = Investigator's Global Assessment; LSM = least squares mean; N = number of patients in the analysis population; n = number of patients in the specified category; N2 = number of eligible patients for categorical assessment. For Itch NRS improvement, only patients with baseline severity of 4 or more points were included in the analysis; NRS = Numeric Rating Scale; PBO = placebo; SCORAD75 = 75% improvement in SCORing Atopic Dermatitis; SE = standard error; TCS = topical corticosteroids; W = week.

*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 were statistically significant, without adjustment for multiplicity.

[a] Itch NRS score at Day 2 is defined as the score collected on Day 2 only.

Sources: t_igaresp_nri_itt_wk0to16r.rtf, t_easi507590_nri_itt_wk0to16r.rtf, t_easipchg_mmrm_itt_wk0to16r.rtf, t_itchresp_nri_itt_wk0to16r.rtf, t_itch4_nri_itt_d2r.rtf, t_scorad7590_nri_itt_wk0to16r.rtf, t_adsschg_mmrm_itt_wk0to16r.rtf, and t_skinchg_mmrm_itt_wk0to16r.rtf.

A Phase 3 Multicenter, Double-Blind Study to Evaluate the Long- Term Safety and Efficacy of Baricitinib in Adult Patients with Atopic Dermatitis (JAHN).

In the first 52-week period of the long term extension study (JAHN) all three doses of baricitinib were evaluated (Table 2). Patients were mainly recruited from JAHL, JAHM and JAIY. In the three 16-week

'phase 3' studies (JAHL, JAHM, JAIY), three oral doses of baricitinib were evaluated against placebo: 1-mg, 2-mg, and 4-mg once daily (also see Table 2).

Study JAHN is currently ongoing and the data have been updated during the procedure. Accordingly, all patients from originating monotherapy studies JAHL and JAHM have completed week 52 of study JAHN (68 weeks of total treatment) or have discontinued. All patients originating from combination therapy study JAIY have completed week 16 or have discontinued, and 54% of patients have completed week 24, of JAHN. After Week 52 of Study JAHN, patients were eligible to participate in a downtitration substudy, of which some data were submitted during the application.

Design and objectives

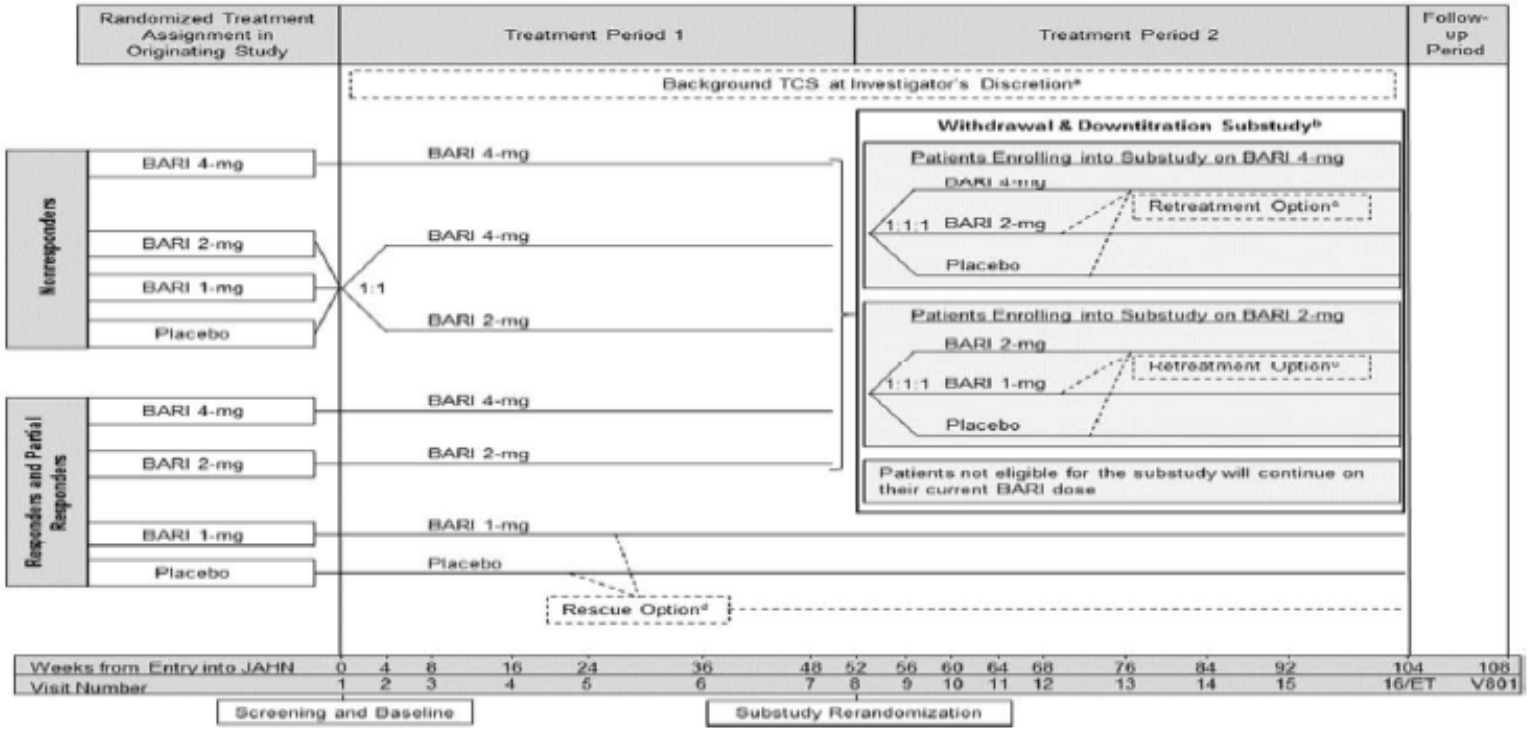
Study JAHN is a Phase 3, multicenter, double-blind study to evaluate the long-term safety and efficacy of baricitinib 1-mg, 2-mg, and 4-mg once daily (QD) in adult patients with atopic dermatitis (AD) who had completed studies JAHL, JAHM, or JAIY. A sub study/cohort was added to evaluate efficacy and safety of baricitinib 2-mg open-label in adult patients with moderate to severe AD who had not completed an originating study.

In 'maintenance and up-titration' treatment period 1 (week 0 – 52): patients who were responders or partial responders at week 16 of the originating study and have not had rescue treatment, continued their treatment assigned. Non-responders on baricitinib 4 mg continued on the same dose. Non responders on placebo, 1 mg or 2 mg were re-randomised (1:1) to baricitinib 2 mg or 4 mg.

If patients had an…	Then they were classified as…
IGA of 0 or 1 AND were not rescued in the originating study	Responders
IGA of 2 AND were not rescued in the originating study	Partial responders
IGA of 3 or 4 OR were rescued in the originating study	Nonresponders

In 'withdrawal and down-titration' treatment period 2 (week 52 – 104): patients who are responders or partial responders on 2 mg or 4 mg at week 52 and are otherwise eligible will be re-randomised (1:1:1) to dose continuation, the next lower dose (1 mg or 2 mg), or placebo. Ineligible patients will continue the dose assigned in treatment period 1.

The primary objective was to estimate the effect of long-term therapy with baricitinib on responders and partial responders at entry of study JAHN. A secondary objective was to evaluate the efficacy of increasing baricitinib dose in non-responders, and to evaluate safety of long term treatment with baricitinib.



Abbreviations: BARI = baricitinib; ET = early termination; IGA = Investigator's Global Assessment; TCS = topical corticosteroids.

a Background TCS may be initiated or reinitiated at any time during the study, and are provided as part of rescue or retreatment any time a patient's IGA score becomes ≥3.

b Eligible patients are rerandomized in the withdrawal and down titration substudy. Patients who do not enroll in the substudy remain on their treatment.

c Patients enrolled in the substudy are automatically retreated if their IGA score becomes ≥3.

d Rescue to baricitinib 2-mg or 4-mg is available if their IGA score becomes ≥3.

Figure 12 Design of study JAHN

Methods

Study participants

Participants were mainly included from studies JAHL, JAHM and JAIY. Studies JAHL and JAHM had identical inclusion and exclusion criteria, aiming at an adult population with moderate to severe AD and a recent history of inadequate response/intolerance to topical AD therapies. The inclusion and exclusion criteria for study JAIY were very similar, with the exception that patients with intolerance to TCS were excluded while TCS was to be used concomitantly.

To be eligible for study JAHN following study JAHL, JAHM or JAIY, patients should have completed the final (week 16) visit of the study they were in. For the open label baricitinib 2 mg cohort, inclusion/exclusion criteria were identical to the in/exclusion criteria of JAHL and JAHM, including wash-out of prior topical or systemic therapies.

Treatments

Investigational treatment

Patients could receive baricitinib 4 mg, 2 mg, or 1 mg once daily, or placebo. Responders and non-responders of mono therapy studies JAHL and JAHM were asked to continue baricitinib as monotherapy as long as possible.

Compliance

Patient compliance with investigational treatment was assessed by pill count at each visit. If a patient at his/her own intention had missed more than 20% of doses of study drug, or had taken more than 20% of study drug, he/she was considered significantly noncompliant.

Concomitant treatments

Emollients were to be used daily, use could be increased if needed. Use of TCS was allowed. If symptoms could not be controlled, low- to medium-potency TCS could be used: triamcinolone 0.1% cream and/or hydrocortisone 2.5% ointment. TCIs or crisaborole (a PDE-4 inhibitor as ointment) could be used for problem-areas only. If sufficient improvement was not reached, a higher potency TCS could be used.

Rescue treatment

If a patient started study JAHN as a responder or partial responder, and symptoms worsened to an IGA of 3 or more, patients on 1 mg or placebo were re-randomised (1:1) to 2 mg or 4 mg. Patients on 2 mg or 4 mg were not rescued but continued their dose.

Outcomes

The primary efficacy outcome was IGA 0 or 1 at week 16 (week 32 overall), week 36 (week 52 overall) and week 52 (week 68 overall) for baricitinib 2 mg and 4 mg.
Key secondary outcome was EASI75 at week 16. The other main efficacy outcomes were similar as in the originating studies and included: IGA 0 or 1 over time, EASI75, Itch NRS ≥4 points improvement, SCORAD75, skin pain NRS, ADSS item 2. Patient reported outcomes that were assessed with an

electronic diary, such as Itch NRS and Skin pain NRS, were assessed up to week 32 (week 16 of study JAHN).

Sample size

It is anticipated that 90% of enrolled patients will complete Studies JAHL and JAHM; of these patients, it is expected that approximately 90% of patients will roll over into Study JAHN. Therefore, planned enrollment into Study JAHN from the originating studies JAHL and JAHM will be approximately 970 patients. This study is meant to evaluate patients' long-term response of baricitinib and the sample sizes are not determined to detect differences between baricitinib and placebo in a statistically powered manner.

Randomisation

According to the design (Figure 12) of study JAHN, patients who were on placebo or on baricitinib 1 mg or 2 mg and were non-responders/had needed rescue were re-randomised (1:1) to baricitinib 2 mg or 4 mg. Also patients who needed to be rescued during study JAHN could be re-randomised (see Treatments).

For Period 1, randomisation was performed using a computer-generated random sequence and was stratified by disease severity at baseline of JAHN (IGA 0, 1, 2 versus IGA 3 versus IGA 4), applied using an Interactive Web-based Response System. Using the system, blister packs with blinded investigational treatment are assigned to patients.

Blinding

The double-dummy design was continued for patients originating from JAHL, JAHM and JAIY: one verum tablet and two placebo tablets once daily packed in blisters, to match the three different strengths of baricitinib. Patients in the 2 mg open label cohort were supplied with 2 mg tablets to be taken once daily.

Patients, investigators, and all other personnel involved in the conduct of the study remained blinded to individual originating study treatment assignments for the duration of the study. Members of the safety data monitoring committee reviewed unblinded results by treatment group. Sponsor unblinding occurred after the reporting database was validated and locked for interim statistical analysis; patients and investigators remained blinded. Sponsor unblinding to Week 16 data occurred on 10 May 2019.

Statistical methods

Populations and treatment groups

Analyses were performed on the modified ITT population, which included all randomised patients who had received at least 1 dose of the investigational product. Since all patients in the originating studies who consented to enrol in Study JAHN received the investigational product, the ITT and modified ITT populations in Study JAHN were identical and, thus, no efficacy analyses using the ITT were produced in Study JAHN.

For Study JAHN patients were analysed according to their treatment group from the originating studies and response status (responder, partial responder, and nonresponder) upon entry into the long-term extension study:

- Responders and partial responders were patients entering Study JAHN who had an IGA score of 0, 1, or 2 AND were never determined by the investigator to require rescue treatment during the originating study.
- Non responders were patients who did not meet the responder and partial responder definition (that is, patients with an IGA of 3 or 4, or who were rescued during the originating study).

The following table defines the efficacy analysis populations for the study:

Table 22 Efficacy analysis populations for the study JAHN

Efficacy analysis population	Definition	Analyses performed
Study JAHN		
Modified ITT (mITT)	All randomised patients who received at least 1 dose of investigational product in Study JAHN. Patients were analysed according to the treatment to which they were assigned. The efficacy analyses up to Week 24 of Study JAHN (overall treatment Week 40) include all mITT patients.	All efficacy analyses
Week 36 Efficacy Evaluable Population	All patients who reached Week 36 of Study JAHN by 2 July 2019, or who discontinued the study, but would have reached Week 36 by 2 July 2019.	
ITT	All patients enrolled in Study JAHN	All patients took at least 1 dose of investigational product in Study JAHN. Therefore, the ITT and mITT populations were identical, and no efficacy analyses using ITT were produced

Analyses performed

Primary and secondary discrete efficacy variables will be descriptively summarized by treatment group in terms of frequencies and percentages. Treatment comparisons of discrete efficacy variables between treatment groups may be made using a logistic regression analysis with disease severity (IGA 0 or 1 versus IGA 2), and treatment group in the model. Other factors may be included in the model. If the logistic regression model is performed, then the p-value from the logistic model, percentages, difference in percentages, and (100 minus alpha)% confidence interval (CI) of the difference in percentages using the Newcombe–Wilson method (Newcombe 1998) without continuity correction will be reported. When logistic regression sample size requirements are not met (<5 responders in any category for any factor), the p-value from the Fisher exact test is produced instead of the odds ratio and CI.

Continuous efficacy variables will be descriptively summarized by treatment group in terms of number of patients, mean, standard deviation, median, minimum, and maximum. When evaluating these continuous measures over time, a restricted maximum likelihood-based mixed model for repeated measures (MMRM) may be used. The model will include treatment, baseline severity, visit, and

treatment-by-visit-interaction as fixed categorical effects and baseline score and baseline score-by-visit-interaction as fixed continuous effects. Other factors may be included in the model. An unstructured (co)variance structure will be used to model the between- and within-patient errors. If this analysis fails to converge, other structures will be tested. The Kenward–Roger method will be used to estimate the degrees of freedom. Type III sums of squares for the least-square means (LSM) will be used for the statistical comparison; 95% CI will also be reported.

Handling of dropouts and missing data

In Study JAHN, data were censored after permanent study drug discontinuation, or, for Responders and Partial Responders, as defined below, in the placebo or baricitinib 1-mg groups, after rescue to a higher dose, that is, baricitinib 2-mg or 4-mg.

The Statistical Methods appendices of the individual clinical study reports (CSRs) describe the procedures for handling missing data whether missingness is due to a missed visit, failure to enter diary data, or due to censoring due to use of rescue therapy or permanent study drug discontinuation.

After applying the censoring rules, different imputation methods were applied for categorical and continuous endpoints, as summarised below.

Table 23 Imputation methods were applied for categorical and continuous endpoints

Endpoint	Imputation method used	Details
Dichotomous and categorical	Nonresponder imputation (NRI)	Defines missing observations as non-response. NRI was the primary imputation rule for categorical endpoints. For efficacy responses at Week 36 of Study JAHN (overall treatment week 52), NRI was applied to patients who discontinued the study, but would have reached the Week 36 visit had they continued in the study. NRI was not applied to patients who were continuing in the study, but had not reached the Week 36 (overall treatment Week 52) as of the data cut-off date.
Continuous	Mixed model for repeated measures (MMRM)	Assumes missing observations are missing-at-random. The MMRM borrows information from patients in the same treatment arm and estimates the treatment effects that would be obtained had all patients remained on their initial treatment throughout the study. The MMRM framework was the primary imputation method for continuous endpoints.
	Modified last observation carried forward (mLOCF)	Replaces missing observations with the most recent non-missing uncensored post-baseline assessment. The mLOCF assumes the effect of treatment remains the same as directly prior to the event which caused the missing data. The mLOCF imputation methodology provided sensitivity analyses to support the MMRM.
	Modified baseline observation carried forward (mBOCF)	For patients who permanently discontinue study drug due to an adverse event or death: Replaces missing observations with the baseline observation. For patients who discontinue study drug for any other reason: Replaces missing observations with

		the last nonmissing observation before discontinuation of study drug. The mBOCF imputation method was used as a sensitivity analysis for Nonresponders, as defined below, in Study JAHN only.
Categorical and continuous	Placebo multiple imputation (pMI)	Replaces missing observations with multiple imputations from the predictive posterior distribution from the placebo group. The pMI assumes the response of all patients with missing data would be the same as that of placebo-treated patients. The pMI methodology provided sensitivity analyses to support NRI and MMRM.
Primary endpoint	Tipping point analyses	Sets data to missing after application of the primary censoring rule. All missing data were imputed with values ranging from the worst possible result to the best possible result. The tipping point methodology is a sensitivity analysis that investigates the assumption that would be required with patients with missing data concerning how much better the response rate would have to be in placebo-treated patients than in baricitinib-treated patients. The tipping point analysis varies response rates in patients with missing data to determine at what point differences between groups cease to be statistically significant.

Sensitivity analyses

In Study JAHN, sensitivity analyses used Modified Last observation carried forward (mLOCF) for continuous outcomes for Nonresponders, that is, patients who had an IGA of 3 or 4 at baseline of Study JAHN, or who required rescue at any point during the originating study. Study JAHN used pMI as a sensitivity analysis for the primary endpoint for Responders and Partial Responders, that is, patients with an IGA of 0, 1, or 2 at baseline of Study JAHN who did not require rescue at any point during the originating study.

Multiplicity adjustment

As this study was designed to assess the long-term efficacy and safety of baricitinib in patients with atopic dermatitis, no adjustments for multiple comparisons was utilized in the statistical analyses for this study.

Results

Participant flow

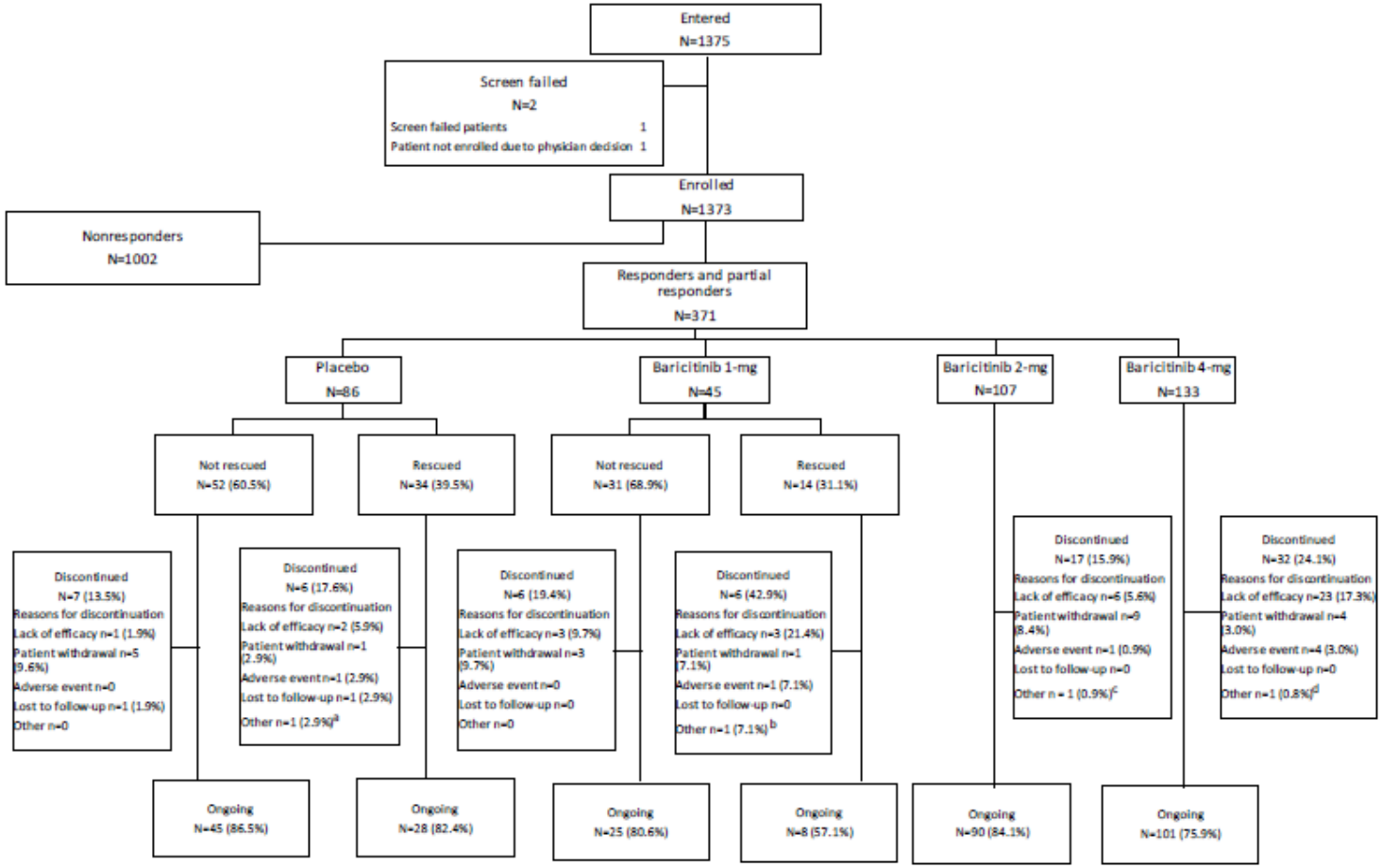
From studies JAHL, JAHM, and JAIY, 1375 patients entered study JAHN and 1373 were included (Figure 13). N=371 patients who were responder or partial responders in the originating study continued their treatment. N=1002 patients were non-responders and accordingly, 807 of them were re-randomised to baricitinib 2 mg or 4 mg while 195 non-responders to baricitinib 4 mg continued their dose (Figure 14).

Of the 1081 included patients from JAHM and JAHL, all patients had reached week 52 or had discontinued. Of the 292 patients included from study JAIY, all patients had reached week 16 and 54% had reached week 24.

Of the 133 responders and partial responders on baricitinib 4 mg, 32 (24%) discontinued and 101 (76%) were ongoing. Of the 107 responders and partial responders on baricitinib 2 mg, 17 (16%) discontinued and 90 (84%) were ongoing.

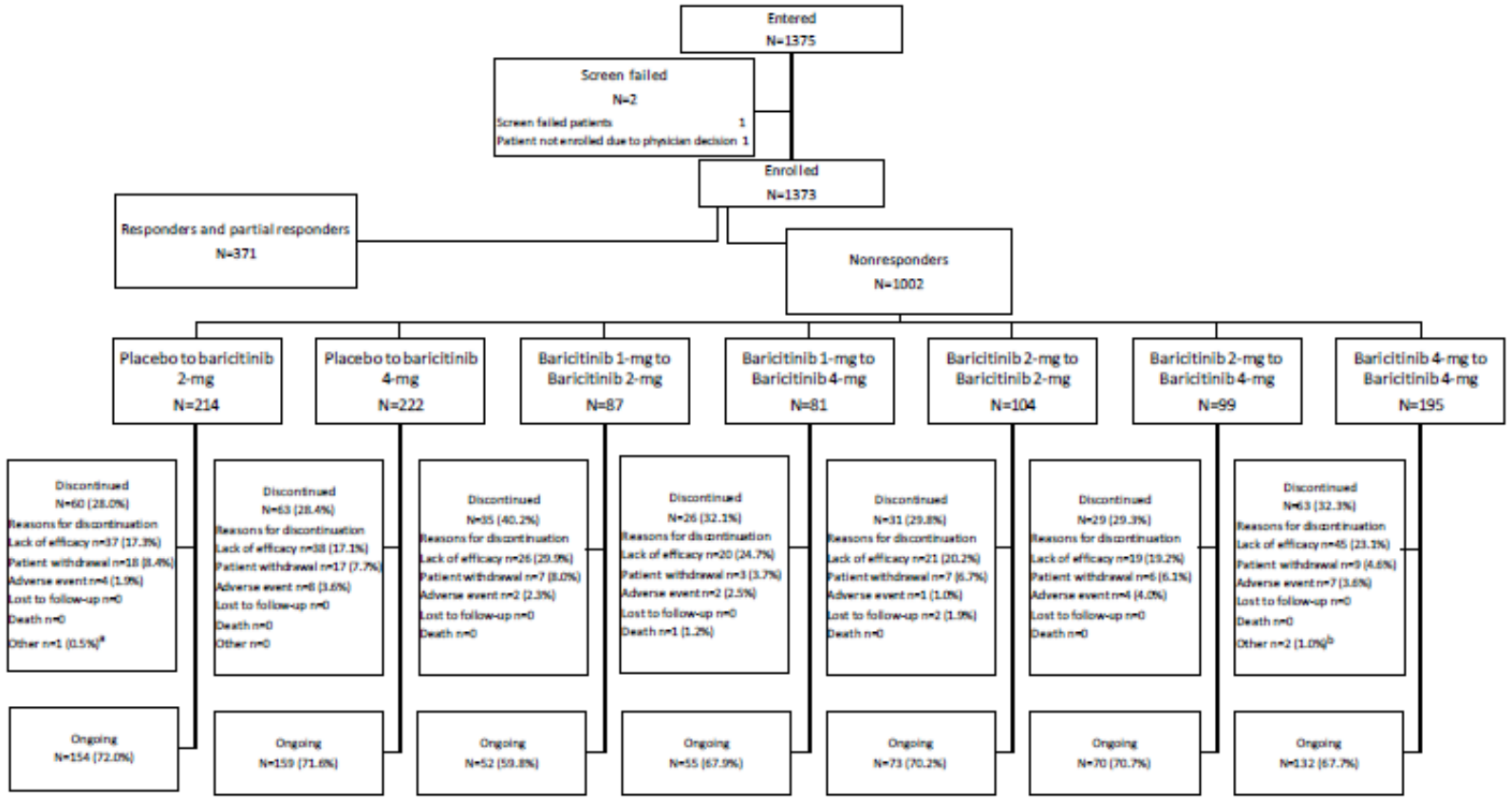
Of the 195 non-responders on baricitinib 4 mg who thus continued the 4 mg dose, 63 (32%) discontinued, usually (n=45) due to a lack of efficacy; 132 (68%) were ongoing in study JAHN.

There were 247 patients included in the baricitinib 2 mg open label cohort. All patients reached week 16, 85% had reached week 24 and 39% had reached week 36.



Abbreviations: N = number of patients in group; n = number of patients in subgroup.
[a] Pregnancy.
[b] Due to pre-existing condition of hyperbilirubinemia.
[c] Treatment with prohibited medication that required permanent discontinuation per protocol.
[d] Patient not able to attend scheduled study visits due to work.

Figure 13 ***Patient flow of responders and partial responders in study JAHN***



Abbreviations: N = number of patients in group; n = number of patients in subgroup.

[a] Poor compliance

[b] One patient had HBV DNA detected with value above limit of quantitation and one patient due to surgery ; DNA = deoxyribonucleic acid; HBV = hepatitis B virus.

Figure 14 ***Patient flow of non-responders in study JAHN***

Recruitment

Study JAHN started in March 2018 (first patient first visit), with a cut-off date for interim analysis at 2 July 2019, followed by a data cut-off at 13 December 2019 and database lock at 29 January 2020.

About 88% of the patients having completed one of the studies, JAHL, JAHM and JAIY, continued in the long term follow-up study JAHN. Of these 1373 patients, 50% were included in centres in European countries.

In addition, baricitinib-naïve patients were recruited for an open label cohort treated with baricitinib 2 mg. Of the 247 included patients, about 50% were included in centres in European countries.

Conduct of the study

In study JAHN there had been two protocol amendments. The first amendment was performed before the first patient visit and mainly concerned a widening of options to provide TCS if triamcinolone or hydrocortisone are not available, and a change in criteria for restarting investigational drug after a VTE from 'after appropriate treatment and resolution of VTE' to '…after evaluation and institution of appropriate treatment for VTE'. In case of remaining significant risk or in case of a second VTE, investigational treatment was to be discontinued permanently. The second amendment was performed 1 day after the first patient visit. It mainly concerned the addition of study JAIY to studies JAHL and JAHM as originating study, and the addition of monitoring tests for confirmed VTE in alignment with the other 'phase 3' studies.

Important protocol deviations were defined as in the originating studies. In study JAHN 25 (2%) of patients had at least 1 important protocol deviation (usually significant non-compliance) equally divided over baricitinib treated groups. In the open-label cohort, 3 patients had at least 1 important protocol deviation (non-compliance). Patients with important protocol deviations remained in the analysis populations.

Baseline data

Baseline demographical and disease characteristics are presented from baseline of the originating study, for responders/partial responders and non-responders separately.

In responders and partial responders, the patient numbers in the four treatment groups varied between n=45 for baricitinib 1 mg and n=133 for 4 mg (Table 24). The mean age was about 34 years and between 36% and 48% were female. Mean disease duration ranged from 22 years to 25 years.

In non-responders, the patient numbers in the 7 treatment groups varied between n=81 for patients re-randomized from baricitinib 1 mg to 4 mg and n=214 and n=222 for patients re-randomised from placebo (Table 25). The mean age varied between 33 and 36 years and between 32% and 41% were female. Mean disease duration ranged from 24 years to 27 years.

Patients included in the baricitinib 2 mg open label cohort were on average 35 years old, 45% were female, and mean disease duration was 25 years. The baseline disease characteristics (not shown) were also very similar to the disease characteristics at baseline in studies JAHL, JAHM and JAIY.

In responders and partial responders, baseline disease characteristics were descriptively similar between the four treatment groups (Table 24). Similarly, in Non-responders the baseline disease characteristics were descriptively similar between the 7 treatment groups (Table 25). Overall the

proportion of patients with an IGA of 4, and the mean values for the EASI, SCORAD, BSA affected and POEM, were higher in the non-responder treatment groups as compared to the responder/partial responder treatment groups.

Table 24 ***Baseline disease characteristics of Responders and Partial responders in study JAHN***

Baseline attribute	PBO N=86	BARI 1-mg N=45	BARI 2-mg N=107	BARI 4-mg N=133
IGA of 4, %	33	18	35	32
EASI, mean (SD)	26 (11)	25 (9)	27 (9)	27 (11)
SCORAD, mean (SD)	63 (13)	58 (12)	64 (13)	64 (12)
BSA affected, mean (SD)	41 (21)	40 (18)	44 (20)	45 (20)
POEM, mean (SD)	18 (7)	16 (6)	19 (7)	20 (6)
ADSS item 2, mean (SD)	2 (2.8)	1 (1.8)	2 (3.1)	2 (3.1)
DLQI, mean (SD)	13 (7.4)	10 (6.4)	13 (7.6)	13 (7.5)
Itch NRS, mean (SD)	7 (2.2)	5 (1.9)	6 (2.2)	7 (2.1)
Skin Pain NRS, mean (SD)	6 (2.4)	5 (2.1)	6 (2.5)	6 (2.6)
PGI-S-AD, mean (SD)	4 (0.9)	3 (0.8)	4 (0.8)	4 (0.8)
HADS anxiety, mean (SD)	6 (4.4)	6 (3.6)	6 (4.2)	6 (4.0)
HADS depression, mean (SD)	5 (4.2)	4 (3.2)	5 (3.9)	5 (4.0)

Abbreviations: ADSS = Atopic Dermatitis Sleep Scale; BARI = baricitinib; BSA = body surface area; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; HADS = Hospital Anxiety Depression Scale; IGA = Investigator's Global Assessment; N = number of patients in group; NRS = Numeric Rating Scale; PBO = placebo; PGI-S-AD = Patient Global Impression of Severity–Atopic Dermatitis; POEM = Patient Oriented-Eczema Measure; SCORAD = SCORing Atopic Dermatitis; SD = standard deviation.

Table 25 Summary of Selected Disease Characteristics at Baseline of Originating Study for Nonresponders

Baseline attribute	PBO to BARI 2-mg N=214	PBO to BARI 4-mg N=222	BARI 1-mg to BARI 2-mg N=87	BARI 1-mg to BARI 4-mg N=81	BARI 2-mg to BARI 2-mg N=104	BARI 2-mg to BARI 4-mg N=99	BARI 4-mg to BARI 4-mg N=195
IGA of 4, %	51	51	54	54	53	52	56
EASI, mean (SD)	33 (13)	33 (13)	32 (14)	33 (11)	33 (14)	35 (14)	36 (13)
SCORAD, mean (SD)	69 (13)	69 (14)	69 (14)	69 (13)	70 (14)	71 (13)	72 (13)
BSA affected, mean (SD)	54 (22)	54 (23)	53 (22)	54 (21)	53 (24)	57 (23)	58 (22)
POEM, mean (SD)	22 (6)	21 (6)	22 (5)	21 (6)	22 (5)	22 (5)	22 (5)
ADSS item 2, mean (SD)	3 (3.9)	3 (4.3)	2 (3.2)	2 (2.8)	2 (3.8)	2 (3.1)	3 (4.2)
DLQI, mean (SD)	15 (8)	14 (8)	16 (8)	14 (7)	15 (8)	15 (8)	14 (8)
Itch NRS, mean (SD)	7 (1.9)	7 (2.1)	7 (2.0)	6 (2.3)	7 (2.2)	7 (1.9)	7 (2.0)
Skin Pain NRS, mean (SD)	7 (2.5)	6 (2.5)	6 (2.6)	6 (2.5)	7 (2.4)	6 (2.5)	6 (2.4)
PGI-S-AD, mean (SD)	4 (0.7)	4 (0.9)	4 (0.8)	4 (0.9)	4 (0.8)	4 (0.7)	4 (0.8)
HADS anxiety, mean (SD)	7 (4.5)	6 (3.9)	7 (4.2)	6 (4.4)	7 (4.3)	6 (4.0)	7 (4.6)
HADS depression, mean (SD)	6 (4.3)	5 (4.1)	6 (4.2)	5 (4.5)	6 (4.5)	4 (3.8)	5 (4.0)

EASI = Eczema Area and Severity Index; HADS = Hospital Anxiety Depression Scale; IGA = Investigator's Global Assessment; N = number of patients in group; NRS = Numeric Rating Scale; PBO = placebo; PGI-S-AD = Patient Global Impression of Severity–Atopic Dermatitis; POEM = Patient-Oriented Eczema Measure; SCORAD = SCORing Atopic Dermatitis; SD = standard deviation.

All 247 patients who were included in the baricitinib 2 mg open label cohort reported prior use of TCS, TCI, or systemic treatments. TCS was used by 94% of included patients, TCI was used by 38%, and 58% had used systemic treatment most often corticosteroids (43% of total) but also ciclosporin (20% of total). Biologicals were infrequently used (3% of total).

Numbers analysed

All 1373 (from originating studies) and 247 patients (open label 2 mg cohort) who were included received at least 1 dose of investigational treatment and were analysed in ITT, modified ITT and Safety sets that were identical. The results of the mITT analyses were separately presented for responders/partial responders from JAHL/JAHM, responders/partial responders from JAIY, the non-responders from JAHL/JAHM and from JAIY, and the 2 mg open label study.

Compliance and rescue

Of the 1373 patients coming from one of the three originating studies, 1349 (99%) were compliant to investigational treatment during study JAHN. Of the 243 patients included in the open label cohort, 236 (99%) were complaint.

Patients on baricitinib 4 mg or 2 mg continued their dose in case of worsening of disease activity (IGA), no rescue was defined.

Outcomes and estimation

To assess maintenance of efficacy, primary and main secondary outcomes were assessed through week 52 of Study JAHN. For patients who were treated with baricitinib in studies JAHL, JAHM and JAIY, this is equivalent to 68 weeks of continuous treatment with baricitinib. Results are presented separately for patients coming from JAHL/JAHM or JAIY, and by responder status at baseline of JAHN.

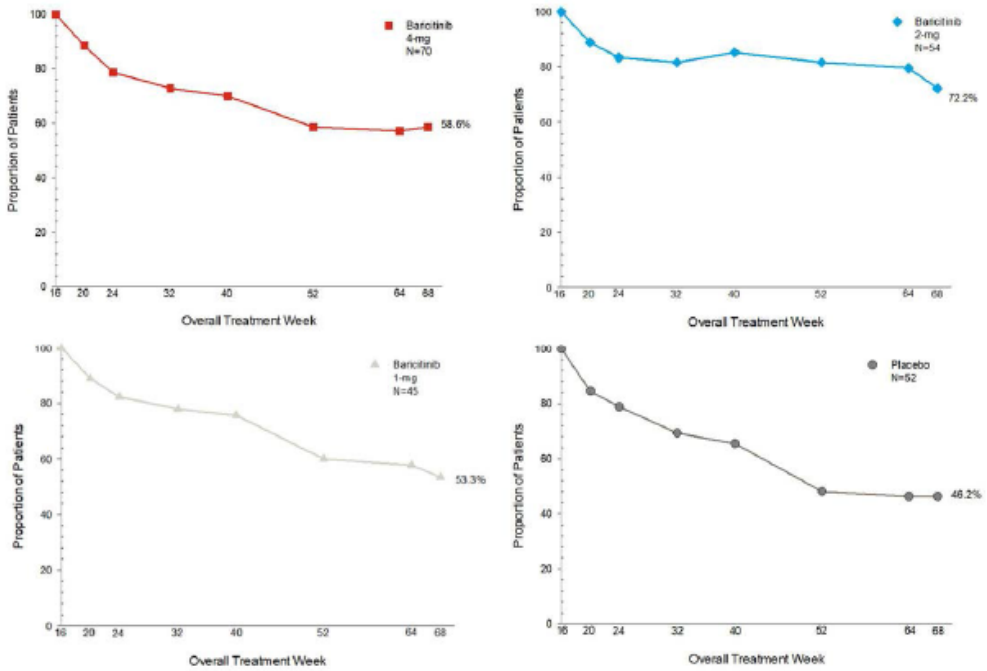
- For patients who were responders or partial responders on placebo, 1 mg, 2 mg or 4 mg, the dose was continued.

- For patients who were non-responders on 4 mg, the dose of 4 mg was continued.

To assess uptitration from 2 mg to 4 mg, patients who were non-responders on 2 mg were re-randomised to dose continuation or to 4 mg.

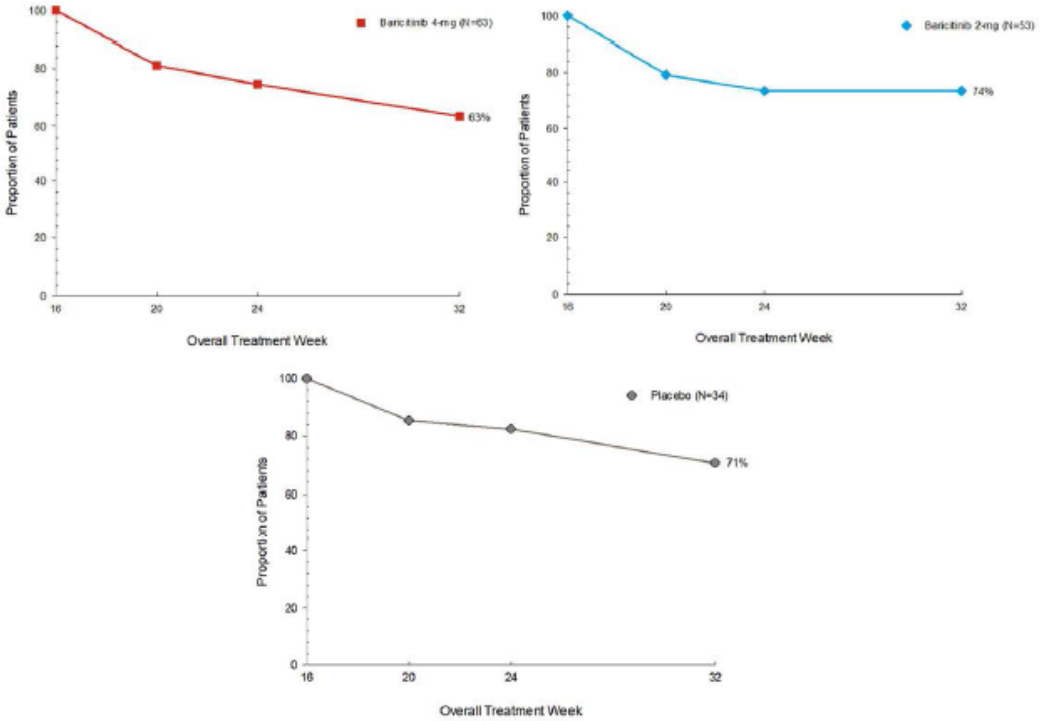
Maintenance of response (IGA 0 or 1 or 2)

By design, patients who were responders or partial responders at week 16 of one of the originating studies had a IGA of 0, 1 or 2 at baseline of JAHN (Figures 15-16). In the baricitinib 2 mg group, the proportion of patients with an IGA<3 remained large from week 16 to week 52 for patients from monotherapy (Figure 15) and from combination therapy (Figure 16). In the baricitinib 4 mg, 1 mg and placebo groups, the decrease in the proportion of patients with a response was relatively larger than with 2 mg (Figure 15 and Figure 16). Concomitant TCS was allowed in JAHN, and does not lead to missingness and imputations.



Abbreviations: IGA = Investigator's Global Assessment; N = number of patients in the modified intent-to-treat population.

Figure 15 Maintenance of response (IGA 0 or 1 or 2) in responders and partial responders on monotherapy in study JAHN.



Abbreviations: IGA = Investigator's Global Assessment; mITT = modified intent-to-treat; N = number of patients in the mITT population.

Figure 16 Maintenance of response (IGA 0 or 1 or 2) in responders and partial responders on combination therapy in study JAHN.

IGA 0 or 1 (primary outcome)

In responders and partial responders on monotherapy, the proportion of patients with an IGA 0 or 1 increased from week 16 to week 52 in the baricitinib 2 mg group, and decreased in the other groups including baricitinib 4 mg (Table below). In week 52 (overall), the proportion of patients with an IGA 0 or 1 was highest in the baricitinib 2 mg group, exceeding the 1 mg and 4 mg groups that were similar. In responders and partial responders on combination therapy, the proportion of patients with an IGA 0 or 1 at week 16 and week 24 was highest in the 2 mg group (Tables below).

Table 26 ***Proportion of patients with IGA 0 or 1 in responders and partial-responders on monotherapy entering study JAHN.***

	PBO N1=52	BARI 1-mg N1=45	BARI 2-mg N1=54	BARI 4-mg N1=70
Week 0 (overall treatment week 16)[a]				
Response, n (%) (95% CI)	18 (34.6%) (23.2%, 48.2%)	25 (55.6%) (41.2%, 69.1%)	25 (46.3%) (33.7%, 59.4%)	32 (45.7%) (34.6%, 57.3%)
Week 16 (overall treatment week 32)[a]				
Response, n (%) (95% CI)	19 (36.5%) (24.8%, 50.1%)	21 (46.7%) (32.9%, 60.9%)	32 (59.3%) (46.0%, 71.3%)	34 (48.6%) (37.2%, 60.0%)
Week 36 (overall treatment week 52)[b]	PBO N2=47	BARI 1-mg N2=35	BARI 2-mg N2=45	BARI 4-mg N2=64
Response, n (%) (95% CI)	11 (23.4%) (13.6%, 37.2%)	12 (34.3%) (20.8%, 50.8%)	30 (66.7%) (52.1%, 78.6%)	24 (37.5%) (26.7%, 49.7%)

Abbreviations: BARI = baricitinib; CI = confidence interval; IGA = Investigator's Global Assessment; N1= number of patients in the modified intent-to-treat population; N2 = number of patients in the modified intent-to-treat Week 36 Efficacy Evaluable population; n = number of patients in the specified category; mITT = modified intent-to-treat; NRI = nonresponder imputation; PBO = placebo.

[a] Using NRI in the mITT population.

[b] Using NRI in the mITT Week 36 Efficacy Evaluable population.

Table 27 ***Proportion of patients with IGA 0 or 1 in responders and partial-responders on combination therapy entering study JAHN.***

	PBO	BARI 2 mg	BARI 4 mg
IGA 0 or 1			
Week 0 (Overall treatment week 16)[a]			
Response, % (n/N) (95% CI)	35.3 (12/34) (21.5, 52.1)	39.6 (21/53) (27.6, 53.1)	49.2 (31/63) (37.3, 61.2)
Week 16 (Overall treatment week 32)[a]			
Response, n/N (%) (95% CI)	47.1 (16/34) (31.5, 63.3)	45.3 (24/53) (32.7, 58.5)	31.7 (20/63) (21.6, 44.0)
Week 24 (Overall treatment week 40) – Efficacy Evaluable Population[b]			
Response, n/N2 (%) (95% CI)	40.0 (6/15) (19.8, 64.3)	45.2 (14/31) (29.2, 62.2)	36.0 (9/25) (20.2, 55.5)

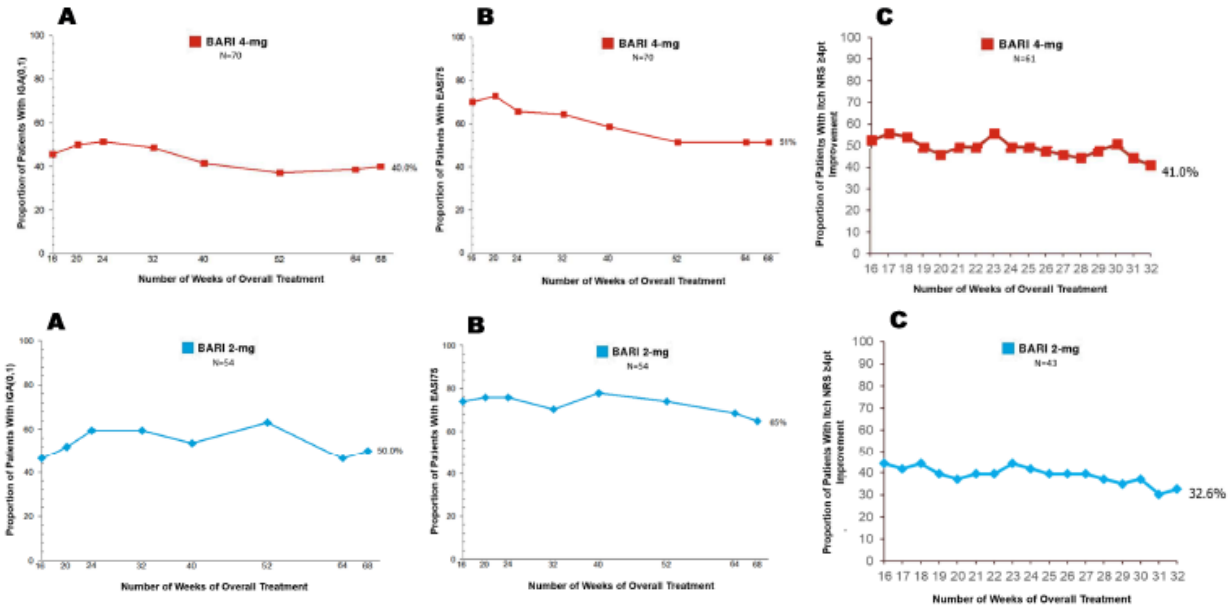
Abbreviations: EASI75 = 75% improvement in Eczema Area and Severity Index; IGA = Investigator's Global Assessment; mITT = modified intent-to-treat; N = number of patients in the analysis population; n = number of patients in the specified category; N2 = number of patients in the Week 24 efficacy evaluable population; NRI = nonresponder imputation; NRS = Numeric Rating Scale.

[a] Using NRI in the mITT population.

[b] Using NRI in the mITT Week 24 Efficacy Evaluable population.

Note: Confidence intervals were constructed using Newcombe-Wilson method, without continuity correction.

For the 70 responders or partial responders on monotherapy with baricitinib 4 mg, the proportion of patients with an IGA of 0 or 1 was 46% at week 16 (baseline of JAHN), the other 53% were partial responders with an IGA of 2 (Figure 17). The proportion with an IGA 0 or 1 increased to week 24 and then declined to 40% at week 68. For the 54 responders or partial responders on baricitinib 2 mg, the proportion of patients with an IGA of 0 or 1 was 46% at week 16 (Figure 17). The proportion with an IGA 0 or 1 increased to week 52, then declined somewhat, to increase again to 50% at week 68.



Abbreviations: EASI75 = 75% improvement in Eczema Area and Severity Index; IGA = Investigator's Global Assessment; N = total number of patients in group; NRS = Numeric Rating Scale.
Note: Itch NRS results are only available through Week 16 of Study JAHN (32 weeks of overall treatment) due to patient daily diary used for the first 16 weeks of Study JAHN.

Figure 17 Responders/partial responders on monotherapy continuing baricitinib 2 mg or 4 mg and proportions over time of IGA 0/1, EASI75, and Itch ⩾4 points improvement in study JAHN

Eczema Area and Severity Index (EASI75)

In responders and partial responders on monotherapy, the proportion of patients with an EASI75 response declined from week 16 to week 52 in the placebo group and baricitinib 1 mg and 4 mg groups, and remained stable in the baricitinib 2 mg group (Table 28). On 4 mg, the proportion of patients with an EASI75 response was 70% at week 16 which gradually declined to 51% at week 52. For responders and partial responders continuing baricitinib 2 mg, the proportion of patients with an EASI75 was 74% at week 16 which remained stable to 65% at week 52. Similarly, in the responders and partial responders on combination therapy, EASI75 responses were highest for the 2 mg dose (Table 29). At week 24 of JAHN, the proportion with EASI75 was 68% in the 2 mg group and 48% in the 4 mg group.

Thus, on follow-up in responders and partial responders on monotherapy and on combination therapy, the proportion with EASI75 response was numerically highest in the baricitinib 2 mg groups.

Table 28 ***Proportion of patients with EASI75 in responders and partial-responders on monotherapy entering study JAHN.***

	PBO N=52	BARI 1-mg N=45	BARI 2-mg N=54	BARI 4-mg N=70
Week 0 (overall treatment week 16)[a]				
Response, n (%) (95% CI)	30 (57.7) (44.2, 70.1)	32 (71.1) (56.6, 82.3)	40 (74.1) (61.1, 83.9)	49 (70.0) (58.5, 79.5)
Week 16 (overall treatment week 32)[a]				
Response, n (%) (95% CI)	22 (42.3) (29.9, 55.8)	28 (62.2) (47.6, 74.9)	38 (70.4) (57.2, 80.9)	45 (64.3) (52.6, 74.5)
Week 36 (overall treatment week 52)[a]				
Response, n (%) (95% CI)	23 (44.2) (31.6, 57.7)	21 (46.7) (32.9, 60.9)	40 (74.1) (61.1, 83.9)	36 (51.4) (40.0, 62.8)
Week 48 (overall treatment week 64)[a]				
Response, n (%) (95% CI)	21 (40.4) (28.2, 53.9)	21 (46.7) (32.9, 60.9)	37 (68.5) (55.3, 79.3)	36 (51.4) (40.0, 62.8)
Week 52 (overall treatment week 68)[a]				
Response, n (%) (95% CI)	20 (38.5) (26.5, 52.0)	23 (51.1) (37.0, 65.0)	35 (64.8) (51.5, 76.2)	36 (51.4) (40.0, 62.8)

Abbreviations: BARI = baricitinib; CI = confidence interval; EASI75 = improvement of at least 75% from baseline of originating study in Eczema Area and Severity Index; N = number of patients in the modified intent-to-treat population; n = number of patients in the specified category; PBO = placebo.

[a] Using NRI in the modified intent-to-treat population.

Table 29 ***Proportion of patients with EASI75 in responders and partial-responders on combination therapy entering study JAHN.***

	PBO	BARI 2 mg	BARI 4 mg
EASI75			
Week 0 (Overall treatment week 16)[a]			
Response, n/N (%) (95% CI)	52.9 (18/34) (36.7, 68.5)	77.4 (41/53) (64.5, 86.5)	71.4 (45/63) (59.3, 81.1)
Week 16 (Overall treatment week 32)[a]			
Response, n/N (%) (95% CI)	55.9 (19/34) (39.5, 71.1)	67.9 (36/53) (54.5, 78.9)	55.6 (35/63) (43.3, 67.2)
Week 24 (Overall treatment week 40) – Efficacy Evaluable Population[b]			
Response, n/N2 (%) (95% CI)	53.3 (8/15) (30.1, 75.2)	67.7 (21/31) (50.1, 81.4)	48.0 (12/25) (30.0, 66.5)

Abbreviations: EASI75 = 75% improvement in Eczema Area and Severity Index; IGA = Investigator's Global Assessment; mITT = modified intent-to-treat; N = number of patients in the analysis population; n = number of patients in the specified category; N2 = number of patients in the Week 24 efficacy evaluable population; NRI = nonresponder imputation; NRS = Numeric Rating Scale.

[a] Using NRI in the mITT population.

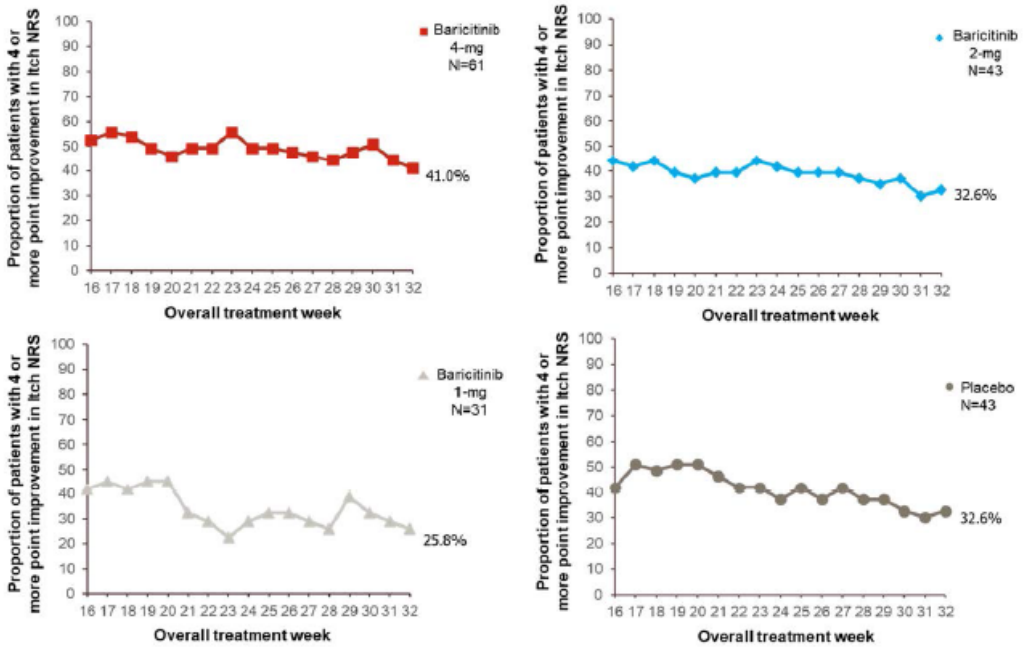
[b] Using NRI in the mITT Week 24 Efficacy Evaluable population.

Note: Confidence intervals were constructed using Newcombe-Wilson method, without continuity correction.

Itch NRS ≥4 points improvement

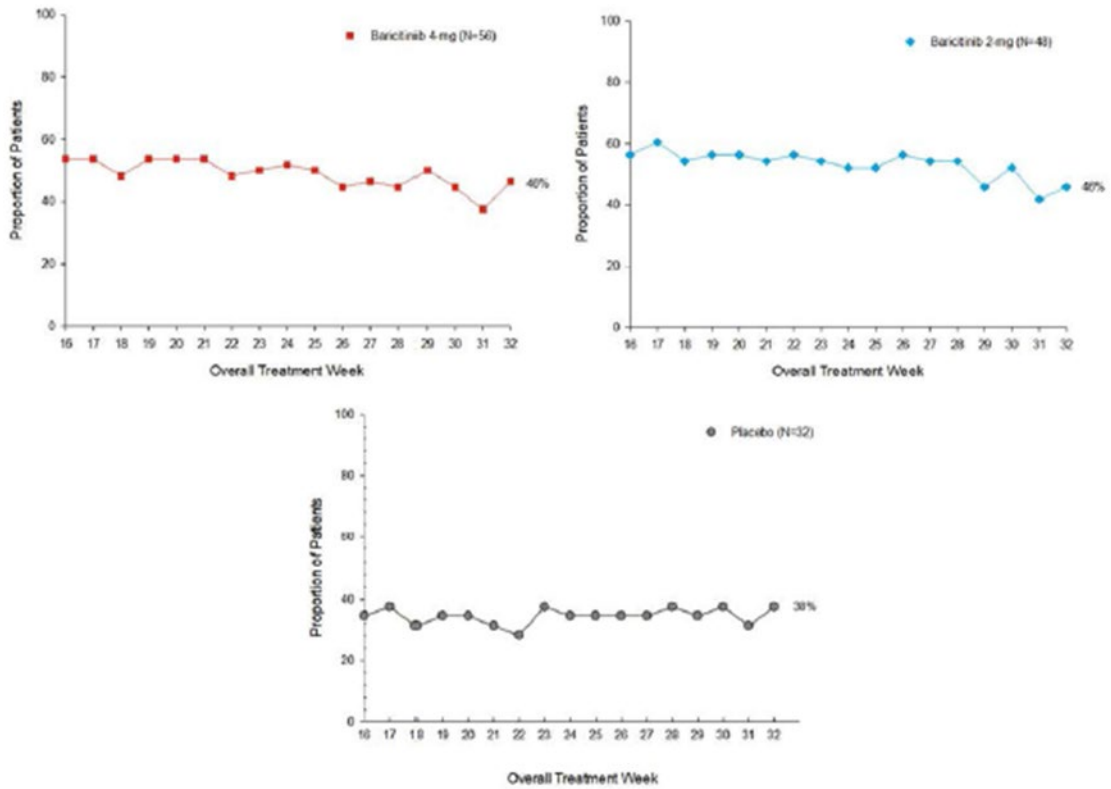
For responders and partial responders on monotherapy continuing baricitinib 4 mg, the proportion of patients with an improvement ≥4 points from baseline in Itch NRS was 53% at week 16 which gradually declined to 41% at week 32 (Figure 18). For responders and partial responders continuing 2 mg, the proportion of patients with an Itch NRS improvement ≥4 points was 44% at week 16 which gradually declined to 33% at week 32.

For responders and partial responders on combination therapy continuing baricitinib 4 mg, the proportion with a response in Itch NRS (≥4 points improvement) was 54% which became 46% at week 16 (Figure 19). For patients continuing 2 mg this was similar: 56% at baseline of JAHN which also became 46% at week 16.



Abbreviations: N = number of patients in the modified intent-to-treat population with Itch NRS score of 4 or more points at baseline of originating study; NRI = nonresponder imputation; NRS = Numeric Rating Scale.
Using NRI in the modified intent-to-treat population with Itch NRS score of 4 or more points at baseline of originating study.

Figure 18 ***Responders/partial responders on monotherapy in study JAHN***



Abbreviations: mITT = modified intent-to-treat; N = number of patients in the mITT population; NRS = Numeric Rating Scale.

Figure 19 ***Responders/partial responders on combination therapy in study JAHN***

Atopic Dermatitis Sleep Scale (ADSS)

ADSS sleep item 2 concerns the number of times a patient woke up at night. For responders and partial responders on monotherapy continuing baricitinib 4 mg, the mean (SD) change in number of awakenings was -1.9 (3.4) at week 16 and -1.8 (3.4) at week 32. For responders and partial responders continuing baricitinib 2 mg, the mean (SD) change in number of awakenings was -1.3 (3.7) at week 16 and -1.3 (3.9) at week 32.

For responders and partial responders on combination therapy continuing baricitinib 4 mg, the mean (SD) change in number of awakenings was -1.6 (2.7) at week 16 and -1.2 (1.4) at week 32. For the patients continuing 2 mg this was -1.7 (1.9) at week 16 and -1.8 (1.9) at week 32.

Skin pain NRS

For responders and partial responders continuing baricitinib 4 mg, the mean (SD) change in Skin pain NRS was -3.8 (2.3) at week 16 and -3.2 (2.4) at week 32. For responders and partial responders continuing baricitinib 2 mg, the mean (SD) change in Skin pain NRS was -3.5 (2.9) at week 16 and -2.7 (3.3) at week 32.

For responders and partial responders on combination therapy continuing baricitinib 4 mg, the mean (SD) change in Skin pain NRS was -3.8 (2.8) at week 16 and -3.5 (3.2) at week 32. For the patients continuing 2 mg this was -4.0 (2.3) at week 16 and -3.7 (2.6) at week 32.

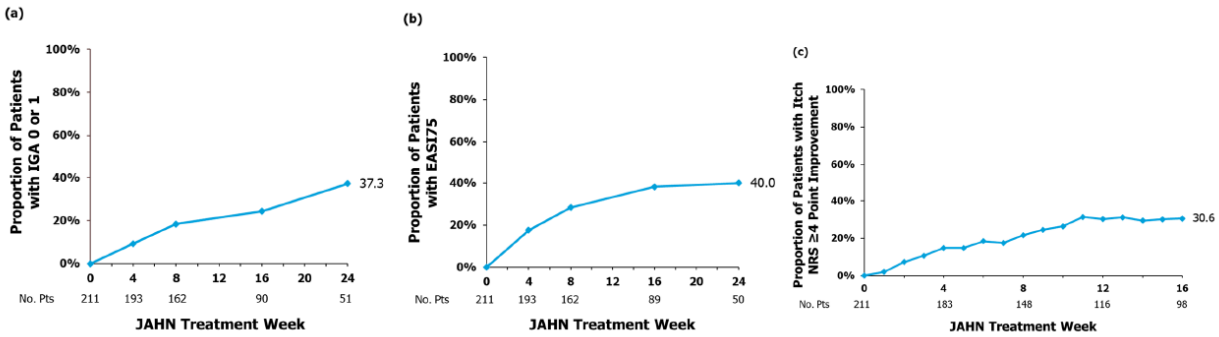
Dermatology Life Quality Index (DLQI)

For responders and partial responders continuing baricitinib 4 mg, the mean (SD) change in DLQI was -9.6 (6.7) at week 16 and -7.4 (6.5) at week 52. The proportion of patients with a DLQI improvement ≥4 points was 71% at week 52. For responders and partial responders continuing baricitinib 2 mg, the mean (SD) change in DLQI was -8.0 (6.8) at week 16 and -7.5 (6.3) at week 52. The proportion of patients with a DLQI improvement ≥4 points was 66% at week 52.

For responders and partial responders on combination therapy continuing baricitinib 4 mg, the proportion of patients with a DLQI improvement ≥4 points was 67% at week 32. This was 76% for patients continuing 2 mg.

Ancillary analyses

The baricitinib 2 mg open label cohort within study JAHN consisted of patients who were naïve to baricitinib (Figure 20). The proportion of patients with an IGA 0 or 1 increased steadily from baseline to 31% at week 24, the proportion of patients with an EASI75 response increased to 39% at week 24. Itch NRS was assessed up to week 16 from baseline, at week 12 the proportion with a response ≥4 points in Itch NRS was 27% and remained stable up to week 16.



Abbreviations: EASI75 = improvement of at least 75% from baseline in Eczema Area and Severity Index; IGA = Investigator's Global Assessment; ITT = intent-to-treat; NRS = numeric rating scale; No. Pts = number of patients at specified time point.
Note: Data for Itch NRS are only shown up to Week 16 of Study JAHN as data from daily diaries were only collected up to this time point.
Sources: t_igaresp_obs_olitt_wk0to36.rtf; t_easi507590_obs_olitt_wk0to36.rtf, and t_itchresp_obs_olitt_wk0to16.rtf.

Figure 20 Patients starting baricitinib 2 mg and IGA 0/1, EASI75, and Itch ⩾4 points improvement in the open-label cohort within study JAHN

Subgroup analyses were performed for week 16 results of IGA 0 or 1, EASI75 and Itch NRS improvement ≥4 points, in the following pre-defined subgroups: gender, age, weight, body mass index, race, renal function, disease severity based on baseline IGA, geographic region, and previous therapy. Subgroup analyses were performed for the pooled mono therapy studies JAHL and JAHM, and combination therapy study JAIY separately, by testing treatment (baricitinib 4 mg, 2 mg, 1 mg, placebo) by subgroup interactions.

Statistically significant (p<0.10) treatment by subgroup interactions were found for gender (all studies), baseline IGA score (mono therapy studies), TCI failure or inadvisable (mono therapy), ciclosporin failure or ineligible (combination therapy), and region (all studies).

Gender

In the monotherapy studies, overall there was a tendency for males performing worse than females, only the treatment by gender interaction for EASI75 was significant (p=0.059). For baricitinib 4 mg, the IGA 0/1 for males versus females was 13% versus 21%, for EASI75 this was 19% versus 31%.

In the combination treatment study there was a significant treatment by gender interaction for IGA 0/1 (p=0.017) and for EASI75 (p=0.002), to the extent that males performed worse than females in the 4 mg group, which was reversed in the 2 mg group. In the 4 mg group the IGA 0/1 for males versus females was 20% versus 53%, and in the 2 mg group this was 26% versus 21%; for EASI75 a similar kind of effect was seen.

Disease severity (IGA)

In the monotherapy studies there was no statistically significant treatment by baseline IGA (3 or 4) interaction for IGA 0/1 at week 16 (p=0.98), but there was such an interaction for EASI75 (p=0.038). In the baricitinib 4 mg group, IGA 0/1 was 23% in the baseline IGA 3 subgroup and 6% in the IGA 4 subgroup. Similarly, EASI75 was 28% in the IGA 3 subgroup and 17% in the IGA 4 subgroup.

Also in the combination therapy study, the treatment by disease severity interaction was significant (p=0.07) for EASI75 only. In the baricitinib 4 mg group, IGA 0/1 was 46% in the baseline IGA 3 subgroup and 12% in the IGA 4 subgroup. Similarly, EASI75 was 62% in the IGA 3 subgroup and 30% in the IGA 4 subgroup.

A similar trend was seen for baricitinib 2 mg as compared to 4 mg.

Region

Over studies and major outcomes, there was a tendency that responses were higher in the EU subgroup as compared to the rest-of-the-world.

Previous therapy

In the monotherapy studies, only the interaction of treatment by TCI failure/inadvisable was statistically significant, and for IGA 0/1 only (p=0.051). In the baricitinib 4 mg group, IGA 0/1 was 17% for TCI failure and 14% versus no failure; for EASI75 and for the 2 mg group similar numerical trends were seen. The treatment by ciclosporin failure/ineligible interaction was not statistically significant, the responses in IGA 0/1 and EASI75 were numerically slightly lower in case of ciclosporin failure.

In the combination therapy study, the interaction for treatment by ciclosporin failure/ineligible was statistically significant for EASI75 (p=0.023) but not for IGA 0/1 (p=0.59). In the baricitinib 4 mg group the EASI75 response in case of ciclosporin failure was 55% versus 46% in case of absence of failure; in the 2 mg group the effects were reversed: 19% in case of ciclosporin failure and 49% in case of absence of failure. The treatment interactions were not statistically significant for previous systemic therapy and for TCI failure/inadvisable.

There were in total 47 patients in the monotherapy studies and 16 patients in the combination therapy study who had used dupilumab previously. In the monotherapy study, IGA 0/1 was reached by 1/7 (14%) in the baricitinib 4 mg group, 2/16 (13%) in the 2 mg group and 0/10 (0%) in the placebo group. Similarly, EASI75 was reached by 3/7 (43%) on 4 mg, 2/16 (13%) on 2 mg, and 0 on placebo. In the combination therapy group, IGA 0/1 was reached by 4/7 (57%) in the baricitinib 4 mg group and 0/9 (0%) in the 2 mg group; EASI75 was reached by 5/7 (71%) in the 4 mg group and 2/9 (22%) in the 2 mg group.

Summary of main studies

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

Table 30 ***Summary of Efficacy for trials JAHL, JAHM and JAIY.***

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Baricitinib in Adult Patients with Moderate to Severe Atopic Dermatitis (JAHL and JAHM) **A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Baricitinib in Combination with Topical Corticosteroids in Adult Patients with Moderate to Severe Atopic Dermatitis (JAIY)**		
Study identifiers	I4V-MC-JAHL and I4V-MC-JAHM I4V-MC-JAIY	
Design	Multi-centre randomised (1:1:1:2) controlled trial comparing baricitinib 1mg, 2 mg and 4 mg once daily, versus placebo, in adult patients with atopic dermatitis being candidates for systemic treatment (**JAHL** and **JAHM**) Multi-centre randomised (1:1:1) controlled trial comparing baricitinib 2 mg and 4 mg once daily, versus placebo, added to TCS in adult patients with atopic dermatitis being candidates for systemic treatment (**JAIY**)	
	Duration of main phase:	16 weeks

	Duration of Run-in phase: Duration of Extension phase:		not applicable 104 weeks
Hypothesis	Superiority		
Treatments groups	Placebo		249 (JAHL) and 244 (JAHM) and 109 (JAIY)
	Baricitinib 1 mg QD		127 (JAHL) and 125 (JAHM)
	Baricitinib 2 mg QD		123 (JAHL) and 123 (JAHM) and 109 (JAIY)
	Baricitinib 4 mg QD		125 (JAHL) and 123 (JAHM) and 111 (JAIY)
Endpoints and definitions	Primary endpoint	IGA 0 or 1	Investigator's Global Assessment of 0 or 1 ('clear or almost clear') and an improvement of ≥2 points from baseline.
	Secondary endpoint	EASI75	At least 75% improvement in Eczema Area and Severity Index from baseline.
	Secondary endpoint	Itch NRS response	At least 4 points improvement in Itch severity NRS from baseline.
Database lock	17 January 2019 (JAHL) and 24 January 2019 (JAHM) 13 August 2019 (JAIY)		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat. Changes from baseline to week 16.			
Descriptive statistics and estimate variability	Treatment group	Placebo	Baricitinib 2 mg	Baricitinib 4 mg
	JAHL			
	Number of subjects	249	123	125
	IGA 0 or 1	4.8%	11.4%	16.8%
	EASI75	8.8%	18.7%	24.8%
	Itch NRS response	7.2%	12.0%	21.5%
	JAHM			
	Number of subjects	244	123	123
	IGA 0 or 1	4.5%	10.6%	13.8%
	EASI75	6.1%	17.9%	21.1%
	Itch NRS response	4.7%	15.1%	18.7%
	JAIY			
	Treatment group	Placebo +TCS	Baricitinib 2 mg +TCS	Baricitinib 4 mg +TCS
	Number of subjects	109	109	111
	IGA 0 or 1	14.7%	23.9%	30.6%
	EASI75	22.9%	43.1%	47.7%
	Itch NRS response	20.2%	38.1%	44.0%
Effect estimate per comparison	**JAHL**			
	Primary endpoint: IGA 0 or 1	Comparison groups	4 mg versus placebo	
		Difference	12.0%	
		(95%CI)	(5.5% - 19.8%)	
		P-value	**<0.001**	
		Comparison groups	2 mg versus placebo	

	Difference	6.6%
	(95%CI)	(0.9 – 13.7)
	P-value	**0.020**
Secondary endpoint: EASI75	Comparison groups	4 mg versus placebo
	Difference	16.0%
	(95%CI)	(8.0% - 24.7%)
	P-value	**<0.001**
	Comparison groups	2 mg versus placebo
	Difference	9.9%
	(95%CI)	(2.6% - 18.2%)
	P-value	**0.006**
Secondary endpoint: Itch NRS response	Comparison groups	4 mg versus placebo
	Difference	14.3%
	(95%CI)	(6.4% - 23.4%)
	P-value	**<0.001**
	Comparison groups	2 mg versus placebo
	Difference	4.8%
	(95%CI)	(-1.7% - 13.1%)
	P-value	0.17
JAHM		
Primary endpoint IGA 0 or 1	Comparison groups	4 mg versus placebo
	Difference	9.3%
	(95%CI)	(3.3 – 16.8)
	P-value	**0.001**
	Comparison groups	2 mg versus placebo
	Difference	6.1%
	(95%CI)	(0.6 – 13.0)
	P-value	**0.026**
Secondary endpoint: EASI75	Comparison groups	4 mg versus placebo
	Difference	15.0%
	(95%CI)	(7.7% - 23.4%)
	P-value	**<0.001**
	Comparison groups	2 mg versus placebo
	Difference	11.7%
	(95%CI)	(4.9% - 19.8%)
	P-value	**<0.001**
Secondary endpoint: Itch NRS response	Comparison groups	4 mg versus placebo
	Difference	14.0%
	(95%CI)	(6.7% - 22.7%)
	P-value	**<0.001**
	Comparison groups	2 mg versus placebo
	Difference	10.4%
	(95%CI)	(3.7% - 18.7%)
	P-value	**0.002**
JAIY		
Primary endpoint IGA 0 or 1	Comparison groups	4 mg versus placebo
	Difference	16.0%
	(95%CI)	(4.9% - 26.6%)
	P-value	**0.004**

		Comparison groups	2 mg versus placebo
		Difference	9.2
		(95%CI)	(-1.4% - 19.5)
		P-value	0.082
	Secondary endpoint: EASI75	Comparison groups	4 mg versus placebo
		Difference	24.8%
		(95%CI)	(12.2% - 36.3%)
		P-value	**<0.001**
		Comparison groups	2 mg versus placebo
		Difference	20.2%
		(95%CI)	(7.7% - 31.8%)
		P-value	0.002
	Secondary endpoint: Itch NRS response	Comparison groups	4 mg versus placebo
		Difference	23.8%
		(95%CI)	(11.0% - 35.6%)
		P-value	**<0.001**
		Comparison groups	2 mg versus placebo
		Difference	18.0%
		(95%CI)	(5.4% - 29.9%)
		P-value	0.002
Notes	Results in **bold** were statistically significant after adjustment for multiplicity.		

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

No formal meta-analysis was performed. Data of the identical monotherapy studies JAHL and JAHM were pooled for the purpose of subgroup analysis and for comparison with follow-up results after week 16 in study JAHN. Also, for purpose of representation in the Effect Table in the Benefit/Risk section, monotherapy studies JAHL and JAHM were pooled.

Clinical studies in special populations

Not applicable.

Supportive studies

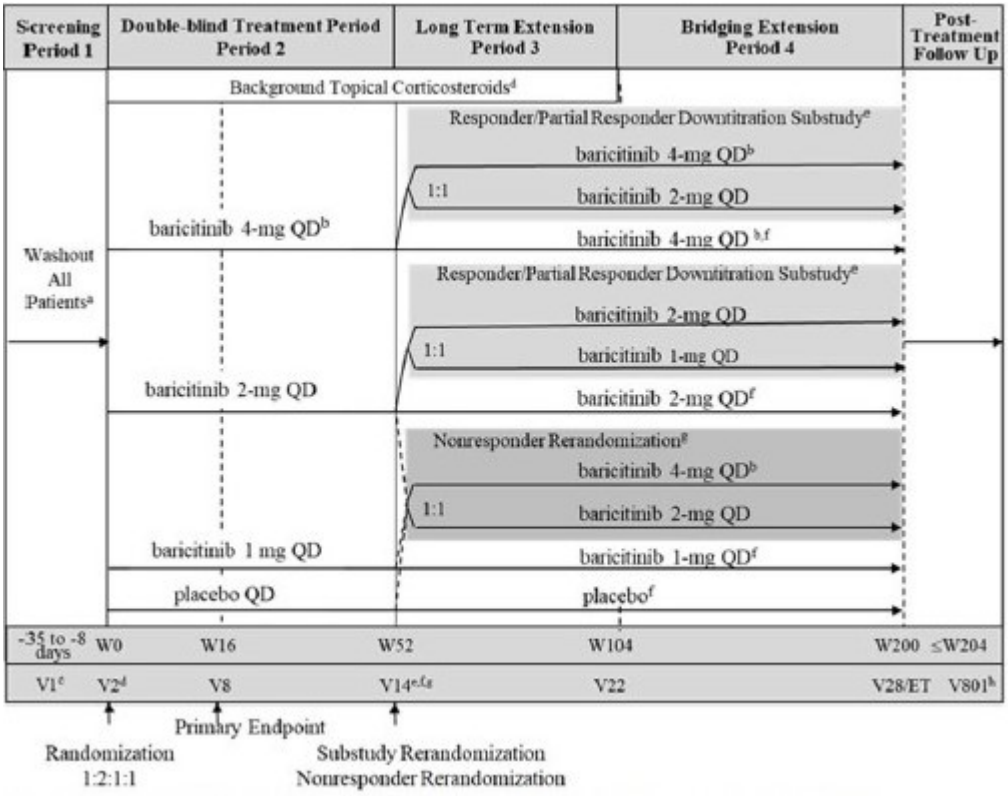
The MAH performed a 'phase 3' study comparing baricitinib (1 mg, 2 mg, 4 mg QD) in combination with TCS, in patients with moderate to severe Atopic Dermatitis who were previously treated with oral ciclosporin or for whom that treatment is contra-indicated.

"A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study Evaluating the Safety and Efficacy of Baricitinib in Combination with Topical Corticosteroids in Adult Patients with Moderate to Severe Atopic Dermatitis Who Have Experienced Failure to Cyclosporine or Are Intolerant to, or Have Contraindication to, Cyclosporine (JAIN)"

Methods

Design

Study JAIN was a multicenter, double-blind, randomized (1:2:1:1), placebo-controlled study to evaluate the efficacy and safety of baricitinib 1mg+TCS, 2mg+TCS and 4mg+TCS versus placebo+TCS, in adult patients with moderate to severe Atopic Dermatitis with failure of ciclosporin or who are intolerant to or have a contraindication to ciclosporin (Figure 21). Primary outcome was EASI75 at week 16, IGA 0 or 1 was a secondary outcome. The first patient first visit was at 15 May 2018 and the interim data cutoff was at 28 Nov 2019.



Abbreviations: AD = atopic dermatitis; eGFR = estimated glomerular filtration rate; ET = early termination; IGA = Investigator's Global Assessment; IP = investigational product; PPD = purified protein derivative; QD = once daily; TB = tuberculosis; TCS = topical corticosteroids; V = visit; W = week.

a Applicable to patients taking topical treatments (excluding emollients) or systemic treatments for AD at the time of screening.

b Maximum dose of baricitinib for patients with renal impairment (defined as eGFR <60 mL/min/1.73 m^2) will be 2-mg QD.

c Patients for whom PPD skin test for the evaluation of TB infection was performed at V1 must return and PPD test must be read 48 to 72 hours after Visit 1 (post-PPD).

d At Visit 2 (W0) and up to Visit 22 (W104), patients will be supplied with mild- and moderate-potency TCS to be applied per the guidelines in Section 7.7.2 of the protocol.

e At Week 52, responders (IGA 0 or 1) and partial responders (IGA 2) who were assigned to baricitinib 4-mg or 2-mg, at randomization, are currently receiving IP (does not currently have study drug interrupted), and who have not used high or ultra-high-potency TCS in the previous 14 days will be enrolled into the downtitration substudy. If a patient in the substudy has an IGA ≥3 during Periods 3 or 4, they will be retreated automatically with their presubstudy baricitinib dose for the remainder of the study.

f At Week 52, responders (IGA 0 or 1) and partial responders (IGA 2) in the baricitinib 4-mg or 2-mg groups who are not eligible for the randomized downtitration substudy and those who are in the baricitinib 1-mg or placebo groups will remain on their current dose of IP. If worsening of AD symptoms occurs any time during Periods 3 or 4 such that a patient's IGA is ≥3, with the exception of patients in the baricitinib 4-mg group, they will be rerandomized automatically at a 1:1 ratio to baricitinib 2-mg QD or baricitinib 4-mg QD. Rerandomization will only occur once. Patients in the baricitinib 4-mg group will remain on 4-mg.

g Beginning at Visit 14 (Week 52), nonresponders (IGA ≥3) in the placebo, baricitinib 1-mg, or baricitinib 2-mg groups will be rerandomized at a 1:1 ratio to baricitinib 4-mg or baricitinib 2-mg QD. Nonresponders randomized to baricitinib 4-mg at baseline will remain on 4-mg. After rerandomization, patients will remain on the same dose of baricitinib for the remainder of the study.
h Occurs approximately 28 days after the last dose of IP. Not required for patients who have been off drug for 28 days or more at the time of their last visit.

*Figure 21 Design of **study JAIN***

Study participants

Patients were included if they were 18 years or older and had AD for at least 1 year. They should have moderate to severe AD, as defined by an EASI score ≥16, an IGA >2, and a BSA ≥10%, while having had a recent inadequate response to topical therapies and had a documented history of inadequate response, intolerance, or contraindication to ciclosporin use.

Treatments

In the double-blind treatment period, patients received baricitinib 1 mg QD, baricitinib 2 mg QD, baricitinib 4 mg QD, or placebo QD, for 16 weeks, added to a standardised regimen of TCS. Blinding was maintained using double-dummies.

Patients had to wash-out from topical and systemic AD treatments before baseline. Background TCS therapy was triamcinolone 0.1% cream or equivalent-potency TCS applied twice daily, until lesions were under control (clear or almost clear), then it was switched to hydrocortisone 2.5% ointment or equivalent-potency TCS for 7 days after which it could be stopped and restarted if lesions reappeared. Patients had to apply emollients throughout the study.

Rescue therapy was included, with higher potency TCS as the first step.

Outcomes

Primary outcome was the proportion of patients with at least a 75% change from baseline at week 16 in Eczema Area and Severity Index (EASI) score (EASI75).

Main secondary outcomes were: mean percent change in EASI score, mean change in itch severity on a NRS; mean change in pain severity on a NRS; change in the number of awakenings at night due to itch (ADSS item 2); the proportion of patients with an Investigator's Global Assessment (IGA) score of 0 or 1; the proportion of patients with at least 75% improvement in the SCORing Atopic Dermatitis scale (SCORAD). (*See the main studies for further explanation of outcomes.*)

Primary outcome was EASI75 at week 16, secondary outcomes were: change in EASI, Itch NRS, Pain NRS, ADSS item 2, IGA 0 or 1, and SCORAD75.

Statistical methods

The analyses for efficacy were based on the ITT population. NRI was applied to missing values of the primary outcome and other categorical outcomes. A graphical multiple testing approach was employed for testing the primary outcome (EASI75) of the three dose groups against placebo at an α of 5%.

Participant flow

There were 566 patients screened and 463 patients were randomised to one of the four treatment groups. All randomised patients but one had received at least 1 dose of study drug. In total, 72 (77%)

placebo patients and ~93% of patients in the baricitinib 2mg and 4mg groups completed the 16 week study period. Most patients who discontinued in the 2mg and 4 mg groups did so because of lack of efficacy.

Baseline data

At baseline, there were numerical between-group differences in gender; age, disease duration, disease severity (IGA of 4, EASI, BSA affected, itch, pain) and use of prior therapies were numerically similar. The majority (63% - 70%) of patients had used ciclosporin before, non-use usually was due to contra-indications. Most (70%) patients were from Europe.

Outcomes and estimation

All 463 randomised patients were included in the efficacy analyses (ITT). Nearly all (97%) patients were compliant with study medication.

Main efficacy data are presented in Table 31. The data for the 1mg group are not shown:

Table 31 Efficacy of baricitinib in combination with TCS[a] at week 16 in BREEZE-AD4 (FAS)[b]

Study	**BREEZE- AD4**		
Treatment group	*PBOa*	*BARI 2 mga*	*BARI 4 mga*
N	93	185	92
EASI-75, % respondersc	17.2	27.6	31.5**
IGA 0 or 1, % respondersc, e	9.7	15.1	21.7*
Itch NRS (≥ 4 point improvement), % respondersc, f	8.2	22.9*	38.2**
Change in DLQI mean (SE)d	-4.95 (0.752)	-6.57 (0.494)	-7.95* (0.705)

BARI = Baricitinib; PBO = Placebo

* statistically significant vs placebo without adjustment for multiplicity; ** statistically significant vs placebo with adjustment for multiplicity.

a All patients were on concomitant topical corticosteroids therapy and patients were permitted to use topical calcineurin inhibitors.

b Full analysis set (FAS) includes all randomised patients.

c Non-Responder Imputation: Patients who received rescue treatment or with missing data were considered as non-responders.

d Data collected after rescue therapy or after permanent study drug discontinuation were considered missing. LS means are from Mixed Model with Repeated Measures (MMRM) analyses.

e Responder was defined as a patient with IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥ 2 points on 0-4 IGA scale.

f Results shown in subset of patients eligible for assessment (patients with itch NRS ≥ 4 at baseline).

Development and validation of the Atopic Dermatitis Sleep Scale (ADSS)

The MAH has performed validation studies of the 3-item patient-assessed Atopic Dermatitis Sleep Scale (ADSS) and submitted a report summarising the evidence of its measurement properties. The ADSS is a 3-Item, patient-administered questionnaire developed to assess the impact of itch from AD on sleep disturbance including difficulty falling asleep due to itch (Item 1), number of night time awakenings due to itch (Item 2), and difficulty getting back to sleep after waking due to itch last night (Item 3). Items 1 and 3 are rated using Likert scales ranging from 0 'not at all' to 4 'very difficult'. Item 2 is rated as the number of times one woke up last night, ranging from 0 to 29. The items are scored individually, there is no total score.

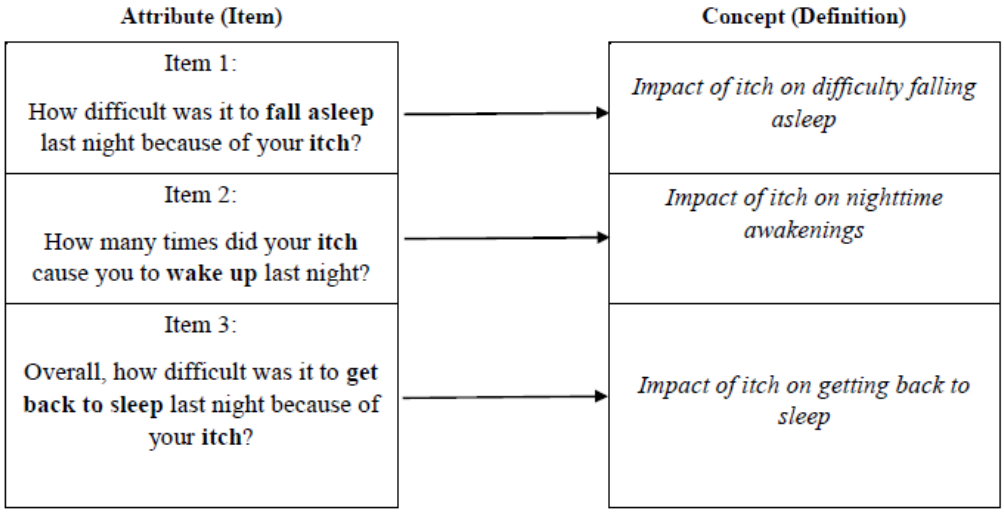


Figure 22 ***Atopic Dermatitis Sleep Scale (ADSS)***

Content validity was evaluated using targeted literature review and semi-structured interviews for item generation and debriefing, with 31 adolescent and 63 adult patients with AD. Individual item performance (item distribution, and floor and ceiling effects) and the measurement properties (reliability, construct validity, responsiveness, and estimation of meaningful change) of the ADSS items were assessed using data from studies JAHL and JAHM.

Results for test-retest reliability among stable patients showed ICC values ranging from 0.75 to 0.84 (Item 1), 0.59 to 0.92 (Item 2), 0.68 to 0.78 (Item 3). Construct validity was evaluated using correlations with other outcomes in comparison with a priori hypotheses. ADSS items were cross-sectionally moderately correlated with other patient reported outcomes (PGI-S-AD, DLQI, POEM) in studies JAHL and JAHM. When patients were categorized into subgroups based on PGI-S-AD and POEM, the groups of patients with lower disease severity experienced a significantly less sleep disturbance due to itch ($p<0.01$ for all comparisons in studies JAHL and JAHM). Ability to detect change was tested based on responder/non-respondership in POEM, changes of ADSS items between baseline and week 16 were different for responder and non-responders in POEM. To derive a minimal clinically important difference in ADSS items, thresholds of change (very marked improvement, marked improvement, minimal improvement, etc.) in PGI-S-AD scores at week 4 and at week 16 were used. The mean score of patients with a moderate change in PGI-S-AD was used to define a MCID of -1.5, a minimal change was equated with a change of -1 and a large change with -3. The anchor variable suggested that a

conservative threshold of 1.25-points for Items 1 and 3 and 1.5-points for Item 2 over 16 weeks was an appropriate criterion to interpret a treatment benefit.

The MAH concluded that the psychometric properties of the ADSS were evaluated in terms of individual item performance (item distribution and floor and ceiling effects), and psychometric properties (test-retest reliability, construct validity, known-groups validity, ability to detect change, and estimation of meaningful change. The Minimal Change Threshold provided were -1.25 for ADSS Items 1 and 3, and -1.5 for ADSS Item 2. All psychometric properties were found to be at least excellent (with the exception of the response rate of the ADSS Item 3) which supports the use of the ADSS for assessing overall AD severity in moderate to severe AD.

Development and validation of a Numerical Rating Scale for Skin Pain

The Skin Pain NRS is a single-item measure designed to capture information on the self-reported skin pain severity by rating "the worst level of skin pain in the past 24 hours." The patient reports this severity by selecting the number/integer from 0 (no pain) to 10 (worst pain imaginable).

The content validity of the Skin Pain NRS was supported through a targeted literature review and (qualitative content elicitation and cognitive) interviews with AD patients. Individual item performance (item distribution and floor and ceiling effects) and measurement properties (reliability, construct validity, responsiveness, and estimation of meaningful change) of the Skin Pain NRS were assessed using data from studies JAHL and JAHM.

Test-retest reliability analyses showed substantial agreement in scores among stable patients with the ICC ranging from 0.77 to 0.85. Regarding construct validity, correlations between the patient-reported Skin Pain NRS and other assessments included in Studies JAHL and JAHM were generally moderate to large at baseline and remained moderate at Week 16. The strongest cross-sectional association was present between the Skin Pain NRS and PGI-S-AD ($r \geq 0.69$). When patients were categorized into subgroups based on PGI-S-AD and POEM, the groups of patients with lower disease severity experienced a significantly less skin pain severity ($p < .01$ for all comparisons in Studies JAHL and JAHM). To evaluate the ability to detect change, tests of Skin Pain NRS changes between baseline and week 16 to discriminate responders and non-responders based on the change in the POEM were conducted. Statistically significant differences in mean changes indicated that Skin Pain NRS was sensitive enough to detect these important changes in disease severity ($p < .05$ for all). Finally, anchor-based analyses were utilized to derive a clinical interpretation of the Skin Pain NRS with the weekly mean PGI-S-AD serving as the anchor variable. The anchor variable suggested that a conservative threshold s in Skin Pain NRS over 16 weeks was an appropriate criterion to interpret a treatment benefit at Week 16 in patients with AD. Approximately a 4-point change at Week 16 mean Skin Pain NRS is able to significantly distinguish betweenresponders and non-responders in PGI-S-AD.

The MAH concluded that the evidence provided demonstrates that the Skin Pain NRS has sufficient reliability, validity, responsiveness, and interpterion standards to be considered a well-defined and reliable PRO instrument that is fit for purpose and suitable to be used in clinical trials to evaluate a labeling claim in patients with moderate-to-severe AD.

2.4.3. Discussion on clinical efficacy

Data of 6 randomised double-blind placebo-controlled studies of baricitinib in patients with AD were submitted:

- A 'phase 2' study (JAHG) of 2 mg and 4 mg added to TCS, of 16-weeks.

- Two identical 'phase 3' studies (JAHL and JAHM) of 1 mg, 2 mg, 4 mg monotherapy, of 16 weeks.
- A 'phase 3' study (JAIY) of 2 mg and 4 mg added to TCS and allowing for concomitant TCI, of 16-weeks.
- A 'phase 3' long-term extension study (JAHN) including dose continuation of 2 mg and 4 mg in responders and partial responders for in total 52 weeks, followed by a randomised down-titration/stop sub-study. Total duration is 104 weeks.
- A 'phase 3' study (JAIN) of baricitinib added to TCS of 16 weeks (with follow-up phases).

Study JAHN is ongoing and data were updated during the procedure. Patients were mainly recruited from JAHL, JAHM and JAIY. A sub study/cohort was added to evaluate efficacy and safety of baricitinib 2-mg open-label in adult patients with moderate to severe AD who had not completed an originating study.

In addition, Study JAIN is an ongoing Phase 3 study investigating the efficacy and safety of baricitinib in patients who experienced failure with ciclosporin or are intolerant to or have a contraindication to ciclosporin. Similar to Study JAIY, patients in Study JAIN are permitted to use low- and moderate-potency TCS as concomitant therapy throughout the study.

Design and conduct of clinical studies

It is considered that in principle, the package of 16-week monotherapy studies JAHL and JAHM, 16-week combination therapy study JAIY, 36-week (52-week in total) period 1 of follow-up study JAHN, supported by dose-finding study JAHG, is sufficiently informative to assess benefit-risk in the atopic dermatitis indication. Though study JAHN is ongoing, period 1 of 52 weeks was completed yet all patients coming from studies JAHL and JAHM. Efficacy data from patients coming from study JAIY were not complete but are available for 50% of patients up to week 24. The MAH also updated the results of the patients in the baricitinib 2 mg open label study. Final results of the step down/stop sub study performed in study JAHN will be available after the final database lock, which is projected to occur in 2023. In the response to the first RSI, an update of the study JAHN was submitted, along with interim data from the ongoing Study JAIN. The data cutoff of JAIN was 28 November 2019 when all patients had completed at least 24 weeks of treatment.

The studies were identical (JAHL and JAHM) or nearly identical (JAIY) regarding in/exclusion criteria and the included populations were quite similar regarding baseline characteristics. In study JAHM the proportion with an IGA of 4 was ~8% higher as compared to study JAHL, which is not considered clinically relevant seen the similarity between the studies in baseline values of other disease outcomes. In alignment with the requested indication, the disease characteristics do reflect a population with moderate to severe AD who are candidates for systemic therapy. This is notably reflected by the nearly equal proportions of patients with an IGA of 3 ('moderate') or 4 ('severe') and the mean values for EASI and BSA affected, but is also reflected in mean values of other secondary outcomes such as Itch NRS, Skin pain NRS, and DLQI. By design, all included patients had used TCS and/or systemic therapies before. Nearly all patients had used TCS and a majority had used TCIs or systemic treatments. The CHMP considered that this sufficiently reflects the intended population. The distributions are such that this will support performance of subgroup analyses, such as failure of TCIs and failure of systemic therapies. The exclusion criteria are not overly restrictive.

The choice for 2 mg and 4 mg as doses to be studied in the 'phase 3' AD studies are agreed by CHMP. Baricitinib 4 mg and 2 mg are also the approved doses for the treatment of RA, with 4 mg as the standard dose. In psoriasis, doses from 2 mg up to 10 mg were tested in a dose-ranging study; while

4 mg was effective and 2 mg only effective on itch, higher doses than 4 mg did not have a favourable safety profile. In the 'phase 2' AD study, the 4 mg dose was significantly superior to placebo in the primary outcome, EASI50 at week 16. The 2 mg dose was not statistically significant in the primary outcome, but the response was numerically only slightly smaller than the 4 mg dose. Superiority of baricitinib against placebo already began to appear at week 4 in EASI50 and other outcomes. Based on the overall efficacy results of the dose-finding study, it can be presumed that baricitinib 4 mg could be the most effective dose but that 2 mg may also be effective.

Concomitant use of emollients during the studies reflects practical use. Concomitant use of TCS in the combination study was protocolised and started with a moderate-potency TCS that was switched to a low-potency TCS when lesions were clear or almost clear, which was then stopped after 7 days. TCS was to be resumed if lesions reappeared. Use of TCIs was permitted for areas of sensitive skin, for which TCS is not recommended. This use of concomitant TCS and TCIs reflects practical use on a standardised manner. While the initiation of rescue treatment includes a subjective component, the way rescue treatment should be used was well-defined in the protocols and rescue treatment was documented in the CRF.

The primary outcome was reaching an IGA 0 or 1 with an improvement ≥2 points from baseline. This is agreed as a clinically meaningful outcome, in line with the CHMP Scientific Advice. As all included patients have an IGA of 3 or 4 at baseline, all patients having an IGA of 0 or 1 will have had an improvement of ≥2 points. As IGA relies on examination, the use of a validated version and training of examiners is endorsed. EASI75 was a key secondary outcome, which is agreed. SCORAD is a well-known outcome measure for AD and its inclusion as secondary outcome therefore is agreed. Measures for itch, sleep disturbance, skin pain, and health-related quality of life were also included, which is endorsed to reflect the range of manifestations and consequences of AD. The MAH performed validation studies for the ADSS and Skin pain NRS, which is endorsed. The validity and the measurement properties of these measures is considered to be sufficiently supported. However, the minimal clinically important difference of 1.5 awakenings for ADSS items 2 was not understood by the CHMP. Therefore, it has been rounded-up to 2 when this outcome was included in section 5.1 of the SmPC.

Sample size for the monotherapy studies and combination therapy study was based on the results of (combination) dose-finding study JAHG and aimed at least finding a difference of 20% in IGA 0 or 1 response, with placebo. Using a background of TCS in the dose-finding study/proof of concept study is understood, but post-hoc it appears that the treatment effect in IGA 0 or 1 was lower than expected based on JAHG results.

The procedure for randomisation and stratification was adequate. Because baricitinib 1 mg, 2 mg and 4 mg tablets differ in size, a double dummy design was implemented. Consequently, patients in studies JAHL and JAHM had to take 3 tablets daily (one for each dose) and in JAIY patients had to take 2 tablets. The measures to keep patients and investigators and other personnel blinded appear to be appropriate. The analysis populations and statistical analyses were considered adequate.

For purpose of representativeness to the European population, a sufficient number of patients were included in several EU countries: 54% in JAHL, 46% in JAHM, and 35% in JAIY.

The degree of completion of the 16-week studies was high (>90%) and the vast majority of patients continued in the follow-up study JAHN. It is reassuring that discontinuations were lowest in the baricitinib 4 mg (highest dose) treated groups. Few patients discontinued due to adverse events, usually from the baricitinib treated groups. All randomised patients were included in the ITT population and nearly all patients could be included in the PP population, which is favourable. It can be anticipated that there will not be much difference in results between ITT and PP analyses.

The number of protocol amendments was limited and did not concern major changes in the conduct of the studies. The number of protocol violations was limited in number and usually concerned violations of in/exclusion criteria and significant non-compliance to study treatment. According to the MAH, all studies were conducted in accordance with Good Clinical Practices and applicable local laws and regulations.

Compliance to investigational treatment was high. In each of the studies JAHL, JAHM and JAIY, few patients were classified as non-compliant and compliance was ≥98%.

In monotherapy studies JAHL and JAHM most patients used rescue treatment, usually TCS and seldom systemic medications. Use of rescue was lowest in the baricitinib 4 mg groups (41% and 59%), equally higher in the 2 mg and 1 mg groups and highest in the placebo groups (67% and 77%). Rescue treatment was used as early as week 1 in all treatment groups, but more patients used rescue earlier in the placebo groups than in the baricitinib treated groups in a dose-dependent way. This means that in essence, combination therapy was an important component of the treatments studied in 'monotherapy' studies JAHL and JAHM. In dedicated combination therapy study JAIY, all patients already were on TCS at baseline, and rescue treatment was used much less than in the monotherapy studies. In JAIY rescue was used in ~5% of the baricitinib 2 mg and 4 mg groups and in 9% of the placebo-treated patients. The frequent use of rescue medication in JAHL and JAHM means that the estimand that includes the use of combination therapy ('secondary censoring') becomes important for the interpretation of the results of efficacy outcomes.

Supportive study JAIN provides efficacy (and safety) data in patients for whom ciclosporin failed or is no option. This is an important subpopulation within the indication, to consider in clinical practice. Its design followed the outline of the pivotal studies and is considered to be reasonably well performed.

Efficacy data and additional analyses

The effects of baricitinib on IGA 0 or 1 were largest for the 4 mg dose in all three studies. In both monotherapy studies and in the combination therapy study, baricitinib 4 mg was statistically significantly more effective than placebo regarding IGA 0 or 1 at week 16 (primary outcome). Baricitinib 2 mg was statistically significantly more effective than placebo in reaching IGA 0 or 1 in the monotherapy studies, but not in the combination therapy study. Baricitinib 1 mg was not more effective than placebo. The analyses on the primary outcome were supported by the several pre-planned sensitivity analyses.

- In the monotherapy studies JAHL and JAHM, IGA 0 or 1 was reached by 17% and 14% of patients in the baricitinib 4 mg groups (both $p<0.001$), 11% and 11% in the 2 mg groups (both $p<0.05$), 12% and 9% in the 1 mg groups (both NS), 5% and 5% in the placebo groups. The difference (95%CI) with placebo was 12.0% (5.5% – 19.8%) and 9.3% (3.3% – 16.8%) for the 4 mg groups and 6.6 (0.9% – 13.7%) and 6.1 (0.6% – 13.0%) for the 2 mg groups, which was significant after adjustment for multiplicity.
- In the combination therapy study JAIY, IGA 0 or 1 was reached by 31% of patients in the baricitinib 4 mg group ($p<0.01$), 24% in the 2 mg group (NS), and 15% in the placebo group. The difference (95%CI) with placebo was 16.0% (4.9% – 26.6%) for the 4 mg group and 9.2 (-1.4% – 19.5%) for the 2 mg group, which was significant after adjustment for multiplicity for the 4 mg dose group.
- The effect of baricitinib 4 mg and 2 mg on IGA 0 or 1 appeared after 2-4 weeks of treatment in studies JAHL, JAHM and JAIY (Figure 8).

Response sizes of secondary outcomes (EASI75, improvement ≥4 points in the Itch NRS, change in ADSS item 2, SCORAD75, Skin pain NRS) were generally similar in the identical monotherapy studies JAHL and JAHM and usually numerically higher in the combination study JAIY. The statistical tests corrected for multiplicity in the main secondary outcomes were supportive for the baricitinib 4 mg dose in all three studies, the support for the 2 mg dose is less robust and it was not supported by the primary and secondary outcomes in the combination therapy study (*Table 32*).

Table 32 Overview of significance tests of primary analyses (p<0.05) in main secondary outcomes, corrected for multiplicity in studies JAHL, JAHM and JAIY.

	JAHL			**JAHM**			**JAIY**	
Outcome at week 16	1 mg	2 mg	4 mg	1 mg	2 mg	4 mg	2 mg	4 mg
IGA 0 or 1	**x**	√	√	**x**	√	√	**x**	√
EASI75	**x**	√	√	**x**	√	√	**x**	√
Itch NRS response	**x**	**x**	√	**x**	√	√	**x**	√
ADSS item 2	**x**	**x**	√	**x**	√	√	**x**	√
SCORAD75	**x**	**x**	√	**x**	√	√	**x**	**x**
Skin pain	**x**	**x**	√	**x**	√	√	**x**	**x**

- In studies JAHL and JAHM, EASI75 at week 16 was reached by 25% and 21% of patient on baricitinib 4 mg, 19% and 18% on 2 mg, 17% and 13% on 1 mg, and 9% and 6% on placebo, which was statistically significant versus placebo for the 4 mg and 2 mg groups. In study JAIY, EASI75 at week 16 was reached by 48% of patient on baricitinib 4 mg + TCS, 43% on 2 mg + TCS, and 23% on placebo + TCS, which was statistically significant for 4 mg only.
- In studies JAHL and JAHM an improvement ≥4 points in the Itch NRS at week 16 was reached by 22% and 19% of patients treated with baricitinib 4 mg, 12% and 15% in patients treated with 2 mg, and 7% and 5% in the placebo groups, which was statistically significant larger as compared to placebo for 4 mg but for 2 mg only in study JAHM. In study JAIY, an improvement in Itch NRS≥4 points was reached by 44% of patients treated with 4 mg, 38% of patients on 2 mg, and 20% of patients on placebo, the difference was statistically significant from placebo for baricitinib 4 mg but not for 2 mg.

The EASI75 response is considered to be key secondary outcome. In essence, the efficacy conclusions for week 16 are the same as for the primary outcome IGA 0 or 1. The treatment effect is dose-dependent and largest for the baricitinib 4 mg dose. In the monotherapy studies, the treatment effect on EASI75 was statistically significant for both baricitinib 2 mg and 4 mg. In the combination therapy study, only the treatment effect for baricitinib 4 mg was statistically significant.

In all three 16-week studies, the results for IGA 0 or 1 and for EASI75 are supported by all other main secondary outcomes including Itch, sleep disturbance (ADSS), patient assessed skin manifestations (SCORAD, POEM), Skin pain, health related quality of life (DLQI), anxiety and depression (HADS). The CHMP therefore considered that the treatment effects found for baricitinib are robust over primary and main secondary outcomes, that the treatment effects are largest for the baricitinib 4 mg dose and if used with TCS, that clinical relevance of the treatment effect is notably supported by the effects on itch, sleep disturbance, skin pain, health-related quality of life and anxiety and depression.

For the baricitinib 4 mg dose, the responses in IGA 0 or 1 were 14% and 17% in the monotherapy studies and 31% in the combination therapy study. The treatment effect can be enhanced if baricitinib is used in combination with TCS. These responses (and the differences with placebo) may be appreciated as relatively low, seen numerically. This treatment effect also falls a bit below the a priori expectations from dose-finding study JAHG. In the monotherapy studies, rescue treatment with TCS was used by a majority of patients. In the baricitinib 4 mg groups, the responses in IGA 0 or 1 were 6% to 8% higher if results were analysed when allowing for rescue treatment. In the combination therapy study where patients already were on TCS, rescue was not much used and did not make a difference in the result on group level. Consequently, the clinical relevance of the treatment effect of baricitinib 4 mg QD administered as monotherapy in both phase III clinical trials was questioned during the application. However, it has to be considered that baricitinib 4 mg as monotherapy was significantly more effective than placebo in reaching the main outcomes IGA 0 or 1 and EASI75 and this was supported by the results of other patient relevant outcomes such as itch, sleep disturbance due to itch, skin pain, DLQI and POEM. It can be argued that the proportions reaching IGA 0 or 1 on monotherapy were pretty low (Effects Table). On the other hand, while IGA 0 or 1 ('clear' or 'almost clear') is the ultimate treatment goal, the CHMP agreed that reaching a response/partial response (IGA 0, 1 or 2) also is a clinically relevant outcome. About 30% of patients in the monotherapy trials reached IGA 0, 1 or 2, compared to ~11% in the placebo groups, which is considered clinically relevant. Therefore, the CHMP concluded that the treatment effect of baricitinib 4 mg QD administered as monotherapy was clinically relevant.

Because the treatment effect in the combination therapy study was larger than in the monotherapy studies, and while this effect also appears to be maintained, concomitant use of TCS appears to be a good treatment option. It can be envisaged that this use will be intermittent, in line with practice guidelines. Hence, at the CHMP's request, the added value of treatment with TCS was included in the Section 4.2 of the SmPC.

The onset of effect in IGA 0 or 1 but also EASI75 becomes apparent between 2 – 4 weeks, for baricitinib 2 mg and 4 mg, with or without concomitant TCS. This is considered a clinically relevant timing for onset of action. From prognostic analyses it appeared that lack of response at week 8 is predictive for a lack of response at later time points.

In maintenance study JAHN, data of patients who continue 4 mg as responders and partial responders suggest that treatment efficacy gradually decreases over time in the 4 mg baricitinib QD arm of originating study responders and partial responders. Seventy (70) patients were analysed at start, 64 patients at week 36. IGA 0/1 decreases from 45.7% at start to 37.5% at week 36 (-8.2%) of study JAHN. This decrease is even more obvious in the group responders and partial responders which drops from 100% at start to 57.8% at week 36 (-42.2%). From these numbers, it can be calculated that there are 38/70 (54%) IGA=2 patients at start (partial responders) and 13/64 (20%) partial responders at week 36, showing a loss of partial response in a majority of patients (2.6 times lower at week 36 compared to start, or a decrease of 62% in number of partial responders). Of note, in the small populations investigated, most endpoints show a better maintenance of effect in the 2 mg baricitinib group compared to the 4 mg baricitinib group. Therefore, the SmPC statement proposed by the MAH "Some patients with initial partial response may subsequently improve with continued treatment beyond 12 weeks" was questioned by the CHMP. The MAH performed a prognostic 'responder' analysis to investigate whether the lack of a partial response at an earlier time point could be predictive of failure to achieve a complete response at a later time point. Single predictors or combinations thereof, analysed at weeks 2, 4 and 8, were assessed for their negative predictive value in EASI75 and Itch NRS $\geq$ 4 and IGA 0,1 response at week 16. These analyses consistently demonstrated that highest sensitivity and negative predictive value were obtained at week 8 of treatment.

Based on the two above points, it has been indicated at the CHMP's request that treatment should be discontinued if no response is reached by week 8 in the Section 4.2 of the SmPC. In addition, the proposed statement that some patients may improve after 12 weeks has been deleted at the CHMP's request.

While there was a maintenance of effect in the patients who were followed up to week 52, the overall maintenance of effect if on monotherapy appeared to be better for the 2 mg dose as compared to the 4 mg dose. In the responders/partial responders continuing baricitinib 4 mg and 2 mg, the IGA 0 or 1 response was similar at baseline of study JAHN with ~46% in both groups (the complementary proportions were partial responders with an IGA of 2). However, after a total follow-up of 32 weeks and 52 weeks, responses were highest in the baricitinib 2 mg treated patients. In the 4 mg treated patients, the response became quite similar to the response in the 1 mg group. While it is known that responses may decline over time, due to regression of the mean, the differential effect is difficult to understand. As the study is still blinded, it is unlikely that expectations have driven the differential result in maintenance. It does not seem likely that concomitant TCS use in the 2 mg group will explain the effect, as use of TCS in study JAHN was generally low and intermittent.

A similar trend as in IGA 0 or 1, with better maintenance in the 2 mg dose as compared to the 4 mg dose, is also seen in EASI75, but less in Itch NRS response. In contrast to IGA 0 or 1 and EASI, Itch NRS slowly declined in both dose groups, with the highest response in the 4 mg group. If all patients on baricitinib 4 mg (responder and partial responders, non-responders) are analysed as a group, it appears that the results on IGA 0 or 1 and EASI75 are more stable. This may happen through regression to the mean and may mean that some patient need more time to develop a response, or develop a response in combination with TCS. While the tendency of a decline in response that is larger for baricitinib 4 mg and less of baricitinib 2 mg is not readily understood, it points out that baricitinib 2 mg may be a good option for maintenance treatment in patients who have reached a satisfactory response. The secondary outcomes on sleep quality (ADSS item 2), skin pain and quality of life (DLQI) are generally supportive for maintenance in the two doses, baricitinib 4 mg and 2 mg. In period 2 of study JAHN a step-down/stop substudy will be performed, and these results may add to the results of this strategy. In line with the posology for RA, the MAH was asked by the CHMP to discuss the option to include a posology recommendation in the SmPC like: '*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*'. In response, this statement was included in the Section 4.2 of the SmPC.

Predefined subgroup analyses were performed for a limited set of variables, which is endorsed by the CHMP. Subgroup analyses were performed separately for monotherapy (pooled studies) and combination therapy, which is agreed by the CHMP. The IGA 0 or 1, EASI75 and Itch NRS improvement ≥4 points were used as outcomes for the subgroup analyses. As the proportion of patients reaching IGA 0 or 1 at week 16 was relatively low, this limits subgroup analyses due to low sample sizes. Therefore, in the assessment it was focussed on IGA 0 or 1 as well as EASI75.

Males overall seem to perform worse than females, but there is a clinically relevant treatment effect also in males. Subgroup analysis for age was redone using tertiles, no age effect was apparent. For patients with moderate levels of disease activity (IGA 3) it was overall easier to reach a response (IGA 0 or 1) as compared to patients with severe disease (IGA 4). Over studies and major outcomes, there was a tendency that responses were higher in the EU subgroup as compared to the rest-of-the-world.

Previous failure of ciclosporin did not seem to have a negative influence on the treatment effect, at least for the 4 mg dose. In case of previous use of TCI, the treatment effect may be somewhat smaller if on monotherapy with baricitinib. The number of patients having used dupilumab before was small, but there was no indication that treatment with baricitinib would be ineffective if patients had previously used dupilumab. The CHMP considered that these results have no further consequences for

the SmPC yet, as treatment effects appear to be present across all subgroups. Study JAIN was specifically performed in patients with ciclosporin failure of for whom ciclosporin is contra-indicated, though this study standardly included concomitant TCS with baricitinib or placebo. Its results confirmed the efficacy of baricitinib in this subpopulation. Because of its relevance to the clinical practice, the study results from study JAIN are included in the Section 5.1 of the SmPC.

The CHMP had concerns about the text proposal concerning SmPC section 5.1 which was considered too extensive. The MAH made a revised proposal for Section 5.1 and considerably shortened section 5.1 of the SmPC to describe the efficacy of baricitinib in Atopic Dermatitis.

2.4.4. Conclusions on the clinical efficacy

In all three studies (JAHL, JAHM, JAIY), baricitinib 4 mg was statistically significant more effective than placebo in reaching IGA 0 or 1 at week 16 (with a ≥2 points improvement from baseline), while adjusting for multiplicity. Baricitinib 2 mg was more effective than placebo in reaching IGA 0 or 1 at week 16 in the monotherapy studies, but not in the combination therapy study. The 1 mg dose was not more effective than placebo. The results were supported by sensitivity analyses.

A significantly larger proportion of patients randomised to baricitinib 4 mg achieved an IGA 0 or 1 response (primary outcome), EASI75, or an improvement of ≥ 4 points on the Itch NRS compared to placebo at week 16

Treatment effects in subgroups (weight, age, gender, race, disease severity, and previous treatment, including immunosuppressants) were consistent with the results in the overall study population.

The effect after 16 weeks appears to be largely maintained over 52 weeks, similar in the patients continuing 2 mg and 4 mg, whether on monotherapy or on combination therapy.

The CHMP concluded that baricitinib 4 mg is the most effective dose, and that the effects can be enhanced by concomitant use of TCS. In clinical practice, concomitant intermittent use of TCS can be expected and this is appropriately reflected in the SmPC. This also is supported by the larger treatment effects in the combination therapy study that were basically maintained over time.

Because maintenance of effects in (partial) responders on 4 mg are well maintained with the 2 mg dose, the SmPC includes the opportunity to lower the dose to 2 mg if a desirable target level of AD is reached. More information will be available upon completion of the down-titration/stop substudy in period 2 of study JAHN (ongoing and the CHMP recommends that the MAH submits the final CSR from study JAHN).

However, as indicated in Section 4.2 of the SmPC, treatment should be discontinued if no response is reached by week 8.

In conclusion, the CHMP considers that the efficacy of baricitinib is supported by the data submitted in the claimed indication: "Atopic Dermatitis: Olumiant is indicated for the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy."

2.5. Clinical safety

Introduction

Currently, Olumiant (baricitinib) is indicated for the treatment of adults with RA, as second-line therapy. Baricitinib has a complex safety profile. Therefore, it is recommended in the SmPC that

baricitinib should only be used under supervision of an experienced specialist. An overview of the safety profile of baricitinib in the currently registered RA indication is provided below.

The following Adverse Drugs Reactions have been included in the SmPC for the RA indication: infections (upper respiratory tract infections, herpes simplex and herpes zoster, gastroenteritis and urinary tract infections), pulmonary embolism/deep venous thrombosis, neutropenia and thrombocytosis, increase of CPK and of weight, LDL-cholesterol and triglycerides, liver function tests (AST, ALT), nausea and acne, swelling of the face and urticaria.

As expected for an immune-modulating drug, baricitinib causes infections. These were mainly upper-respiratory tract infections. Serious infections rates according to ICH criteria were overall low. Although there was no treatment related effect, as precautionary measures, routine monitoring of neutropenia and lymphopenia is included in the SmPC (see section 4.4 of the SmPC) as these are known to be related to infections. Due to its mode of action, baricitinib causes viral reactivation. In RA, herpes zoster and herpes simplex were more frequently reported for baricitinib than for placebo and MTX monotherapy. Due to the risks of complicated herpes zoster infection, several risk minimization measures have been put in place, such as lowering the dose to 2 mg for patients at risk (e.g. in elderly, patients with a history of recurrent infections), the instructions in the SmPC (see section 4.4 of the SmPC) to interrupt treatment at first sign of herpes zoster and a patient' alert card. Thus far, there was no signal of opportunistic infections above the background risk. Because of the mode of action of baricitinib, opportunistic infections are certainly not excluded.

Malignancies did not occur more frequently than expected, but more long-term follow-up is needed to be more certain. A general warning of enhanced risk of malignancies including lymphoma in the general RA patient population has been added to the SmPC (see section 4.4 of the SmPC).

Baricitinib is known to interfere with haematopoiesis above the therapeutic dose. Overall, the rate of anaemia was marginally increased at the proposed dose level of 4 mg. A warning has been included in the SmPC (section 4.4) to monitor Hb routinely. Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving baricitinib. Olumiant should be used with caution in patients with risk factors for DVT/PE (see section 4.4 of the SmPC) and baricitinib should be discontinued if clinical features of DVT/PE occur.

Baricitinib had a clear and consistent inducing effect on cholesterol –both LDL and HDL. Moreover, weight and waist circumference also increased. Thus far, these changes are not been associated with a higher incidence of CV events/MACE for baricitinib, what normally would be expected if cholesterol increases (MACE was overall uncommon). Lipid increments will be further followed in a PASS. Routine monitoring of lipids is recommended in the SmPC (see section 4.4 of the SmPC).

ALT and AST elevations were very common, although severe ALT or AST elevations were overall rare.

Baricitinib 4 mg caused a steady increment of serum creatinine levels of about 5 µg/ml in the total study population (i.e non-renal patients). The Applicant postulated that the increased creatinine was due to an interaction effect of baricitinib on tubular transporters of creatinine, by inhibition of the OCT-2, MATE-1, and MATE-2K transporters. Consequently, GFR estimates based on creatinine levels decreased with on average 8.0 mL/min/BSA from baseline. Possibly, this effect is an interaction at the tubular level of creatinine excretion, and this is no signal of loss of renal capacity. This has been adequately addressed in the SmPC section 5.1. For moderate renal impaired patients, the dose is restricted to 2 mg (SmPC section 4.2), to prevent accumulation of the drug, which is renally cleared.

Also CPK increments were commonly reported. However, these were not clearly accompanied with clinical symptoms of muscle damage, and therefore do not contribute negatively to the overall B/R balance. Myopathy has been included in the RMP as potential risk.

Patient exposure

Data of 5 randomised double-blind placebo-controlled studies of baricitinib in patients with AD were submitted; the long term extension study is still ongoing:

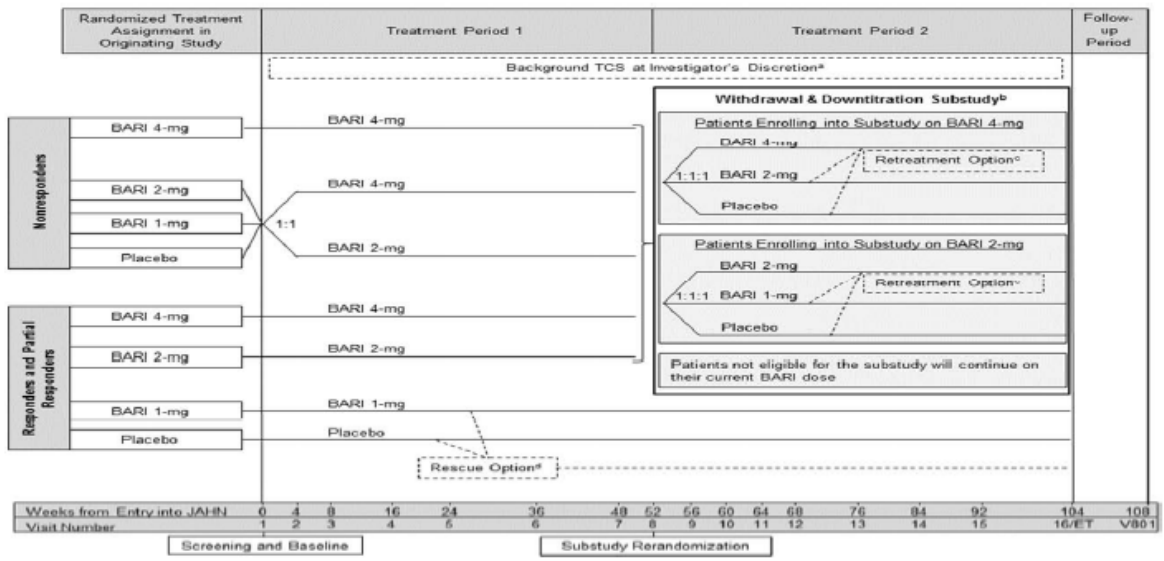
- A 'phase 2' study (JAHG) of 2 mg and 4 mg added to TCS, of 16-weeks.
- Two identical 'phase 3' studies (JAHL and JAHM) of 1 mg, 2 mg, 4 mg monotherapy, of 16 weeks.
- A 'phase 3' study (JAIY) of 2 mg and 4 mg added to TCS and allowing for concomitant TCI, of 16-weeks.
- A 'phase 3' long-term extension study (JAHN) including dose continuation of 2 mg and 4 mg in responders and partial responders for in total 52 weeks, followed by a randomised down-titration/stop sub-study. Total duration is 104 weeks.

Additional safety data were submitted from 3 ongoing studies in patients with AD:

- A 104-week, double-blind, 'phase 3' study of 1 mg, 2 mg and 4 mg in combination with TCS, in patients who have had ciclosporin (JAIN).
- A 104-week, double-blind 'phase 3' monotherapy study of 1 mg and 2 mg (JAIW).
- A 104-week, 'phase 3' open-label long-term extension study of 2 mg (JAIX).

JAIW and JAIX are being performed in the US and Canada.

For more details of the study designs of studies JAHG, JAHL, JAHM and JAHN, it is referred to the efficacy section. A figure of the design of study JAHN can be found below (Figure 23).



Abbreviations: BARI = baricitinib; ET = early termination; IGA = Investigator's Global Assessment; TCS = topical corticosteroids; V = visit.

a Background TCS may be initiated or reinitiated at any time during the study and will be provided as part of rescue or retreatment any time a patient's IGA score becomes ≥3.

b Eligible patients will be re-randomized in the withdrawal and down-titration sub-study. Patients who do not enroll in the sub-study will remain on their treatment.

c Patients enrolled in the sub-study will automatically be retreated if their IGA score becomes ≥3.

d Rescue is available.

Figure 23 ***Design of study JAHN***

Studies JAHG, JAHL, JAHM and JAIY contributed to the placebo-controlled data from baseline to week 16, though not all patients from JAIY had completed the full period. Study JAHN is the long term (104 weeks in total) follow-up of JAHL, JAHM and JAIY.

Unblinded safety data for all patients originating from Studies JAHL and JAHM up to Week 52 in Study JAHN (that is 68 weeks of total treatment duration including the originating studies) were included in this submission. At the time of database lock, not all patients in Study JAHN originating from Study JAIY had been re-randomised based on their responder status at baseline study of JAHN (Figure 24). Since this up-titration phase is a double-blind, randomized period, JAHN data from patients originating from Study JAIY remain blinded and only blinded SAEs were analysed.

At Week 52 in Study JAHN, patients are evaluated for eligibility to enter a randomized, withdrawal, and down-titration sub-study (Figure 23). Study JAHN data beyond Week 52 remain blinded and therefore, only blinded SAE data beyond Week 52 are included in this submission.

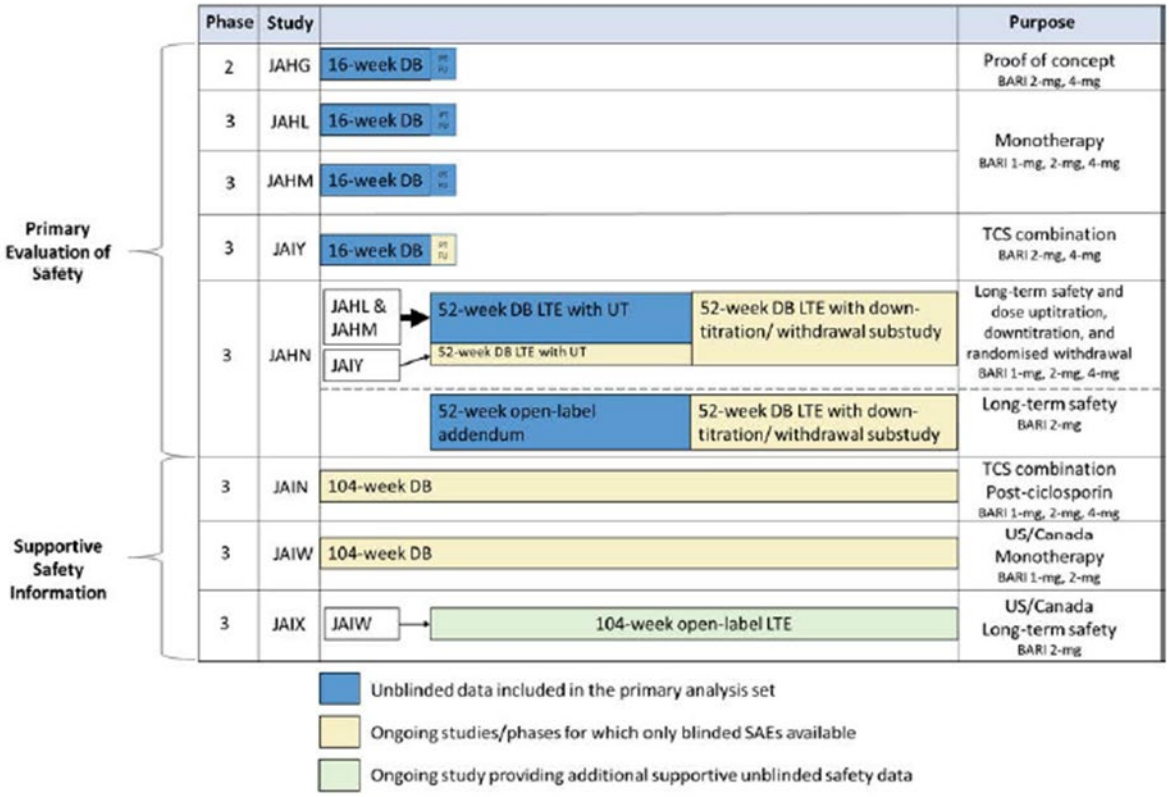


Figure 24 ***Study contributions to the safety data***

For this submission, database lock of study JAIY was at 13 August 2019 and database lock of study JAHN was at 2 July 2019. The other studies were completed and JAHG was locked in 2017, JAHL and JAHM were locked in January 2019.

In the response to the first RSI, an update of the study JAHN was submitted, along with interim data from the ongoing Study JAIN. The data cutoff of JAIN was 28 November 2019 when all patients had completed at least 24 weeks of treatment.

The safety population is defined as all patients who received at least 1 dose of study treatment. The safety data sets of the individual studies were integrated in 'analysis sets' for the evaluation of safety (

Table 33). These sets aim at the short term (16-week) comparison of baricitinib 4 mg and 2 mg with placebo, and the long term (52 weeks + 16 weeks = 68 weeks) comparison of baricitinib 4 mg and 2 mg. In addition, there is an 'all baricitinib' set in which all exposures to baricitinib are integrated, without contrast between doses.

Table 33 ***Integrated short term and long term analysis sets for the evaluation of safety***

Label	**16-Week Placebo Controlled Period**			**Extended Period**	
Analysis Set	**BARI 2-mg AD PC**	**BARI 4-mg AD PC**	**BARI 2-mg AD PC vs 4-mg AD PC**	**Ext BARI 2-mg and 4-mg AD**	**All BARI AD**
Studies included	• JAHG • JAHL • JAHM • JAIY			• JAHG • JAHL/JAHN • JAHM/JAHN • JAIY	
Treatment period	16 weeks			From randomization to 2-mg or 4-mg in JAHG, JAHL, JAHM, and JAIY up to 52 weeks in JAHN	All time periods during treatment with any dose of BARI up to 52 weeks in JAHN
Treatment groups	PBO and BARI 2-mg	PBO and BARI 4-mg	BARI 2-mg and 4-mg	BARI 2-mg and BARI 4-mg Data censored at dose change in JAHN	BARI 1-mg, 2-mg, and 4-mg No censoring of data at dose change
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	Not applicable

Abbreviations: AD = atopic dermatitis; PC = placebo controlled.

In response to the first RSI, 'as-treated' analyses are provided in order to present the occurrence of AEs attributed to dose and treatment regimen at event onset.

These 'as-treated' analysis datasets include descriptive comparisons between:

- PBO and baricitinib 4 mg, PBO and baricitinib 2 mg, and between baricitinib 2 mg and 4 mg during the 16-week PC period (Studies JAHG, JAHL, JAHM, JAIN, and JAIY)
- baricitinib 2 mg and 4 mg during the extended (Ext) period (BARI 2 mg versus 4 mg), and a description of the safety profile for all exposures from all baricitinib doses (1 mg, 2 mg, and 4 mg) within the AD programme (All BARI AD) (Studies JAHG, JAHL/JAHN, JAHM/JAHN, JAIN, and JAIY/JAHN)

The monotherapy studies were not designed to comprehensively evaluate the duration and outcome of TCS rescue events, as the main objective was to evaluate the efficacy and safety of baricitinib as a monotherapy treatment for AD. Once the patients were rescued using TCS, investigators were allowed to continue providing TCS to the rescued patients as needed and per the investigator's recommendation.

The LTE Study JAHN was intended to mimic clinical practice as much as possible by allowing use of concomitant TCS, when needed, per the investigator's assessment. Therefore, treatment arms across the studies could only compare timing of the first rescue, amount of TCS used over the 16-week PC period upon rescue, and frequency of TCS application by the rescued patients.

For the 'as-treated' safety analysis datasets, the following rules were applied to determine if patients were considered 'on monotherapy' or 'on TCS' at the time of the event:

- Patients from the monotherapy Studies JAHL and JAHM that were rescued using TCS due to a lack or loss of response were not censored in these datasets. Patients were considered as 'on monotherapy' up to the point of rescue and were subsequently counted as 'on TCS' for the remainder of the study.
- All patients from the TCS combination Study JAIY were considered as 'on TCS'.
- In the LTE Study JAHN, TCS were allowed any time at the investigator's discretion ('optional use').
    - Patients originating from the Study JAIY were considered as 'on TCS' throughout Study JAHN as they were provided TCS during the originating study.
    - As for the monotherapy studies, patients in Study JAHN originating from Study JAHL/JAHM were counted as 'on TCS' for the remainder of the study from the point of
        - TCS rescue in Studies JAHL and JAHM (unlike in the original 5 integrated analysis datasets, where monotherapy patients were classified as 'monotherapy' even when they were rescued using TCS), and
        - TCS use in Study JAHN if they were not rescued in Studies JAHL and JAHM.

Adverse events were attributed to the dose patients were taking at the time of the onset of the event. Incidence rates (IRs) of AEs were calculated based on patient-years at risk (PYR) including exposure to treatment in the monotherapy and combination therapy, and exposure from the switch or rescue to combination therapy.

In response to the CHMP request to present safety data in which the events are attributed to the dose only, 'as-treated' analyses are provided (Table 34) in which the AEs were attributed to the treatment patients were taking at the time of the onset of the event.

Table 34 ***Integrated 'As-treated' Analysis Sets***

	16-Week Placebo-Controlled Period		Extended Period
Analysis Set/ Name[a]	BARI 4 mg AD PC	BARI 2 mg vs. BARI 4 mg AD PC	Ext BARI 2 mg and BARI 4 mg AD
Treatment groups	PBO, BARI 4 mg	BARI 2 mg, BARI 4 mg	BARI 2 mg, BARI 4 mg
Studies included	JAHG, JAHL, JAHM, JAIN, and JAIY		JAHG, JAHL/JAHN, JAHM/JAHN, JAIN, and JAIY/JAHN
Treatment period	16 weeks		75 weeks from initial randomisation in JAIN; 89 weeks in JAHN LTE.
Purpose[b]	Enables a comparison between dose groups and PBO, during the 16-week PC period as events occur.		The Ext set enables a long-term exposure comparison as events occur between the 2- and 4-mg doses with no censoring of data at dose change in Study JAHN. This includes the same dataset as the BARI 2-mg vs 4-mg AD PC analysis sets, with the addition of data from the long-term extension Study JAHN.

Abbreviations: AD = atopic dermatitis; Ext = extended; LTE = long-term extension; PC = placebo-controlled; vs. = versus.

[a] The 'as-treated' analysis attributes the event to the dose taken at the time of the event.

[b] Patients could also be counted in more than 1 baricitinib dose groups if they were re-randomised or their dose downtitrated to a different dose in Study JAHN.

A total of 2531 patients with AD were exposed to baricitinib at any dose (1 mg, 2 mg, 4 mg) across the entire AD baricitinib development programme (safety population). Overall exposure was 2247.4 patient-years.

For any baricitinib dose

- 1700 patients with AD were exposed for at least 32 weeks, and
- 1106 patients with AD were exposed for at least 52 weeks.

For the 2-mg dose

- 850 patients were treated for at least 32 weeks, and
- 498 patients were treated for at least 52 weeks.

For the 4-mg dose

- 676 patients were treated for at least 32 weeks, and
- 486 patients were treated for at least 52 weeks.

From the patient flow in the integrated safety set (composed of studies JAHG, JAHL, JAHM, and JAIY) it appears that most patients completed the placebo-controlled phase of 16 weeks. On both doses, 2 mg and 4 mg, >100 patients have had >52 weeks of follow-up (Table 35).

Table 35 ***Summary of baricitinib exposure in the AD studies.***

	Updated 16-Week Placebo-Controlled Period JAHG, JAHL, JAHM, JAIY, JAIN			Updated Ext BARI 2 mg and 4 mg AD JAHG, JAHL/JAHN, JAHM/JAHN, JAIY/JAHN, JAIN		Updated All BARI AD[a] JAHG, JAHL/JAHN, JAHM/JAHN, JAIY/JAHN, JAIN, JAIW/JAIX			
Category	**PBO**	**BARI 2 mg**	**BARI 4 mg**	**BARI 2 mg**	**BARI 4 mg**	**BARI 1 mg**	**BARI 2 mg[b]**	**BARI 4 mg**	**All Doses (1, 2, 4 mg)**
Number of patients, N[c]	743	576	489	576	489	538	1580	914	2531
Mean days exposure (SD)	104.1 (26.39)	107.2 (21.29)	109.9 (15.80)	269.8 (169.13)	343.1 (177.67)	167.0 (139.82)	261.1 (162.46)	348.8 (167.56)	324.3 (179.69)
Weeks of Exposure, n (%)									
>0	743 (100)	576 (100)	489 (100)	576 (100)	489 (100)	538 (100)	1580 (100)	914 (100)	2531 (100)
≥16	518 (69.7)	436 (75.7)	378 (77.3)	493 (85.6)	450 (92.0)	390 (72.5)	1286 (81.4)	840 (91.9)	2241 (88.5)
≥32	NA	NA	NA	326 (56.6)	362 (74.0)	114 (21.2)	850 (53.8)	676 (74.0)	1700 (67.2)
≥52[d]	NA	NA	NA	195 (33.9)	215 (44.0)	82 (15.2)	498 (31.5)	486 (53.2)	1106 (43.7)
≥68	NA	NA	NA	93 (16.1)	148 (30.3)	29 (5.4)	202 (12.8)	253 (27.7)	644 (25.4)
Total patient-years	211.8	169.1	147.1	425.5	459.3	245.9	1129.5	872.8	2247.4

Abbreviations: AD = atopic dermatitis; Ext = extended; N = number of patients in the safety analysis set; n = number of patients in the specified category; NA = not applicable.

[a] The Updated All BARI AD by dose group includes all patients who took at least 1 of the doses at randomisation, dose change, rescue, or re-randomisation.

[b] Includes data for patients treated in the open-label addendum to Study JAHN.

[c] The N is based on the number of patients randomised (or enrolled, for the open-label study) to the first dose in the AD programme.

[d] According to the Week 52 minimum protocol window of 4 days = 360 days.

At the CHMP's request, the MAH provided "Exposure by Treatment Groups". The Table 36 provides the exposure for patients based on dose. Please note that these data are based on the 'as-treated' analysis.

Table 36 ***Summary of Study Drug Exposure***

	16-Week Placebo-Controlled Analysis Set			Ext 2-mg and 4-mg 'as-treated' Analysis Set	
	PBO	**2 mg**	**4 mg**	**2 mg**	**4 mg**
Number of patients, N	743	576	489	606	588
Mean days exposure (SD)	104.1 (26.39)	107.2 (21.29)	109.9 (15.80)	262.8 (171.59)	343.9 (176.19)
Weeks of Exposure, n (%)					
>0	743 (100)	576 (100)	489 (100)	606 (100)	588 (100)
≥16	518 (69.7)	436 (75.7)	378 (77.3)	501 (82.7)	540 (91.8)
≥32	--	--	--	328 (54.1)	428 (72.8)
≥52[a]	--	--	--	195 (32.2)	274 (46.6)
Total patient-years	211.8	169.1	147.1	436.0	553.6

Abbreviations: Ext = extended; N= number of patients in the safety analysis set; n= number of patients in the specified category; SD = standard deviation.

[a] According to the Week 52 minimum protocol window of 4 days = 360 days.

Baseline data

Initially submitted database

The baseline data of the integrated safety set are reflecting the baseline characteristics of the originating studies (JAHG, JAHL, JAHM and JAIY). Overall, baseline demographic characteristics were similar for the placebo and baricitinib 2 mg and 4 mg groups (Table 37). The patients were on average 35 years old and more than half of the patients were males. Nearly half of the patients were included in European centres.

Disease duration in all three groups was ~25 years and 70% had experiences disease flares in the past year. Previous treatments were similar between the groups. About 15% had pharmacological treatment for skin infections last year, nearly all (95%) patients have had topical therapy before, usually TCS (~89%) but also TCI (54% - 60%) and oral ciclosporin (31% - 36%) had been used.

Table 37 ***Baseline demographic characteristics***

	16-Week Placebo-Controlled Period			All BARI AD
Attribute	PBO (N = 650)	BARI 2-mg (N = 392)	BARI 4-mg (N = 397)	All Doses (1-mg, 2-mg, 4-mg) (N = 1646)
Age (years), mean (SD)	35.2 (12.9)	35.3 (13.4)	35.1 (13.1)	35.3 (12.9)
Age group, n (%)				
<65	630 (96.9)	378 (96.4)	386 (97.2)	1601 (97.3)
65 to <75	18 (2.8)	11 (2.8)	10 (2.5)	40 (2.4)
75 to <85	2 (0.3)	3 (0.8)	1 (0.3)	5 (0.3)
≥85	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Female, n (%)	254 (39.1)	153 (39.0)	135 (34.0)	624 (37.9)
Male, n (%)	396 (60.9)	239 (61.0)	262 (66.0)	1022 (62.1)
Race				
Caucasian, n (%)	385 (59.4)	230 (58.7)	224 (56.6)	1053 (64.1)
Asian, n (%)	217 (33.5)	137 (34.9)	142 (35.9)	481 (29.3)
Other, n (%)	46 (7.1)	25 (6.4)	30 (7.6)	110 (6.7)
Weight (kg), mean (SD)	73.0 (16.8)	74.1 (17.3)	74.1 (17.0)	73.7 (16.6)
Body mass index, mean (SD)	25.3 (5.1)	25.7 (5.5)	25.4 (5.0)	25.3 (4.9)
Geographic region				
Europe, n (%)	295 (45.4)	165 (42.1)	171 (43.1)	801 (48.7)
Japan, n (%)	119 (18.3)	69 (17.6)	73 (18.4)	263 (16.0)
Asia (excluding Japan), n (%)	99 (15.2)	62 (15.8)	66 (16.6)	212 (12.9)
Central/South America and Mexico, n (%)	68 (10.5)	36 (9.2)	32 (8.1)	199 (12.1)
Rest of the World, n (%)	69 (10.6)	60 (15.3)	55 (13.9)	171 (10.4)

Abbreviations: AD = atopic dermatitis; N = number of patients in the safety analysis set; n = number of patients in specified category; PC = placebo controlled.

Source tables are provided in the Appendix to the Summary of Clinical Safety: Table SCS APP 2.7.4.7.6. for the **BARI 2-mg AD PC** analysis set; Table SCS APP 2.7.4.7. for the **BARI 4-mg AD PC** analysis set; Table SCS APP 2.7.4.7.8. for the **All BARI AD** analysis set.

Patient disposition

Initially submitted database

For the integrated safety analysis sets, patient disposition was analysed for permanent discontinuation of study drug and discontinuation from study. Patients who discontinued study drug were encouraged to

remain in the study through the primary time point for safety monitoring purposes. A patient may have discontinued study drug but completed the planned study period.

In the 16-week placebo-controlled period, more than 90% of patients completed the study (Table 38). Discontinuations occurred most in the placebo group and least in the baricitinib 4 mg group. In the placebo group, most patients discontinued because of lack of efficacy/withdrawal by patient, which also were the most mentioned reasons for withdrawal in the 2 mg group. In the baricitinib 4 mg group, adverse events was the most occurring reason for withdrawal.

In the extended treatment data set, the most occurring reason for withdrawal with 2 mg and 4 mg was lack of efficacy, while adverse events occurred more often in 4 mg and withdrawal by patient occurred more often with 2 mg (Table 39). By design, dose switches were only found in the 2 mg group.

Table 38 ***Patient disposition in the placebo-controlled period.***

	16-Week Placebo-Controlled Period					
Category	**PBO (N=650) n (adj %)**	**BARI 2-mg (N=392) n (adj %)**	**BARI 4-mg (N=397) n (adj %)**	**BARI 2-mg vs. PBO OR (95% CI)**	**BARI 4-mg vs. PBO OR (95% CI)**	**BARI 4-mg vs. BARI 2-mg OR (95% CI)**
Completed study through Week 16	586 (90.3)	360 (92.0)	375 (94.8)	1.3 (0.8, 2.0)	2.1 (1.2, 3.5)	1.5 (0.9, 2.8)
Discontinued study prior to Week 16 due to any reason	64 (9.7)	32 (8.0)	22 (5.2)	0.8 (0.5, 1.2)	0.5 (0.3, 0.8)	0.6 (0.4, 1.1)
Reason for discontinuation from study drug						
Adverse Event	8 (1.2)	3 (0.9)	10 (2.2)	0.6	1.9 (0.7, 4.9)	3.3 (0.9, 12.1)
Lack of efficacy	30 (4.5)	14 (3.5)	5 (1.5)	0.8 (0.4, 1.5)	0.3 (0.1, 0.7)	0.3 (0.1, 1.0)
Lost to follow-up	2 (0.3)	1 (0.3)	2 (0.5)	0.8	1.4	2.0
Physician decision	2 (0.3)	1 (0.2)	0 (0.0)	0.7	0	0
Protocol deviation	2 (0.3)	1 (0.2)	1 (0.2)	0.7	0.7	1.0
Withdrawal by patient	20 (3.1)	11 (2.7)	4 (0.9)	0.9 (0.4, 1.9)	0.3 (0.1, 0.9)	0.3 (0.1, 1.1)
Other	0 (0.0)	1 (0.2)	0 (0.0)	NA	NA	0

Abbreviations: AD = atopic dermatitis; adj % = study-size adjusted percentage; N = number of patients in the safety analysis set; n = number of patients in specified category; NA = not applicable; OR = odds ratio.

Note: 95% CI calculated if ≥4 events in numerator and ≥1 in denominator.

Source tables are provided in the Appendix to the Summary of Clinical Safety: Table SCS APP 2.7.4.7.9. for the **BARI 2-mg AD PC** analysis set; Table SCS APP 2.7.4.7.10. for the **BARI 4-mg AD PC** and **BARI 2-mg AD PC** vs **4-mg AD PC** analysis sets.

Table 39 ***Patient disposition in the extended period.***

	Ext BARI 2-mg and 4-mg AD			All BARI AD
Category	**BARI 2-mg (N = 392) n (adj %)**	**BARI 4-mg (N = 397) n (adj %)**	**BARI 4-mg vs. BARI 2-mg OR (95% CI)**	**All Doses (1-mg, 2-mg, 4-mg) (N = 1646) n (%)**
Ongoing on baricitinib	198 (47.7)	266 (66.3)	2.5 (1.8, 3.5)	1174 (71.3)
Switched baricitinib dose	60 (17.9)	0 (0.0)	0	NA
Permanently discontinued from study drug	134 (34.4)	131 (33.7)	0.9 (0.7, 1.3)	472 (28.7)
Reason for discontinuation from study drug				
Adverse Event	7 (2.0)	21 (5.2)	3.1 (1.3, 7.4)	56 (3.4)
Death	0 (0.0)	0 (0.0)	NA	1 (0.1)
Lack of efficacy	47 (13.3)	49 (14.5)	1.0 (0.7, 1.6)	216 (13.1)
Lost to follow-up	3 (0.9)	2 (0.5)	0.7	6 (0.4)
Physician decision	1 (0.2)	2 (0.6)	2.0	3 (0.2)
Protocol deviation	1 (0.2)	1 (0.2)	1.0	5 (0.3)
Withdrawal by patient	27 (7.5)	12 (3.2)	0.4 (0.2, 0.8)	74 (4.5)
Other	1 (0.2)	0 (0.0)	0	1 (0.1)

Abbreviations: AD = atopic dermatitis; adj % = study-size adjusted percentage; N = number of patients in the safety analysis set; n = number of patients in specified category; NA = not applicable; OR = odds ratio; .

Note: 95% CI calculated if ≥4 events in numerator and ≥1 in denominator.

Source tables are provided in the Appendix to the Summary of Clinical Safety: Table SCS APP 2.7.4.7.11. for the **Ext BARI 2-mg and 4-mg AD** and **All BARI AD** analysis sets.

Adverse events

Overview of Adverse Events

In the placebo-controlled period, treatment emergent AEs occurred more frequently in the baricitinib 2 mg (57%) and 4 mg (58%) groups, as compared to the placebo (52%) group . In all treatment groups, the AEs usually were mild and moderate and seldom severe. SAEs did occur in 2.9% of the placebo group and with 1.6% and 1.8% in the 2 mg and 4 mg groups. Relatively more patients on baricitinib than on placebo discontinued due to AEs, mostly in the 4 mg group.

In the initially submitted, extended phase safety data set, the occurrence of AEs was increased and was larger for the baricitinib 4 mg group (72%) as compared to the 2 mg group (64%). It appeared that the number of SAEs remained at 7 in the baricitinib 2 mg group and became 25 (6.8%) in the 4 mg group. The number of severe and of moderate AEs also was slightly higher in the baricitinib 4 mg group as compared to 2 mg. Discontinuations of study drug or the study occurred more frequently while on baricitinib 4 mg. One death occurred while on baricitinib.

In study JAHN, there was a numerically higher incidence rate (IR) of TEAEs reported in the baricitinib 2-mg and 4-mg groups compared with placebo group from Week 0 to Week 52, but there was no dose relationship seen between 2-mg (143.3) and 4-mg (144.7), With regard to SAEs, no clinically meaningful difference in the IR of SAEs was observed across the treatment groups, with the highest IR reported in the placebo group.

The IR of permanent discontinuations due to study drug was 3.3 for the baricitinib 2-mg group, 4.2 for the 4-mg treatment group, and no patients permanently discontinued due to an AE in the 1-mg or placebo group.

One death occurred during the study in the baricitinib 4-mg treatment group

In the updated 'as treated' safety data IRs for TEAEs were consistently higher for monotherapy compared to TCS combination use regardless of dose group or dataset, except for the baricitinib 4-mg TCS group (346.8) compared to monotherapy (332.7) in the PC period. TEAEs were generally mild to moderate in severity, and severe TEAEs had similar IRs among treatment regimens.

IRs for discontinuations due to AEs were consistently higher for TCS versus monotherapy regardless of dose group or dataset, the highest IR was for 4 mg TCS (10.9) compared to monotherapy (2.0) in the PC period.

Serious adverse event (SAE) IRs appear to be consistently higher for TCS combination therapy versus monotherapy; In the PC period, TCS (6.9) had a higher IR than monotherapy (2.3) in the 2-mg group; and TCS (12.0) IR was higher than monotherapy (3.9) in the 4-mg group. In the extended period, IRs were higher in TCS than in monotherapy for both doses: (4.2 versus 2.2 for 2 mg; 8.0 versus 6.6 for 4 mg) and in the All BARI AD group, TCS (6.7) had a higher IR than monotherapy (4.2). Numerical differences in SAE IRs between doses were observed. Overall, the SAE IRs were higher at 4 mg compared to 2 mg but were lower than PBO in all groups except the baricitinib 4-mg TCS group. The highest IR was noted in the baricitinib 4-mg TCS group within the PC period.

Table 40 ***Overview of Adverse Events***

	16- Week Placebo-Controlled Analysis Set						Ext 2-mg and 4-mg Analysis Set				All BARI AD IR (PYR)	
	PBO IR (PYR)		2 mg IR (PYR)		4 mg IR (PYR)		2 mg IR (PYR)		4 mg IR (PYR)			
	Mono	TCS	Mono	TCS	Mono	TCS	Mono	TCS	Mono	TCS	Mono	TCS
Death IR (PYR)	0.0 (62.1)	0.0 (158.6)	0.0 (42.9)	0.0 (131.8)	0.0 (50.9)	0.0 (101.1)	0.0 (91.9)	0.0 (361.9)	0.0 (122.7)	0.0 (437.2)	0.0 (408.5)	0.1 (1615.4)
SAE IR (PYR)	9.7 (61.7)	9.6 (156.5)	2.3 (42.8)	6.9 (131.2)	3.9 (50.8)	12.0 (99.6)	2.2 (91.4)	4.2 (359.0)	6.6 (121.4)	8.0 (426.7)	4.2 (405.4)	6.7 (1581.9)
TEAE[a] IR (PYR)	347.8 (45.1)	260.5 (106.7)	386.1 (27.2)	329.6 (79.5)	332.7 (32.2)	346.8 (59.7)	273.8 (43.1)	214.1 (158.3)	237.6 (56.0)	200.1 (185.9)	215.2 (203.1)	177.5 (717.6)
Mild	190.1 (52.6)	122.8 (129.4)	221.1 (32.1)	141.4 (103.2)	186.3 (37.6)	140.4 (79.8)	97.3 (69.9)	61.2 (268.2)	83.5 (89.8)	55.8 (315.3)	84.7 (305.9)	49.9 (1201.7)
Moderate	86.2 (55.7)	74.6 (140.8)	79.0 (39.2)	86.1 (115.0)	67.4 (47.5)	96.9 (87.7)	57.3 (75.0)	53.1 (280.7)	48.4 (101.3)	47.7 (346.1)	44.2 (341.5)	44.3 (1268.2)
Severe	14.6 (61.5)	9.0 (156.2)	7.1 (42.5)	13.1 (129.5)	10.0 (50.2)	10.0 (99.8)	7.8 (89.5)	7.4 (352.6)	7.5 (119.9)	7.3 (426.5)	6.8 (399.1)	7.1 (1574.5)
Permanent Discontinuation from Study Drug because of AE or Death IR (PYR)	4.8 (61.9)	6.3 (158.0)	2.3 (42.8)	6.9 (131.0)	3.9 (50.8)	13.0 (100.3)	2.2 (91.7)	4.4 (359.9)	3.3 (122.5)	5.3 (435.6)	3.7 (407.5)	4.5 (1607.7)
Discontinuation from Study because of AE or Death IR (PYR)	1.6 (62.0)	4.4 (158.2)	2.3 (42.8)	6.9 (131.1)	2.0 (50.9)	10.9 (100.5)	2.2 (91.7)	4.4 (360.0)	3.3 (122.5)	5.3 (435.6)	3.7 (407.6)	4.0 (1608.5)

Abbreviations: AD = atopic dermatitis; Ext = extended; IR = incidence rate; Mono = monotherapy; PYR = patient years at risk; TCS = topical corticosteroids.
Note: Interpretation of the results in this table is challenging and has similar limitations to observational data. Using this table to assess a potential dose relationship is problematic due to study and treatment being confounded and risk over time changes due to reasons other than treatment exposure to dose.
[a] Patients with multiple occurrences of the same event are counted under the highest severity.

At the CHMP's request, the MAH provided an overview of AEs based on the 'as treated' analysis. There are no clinically relevant differences in the overview of AEs between the 'as-treated' analysis described in this response (Table 41) and the 'as-randomised' analyses by dose described in the original submission (Table 40). The 'as-treated' analysis showed a smaller magnitude of difference among the IR of SAEs, permanent discontinuations, and temporary interruptions by dose compared to the original submission. A larger difference in IR between doses was noted for TEAEs with a higher IR of TEAEs for 2-mg treated patients compared to 4 mg in the 'as-treated' analysis compared to the 'as-randomised' analysis.

Table 41 *Updated Incidence Rate Overview of Adverse Events*

	16-Week Placebo-Controlled 'as-randomised' Analysis Set[a]			Ext 2-mg and 4-mg 'as-treated' Analysis Set	
	PBO adj % (adj IR) [PYR]	2 mg adj % (adj IR) [PYR]	4 mg adj % (adj IR) [PYR]	2 mg (IR) [PYR]	4 mg (IR) [PYR]
Death	0 [220.7]	0 [174.7]	0 [152.1]	0 [453.7]	0 [570.5]
SAE	2.3 (8.0) [218.0]	1.4 (4.4) [173.9]	2.3 (7.7) [150.3]	(3.8) [449.9]	(7.7) [557.5]
TEAE[b]	43.2 (234.7) [140.1]	49.3 (281.4) [101.4]	51.0 (300.1) [87.4]	(235.4) [174.6]	(208.5) [213.4]

	16-Week Placebo-Controlled 'as-randomised' Analysis Set[a]			Ext 2-mg and 4-mg 'as-treated' Analysis Set	
	PBO adj % (adj IR) [PYR]	**2 mg adj % (adj IR) [PYR]**	**4 mg adj % (adj IR) [PYR]**	**2 mg (IR) [PYR]**	**4 mg (IR) [PYR]**
Mild	25.3 (111.5) [175.2]	29.1 (128.4) [132.8]	29.7 (128.8) [115.2]	(60.5) [330.6]	(50.0) [409.8]
Moderate	15.3 (59.3) [193.1]	17.4 (66.1) [152.3]	18.8 (70.5) [133.3]	(51.8) [343.8]	(45.0) [439.9]
Severe	2.7 (9.4) [216.9]	2.8 (9.4) [171.8]	2.4 (8.1) [149.7]	(7.5) [439.9]	(7.6) [555.8]
Permanent Discontinuation from Study Drug because of an AE or Death	1.4 (4.6) [219.9]	1.5 (4.7) [173.9]	2.1 (6.5) [151.0]	(4.0) [451.6]	(4.7) [568.6]
Discontinuation from Study because of an AE or Death	0.9 (2.8) [220.2]	1.4 (4.4) [174.0]	1.7 (5.1) [151.3]	(4.0) [451.7]	(4.9) [568.4]

Abbreviations: adj = adjusted; AE = adverse event; Ext = extended; IR = incidence rate; PBO = placebo; PYR = patient-years at risk; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Data from the 16-week placebo-controlled period are 'as-randomised' and from the updated data analysis set.

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

Adverse events by System Organ Class

In the placebo-controlled period, AEs did occur most frequently in the SOCs for Infections and Infestations, Skin and subcutaneous disorders, Investigations, Gastrointestinal disorders, and Nervous system disorders (Table below). Infections and infestations were more common in the baricitinib 2 mg (34%) and 4 mg (34%) groups as compared to the placebo group (29%). AEs concerning Investigations occurred about equally in the placebo (3.1%) and baricitinib 2 mg (3.1%) groups and more often in the 4 mg group (8.6%). Nervous system disorders appeared to occur more often in the baricitinib 2 mg (9.2%) and 4 mg (7.9%) groups as compared to placebo (5.6%). Skin and subcutaneous disorders and Gastrointestinal disorders occurred about equally in all three treatment groups (Table 42).

Table 42 ***Adverse Events by SOC in the placebo-controlled period***

System Organ Class	16-Week Placebo-Controlled Period					
	PBO (N = 650) n (adj %)	BARI 2-mg (N = 392) n (adj %)	BARI 4-mg (N = 397) n (adj %)	BARI 2-mg vs. PBO OR (95% CI)	BARI 4-mg vs. PBO OR (95% CI)	BARI 4-mg vs. BARI 2-mg OR (95% CI)
Infections and infestations	187 (28.6)	135 (34.3)	135 (34.0)	1.3 (1.0, 1.7)	1.3 (1.0, 1.7)	1.0 (0.7, 1.3)
Skin and subcutaneous tissue disorders	59 (8.9)	27 (6.9)	41 (9.9)	0.8 (0.5, 1.2)	1.1 (0.7, 1.7)	1.6 (0.9, 2.6)
Investigations	20 (3.1)	13 (3.1)	33 (8.6)	1.0 (0.5, 2.1)	3.0 (1.7, 5.3)	2.6 (1.4, 5.1)
Gastrointestinal disorders	54 (8.2)	36 (9.5)	33 (8.4)	1.2 (0.8, 1.9)	1.1 (0.7, 1.7)	0.9 (0.5, 1.5)
Nervous system disorders	37 (5.6)	33 (9.2)	30 (7.9)	1.7 (1.1, 2.8)	1.5 (0.9, 2.5)	0.9 (0.5, 1.5)
Respiratory, thoracic and mediastinal disorders	31 (4.9)	21 (5.2)	17 (4.0)	1.1 (0.6, 1.9)	0.8 (0.4, 1.5)	0.8 (0.4, 1.5)
General disorders and administration site conditions	35 (5.4)	16 (4.3)	15 (3.7)	0.8 (0.4, 1.4)	0.7 (0.4, 1.3)	0.9 (0.5, 1.9)
Musculoskeletal and connective tissue disorders	22 (3.4)	9 (2.3)	15 (3.5)	0.7 (0.3, 1.5)	1.1 (0.5, 2.1)	1.7 (0.7, 3.9)
Injury, poisoning and procedural complications	28 (4.4)	14 (3.2)	13 (2.9)	0.7 (0.4, 1.4)	0.7 (0.3, 1.4)	0.9 (0.4, 2.0)
Psychiatric disorders	16 (2.4)	7 (1.8)	9 (2.3)	0.8 (0.3, 2.0)	1.0 (0.4, 2.4)	1.3 (0.5, 3.5)
Blood and lymphatic system disorders	12 (1.8)	6 (1.4)	9 (2.2)	0.8 (0.3, 2.3)	1.3 (0.5, 3.1)	1.5 (0.5, 4.3)
Renal and urinary disorders	1 (0.1)	1 (0.2)	7 (2.0)	1.3	10.7 (1.4, 79.4)	7.0 (0.9, 57.8)
Eye disorders	11 (1.8)	7 (1.7)	8 (1.9)	1.0 (0.4, 2.5)	1.1 (0.4, 2.7)	1.1 (0.4, 3.1)
Metabolism and nutrition disorders	11 (1.7)	8 (2.2)	6 (1.7)	1.3 (0.5, 3.4)	1.0 (0.4, 2.7)	0.7 (0.3, 2.1)
Vascular disorders	8 (1.2)	6 (1.7)	5 (1.4)	1.4 (0.5, 4.3)	1.2 (0.4, 3.7)	0.8 (0.2, 2.7)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	5 (0.8)	4 (1.1)	4 (0.9)	1.3 (0.4, 4.8)	1.2 (0.3, 4.6)	1.0 (0.2, 4.0)
Surgical and medical procedures	11 (1.6)	6 (1.7)	3 (0.6)	1.0 (0.4, 2.9)	0.4	0.5
Ear and labyrinth disorders	11 (1.7)	3 (0.8)	2 (0.6)	0.4	0.3	0.7
Cardiac disorders	0	0	2 (0.5)	NA	NA	NA
Reproductive system and breast disorders	6 (0.9)	2 (0.6)	2 (0.5)	0.6	0.5	1.0
Immune system disorders	3 (0.4)	2 (0.4)	0	1.1	0.0	0.0
Hepatobiliary disorders	2 (0.3)	2 (0.5)	0	1.7	0.0	0.0
Congenital, familial and genetic disorders	1 (0.1)	0	0	0.0	0.0	NA

Abbreviations: AD = atopic dermatitis; adj % = study-size adjusted percentage; N = number of patients in the safety analysis set; n = number of patients in specified category; OR = odds ratio; PC = placebo-controlled.
Notes: 95% CI calculated if ≥4 events in numerator and ≥1 in denominator
Source tables are provided in the Appendix to the Summary of Clinical Safety: Table SCS APP 2.7.4.7.41. for the **BARI 2-mg AD PC** analysis set; Table SCS APP 2.7.4.7.42. for the **BARI 4-mg AD PC** and **BARI 2-mg AD PC** vs **4-mg AD PC** analysis sets.

In the initial data of the extended safety data set in AD, most AEs occurred in the SOC for Infections and Infestations and slightly more frequently in the baricitinib 4 mg group (50%) as compared to the 2 mg group (46%). Skin and subcutaneous tissue disorders also were slightly more frequent in the 4 mg group (16%) versus the 2 mg group (11%). AEs concerning Investigations occurred more frequently in the baricitinib 4 mg group (13%) as compared to the 2 mg group (3.7%). Over the SOCs with less frequently occurring AEs, higher percentages were noted for baricitinib 4 mg as compared to 2 mg for: General Disorders and administration site conditions; Eye disorders; Metabolism and nutrition disorders; Psychiatric disorders; Blood and lymphatic system disorders; Vascular disorders; Neoplasms; Renal and urinary disorders; Cardiac disorders.

In the updated safety data set, similar to the original analyses, the most frequently reported AEs in the 'as-treated' safety analysis set were in the 'Infections and infestations' SOC. There were no clinically relevant differences between monotherapy and TCS for baricitinib. No consistent pattern was observed, suggesting that 1 treatment (monotherapy or TCS) has a higher IR of infectious TEAEs than the other.

Use of TCS can potentially place patients at an increased risk of skin infections, both viral and bacterial, but no clinically relevant differences were noted in skin-related infections between TCS and monotherapy regimens. Most of the reported skin infections were classified as nonserious.

In addition to skin infections, use of TCS is associated also with an increased risk of cutaneous adverse effects. Overall, there were no relevant differences between monotherapy and TCS, and dose groups for AEs related to the skin.

There were 4 SOCs that had higher IRs for TCS compared to monotherapy (Musculoskeletal and connective tissue disorders, Psychiatric disorders, Eye disorders, Neoplasms benign, malignant and unspecified), and 5 SOCs where monotherapy had higher IRs than TCS (Metabolism and nutrition disorders, Vascular disorders, Gastrointestinal disorders, Nervous system disorders, and General disorders).

Table 43 ***Adverse Events by SOC in the extended period***

	16-Week Placebo-Controlled Analysis Set						Ext 2-mg and 4-mg Analysis Set				All BARI AD	
	PBO		2 mg		4 mg		2 mg		4 mg			
	Mono IR (PYR)	TCS IR (PYR)	Mono IR (PYR)	TCS IR (PYR)	Mono IR (PYR)	TCS IR (PYR)	Mono IR (PYR)	TCS IR (PYR)	Mono IR (PYR)	TCS IR (PYR)	Mono IR (PYR)	TCS IR (PYR)
Infections and infestations IR (PYR)	121.3 (54.4)	116.9 (133.4)	161.7 (35.3)	152.3 (103.7)	142.9 (41.3)	162.6 (79.3)	130.1 (60.7)	103.7 (227.5)	100.1 (82.9)	102.6 (264.1)	94.7 (283.1)	94.8 (991.7)
Gastrointestinal disorders IR (PYR)	43.5 (59.8)	26.5 (150.9)	52.5 (40.0)	31.5 (124.0)	35.4 (48.0)	38.4 (93.7)	30.9 (81.0)	17.1 (332.4)	18.7 (112.6)	16.2 (394.5)	21.6 (370.5)	14.4 (1481.0)
Nervous system disorders IR (PYR)	26.8 (59.8)	19.0 (152.9)	61.8 (38.8)	26.2 (125.9)	35.6 (47.8)	21.6 (97.0)	33.3 (81.1)	13.0 (337.3)	18.6 (113.2)	9.9 (414.6)	17.6 (380.2)	10.0 (1521.3)
Investigations IR (PYR)	8.1 (61.6)	14.8 (155.0)	4.7 (42.7)	18.5 (129.5)	32.9 (48.6)	23.7 (97.2)	3.3 (90.7)	8.9 (347.7)	18.4 (108.9)	11.1 (415.5)	8.2 (388.4)	9.0 (1544.6)
Skin and subcutaneous tissue disorders IR (PYR)	39.6 (60.7)	27.7 (151.4)	23.7 (42.3)	32.0 (125.0)	31.0 (48.3)	39.8 (95.4)	21.4 (84.2)	17.5 (330.5)	25.2 (107.3)	21.5 (395.0)	18.9 (376.5)	17.6 (1462.7)
General disorders IR (PYR)	29.8 (60.5)	14.9 (154.3)	24.0 (41.6)	14.8 (128.6)	18.2 (49.5)	18.5 (97.4)	12.6 (87.2)	9.2 (347.5)	12.0 (116.9)	9.4 (414.0)	9.4 (394.5)	8.2 (1544.0)
Respiratory, thoracic and mediastinal disorders IR (PYR)	9.7 (61.9)	18.9 (153.2)	24.2 (41.3)	21.2 (127.2)	14.1 (49.8)	15.2 (98.6)	13.8 (86.7)	13.0 (339.5)	12.9 (116.0)	9.9 (414.2)	12.5 (391.3)	9.2 (1528.9)
Musculoskeletal and connective tissue disorders IR (PYR)	8.1 (61.5)	14.9 (154.5)	4.7 (42.8)	21.3 (126.5)	10.0 (49.8)	19.4 (98.1)	6.8 (88.3)	12.8 (334.8)	5.0 (120.0)	10.7 (409.7)	6.4 (392.8)	11.5 (1498.7)
Injury, poisoning and procedural complications IR (PYR)	13.1 (61.0)	13.6 (154.9)	11.8 (42.3)	13.2 (128.5)	10.0 (50.2)	14.3 (98.1)	8.0 (87.7)	7.2 (347.7)	5.8 (119.8)	7.6 (422.1)	6.4 (393.7)	7.4 (1550.2)
Renal and urinary disorders IR (PYR)	0.0 (62.1)	1.9 (158.1)	0.0 (42.9)	1.5 (131.6)	10.0 (49.9)	4.0 (100.3)	3.3 (90.4)	1.7 (358.8)	4.1 (120.8)	1.6 (431.7)	2.5 (404.3)	1.6 (1599.5)

Blood and lymphatic system disorders IR (PYR)	9.8 (61.0)	4.4 (157.4)	0.0 (42.9)	6.1 (130.9)	7.9 (50.5)	8.0 (99.9)	1.1 (91.6)	3.4 (357.1)	5.0 (120.0)	3.5 (430.9)	2.0 (404.7)	2.8 (1594.1)
Metabolism and nutrition disorders IR (PYR)	11.5 (61.1)	5.1 (157.5)	11.9 (41.9)	7.7 (130.2)	7.9 (50.6)	5.0 (100.6)	5.8 (86.9)	3.7 (353.6)	8.5 (118.2)	4.2 (425.4)	6.1 (393.8)	3.6 (1578.0)
Vascular disorders IR (PYR)	4.9 (61.8)	3.8 (157.6)	7.1 (42.3)	5.4 (130.4)	7.9 (50.5)	4.0 (100.5)	6.8 (88.4)	3.9 (355.8)	4.1 (120.6)	4.2 (427.9)	3.7 (400.9)	3.2 (1587.3)
Psychiatric disorders IR (PYR)	19.8 (60.7)	5.1 (157.2)	4.7 (42.8)	10.0 (129.5)	5.9 (50.4)	8.0 (100.3)	3.3 (91.5)	6.0 (351.8)	4.2 (119.4)	5.2 (426.6)	4.0 (402.4)	4.6 (1577.1)
Cardiac disorders IR (PYR)	0.0 (62.1)	0.6 (158.5)	0.0 (42.9)	2.3 (131.2)	2.0 (50.7)	2.0 (100.8)	0.0 (91.9)	2.0 (358.4)	0.8 (122.5)	0.7 (436.5)	0.5 (408.2)	1.0 (1609.0)
Ear and labyrinth disorders IR (PYR)	3.2 (61.6)	7.0 (157.0)	2.3 (42.9)	2.3 (131.4)	2.0 (50.6)	1.0 (101.0)	2.2 (91.5)	1.4 (358.9)	2.5 (121.2)	1.4 (434.1)	1.5 (405.4)	1.7 (1600.4)
Eye disorders IR (PYR)	8.1 (61.8)	8.3 (156.6)	4.7 (42.9)	7.7 (129.7)	2.0 (50.8)	14.2 (98.6)	2.2 (91.5)	6.0 (352.9)	4.2 (120.2)	7.7 (417.5)	3.7 (402.3)	5.6 (1563.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) IR (PYR)	1.6 (62.0)	3.2 (158.1)	2.3 (42.8)	3.8 (131.0)	2.0 (50.9)	4.0 (100.3)	1.1 (91.7)	2.2 (355.6)	1.6 (122.1)	2.6 (427.8)	1.7 (406.9)	2.3 (1587.7)
Reproductive system and breast disorders IR (PYR)	1.6 (61.9)	3.2 (157.8)	2.3 (42.7)	2.3 (131.1)	2.0 (50.7)	1.0 (100.9)	1.1 (91.6)	2.3 (355.5)	1.6 (121.6)	0.9 (434.9)	0.7 (407.0)	1.6 (1594.9)
Surgical and medical procedures IR (PYR)	6.5 (61.4)	6.4 (156.6)	4.7 (42.7)	5.4 (130.6)	2.0 (50.7)	4.0 (100.9)	3.3 (90.7)	5.7 (351.0)	2.5 (121.5)	3.5 (429.8)	2.5 (405.2)	4.1 (1581.6)
Congenital, familial and genetic disorders IR (PYR)	1.6 (62.0)	0.0 (158.6)	0.0 (42.9)	0.0 (131.8)	0.0 (50.9)	0.0 (101.1)	0.0 (91.9)	0.3 (361.2)	0.0 (122.7)	0.0 (437.2)	0.0 (408.5)	0.1 (1614.7)
Hepatobiliary disorders IR (PYR)	1.6 (61.9)	0.6 (158.6)	2.3 (42.7)	0.8 (131.5)	0.0 (50.9)	1.0 (100.9)	1.1 (91.7)	0.8 (361.0)	0.0 (122.7)	1.6 (432.9)	1.2 (406.2)	0.8 (1608.5)
Immune system disorders IR (PYR)	1.6 (61.8)	1.3 (158.5)	0.0 (42.9)	3.1 (131.1)	0.0 (50.9)	1.0 (100.8)	0.0 (91.9)	2.0 (358.4)	0.8 (122.4)	1.2 (434.6)	0.5 (407.4)	1.4 (1603.8)

Abbreviations: AD = atopic dermatitis; CPK = creatine phosphokinase; Ext = extended; IR = incidence rate; Mono = monotherapy; PYR = patient years at risk; TCS = topical corticosteroids; URTI = upper respiratory tract infection; UTI = urinary tract infection.

Note: Interpretation of the results in this table is challenging and has similar limitations to observational data. Using this table to assess a potential dose relationship is problematic due to study and treatment being confounded and risk over time changes due to reasons other than treatment exposure to dose.

Common Adverse Events

In the initial data base, in the placebo-controlled period, headache, increased blood creatine phosphokinase (CPK), upper respiratory tract infection, oral herpes and herpes simplex, upper abdominal pain, did occur more frequently in the baricitinib treated patients as compared to placebo treated patients (Table 44).

In the extended safety data, upper respiratory tract infection and bronchitis, oral herpes and herpes simplex, diarrhoea, increased blood CPK, folliculitis, ALT and AST increased occurred notably more often with baricitinib 4 mg as with 2 mg (Table 44).

Headache was more common in both the baricitinib 2 mg (7.4%) and 4 mg (7.5%) groups as compared to placebo (3.3%). Also, upper respiratory tract infection occurred both in the 2 mg (4.0%) and 4 mg (3.3%) more often than in the placebo group (2.1%). Similarly, upper abdominal pain occurred in the 2 mg (2.0%) and 4 mg (2.4%) more often than in the placebo group (1.2%).

Oral herpes and herpes simplex both occurred about as much in the 2 mg group (1.3% and 2.5%) as in the 4 mg group (1.6% and 2.8%) which was more often as compared to placebo (0.9% and 1.1%). Herpes zoster did not occur in the 4 mg group, but there were cases in the placebo group as well as the 2 mg group. Among the skin conditions, also folliculitis was more frequent in the baricitinib 2 mg (1.9%) and 4 mg (2.2%) groups as compared to placebo (1.5%). In contrast, atopic dermatitis as AE was more frequent in the placebo group and least frequent in the baricitinib 4 mg group.

Increased blood CPK was more common in the baricitinib 4 mg group (4.2%) as compared to the 2 mg group (1.3%) as compared to placebo (0.6%). Diarrhoea occurred more often in the 4 mg as in the 2 mg group, but also occurred in the placebo group more often than with 2 mg.

In the updated extended phase, no consistent pattern was observed, suggesting that 1 treatment (monotherapy or TCS) has a higher IR of infectious TEAEs than the other.

Most of the reported skin infections were classified as nonserious and those most commonly reported were herpes simplex, oral herpes, and folliculitis. Other common reported AEs included nasopharyngitis, upper respiratory tract infection (URTI), and urinary tract infection (UTI). These events are recognised ADRs associated with baricitinib that are included in the baricitinib SmPC. There were no clinically relevant differences between monotherapy and TCS groups for these events.

In contrast to the PC period, AD was reported more frequently in patients on monotherapy for the baricitinib 4-mg dose, and although TCS had a higher IR than monotherapy for the baricitinib 2-mg dose, the difference was of a smaller magnitude than that observed in the PC period. For acne there was not a consistently higher IR seen for the TCS groups. There was a possible dose response in the TCS group in the PC period, but it was not as evident in the extended period. The highest IRs were reported in baricitinib-treated patients (2 mg and 4 mg). Acne is included in the baricitinib EU SmPC as an ADR that has been identified in both the rheumatoid arthritis (RA) and AD indications.

In the SOC 'Gastrointestinal disorders' the most commonly reported AEs were abdominal pain upper, diarrhoea, and nausea. These events were generally reported at higher IRs in monotherapy for each analysis set. There was a possible treatment regimen-related effect at both baricitinib doses, with monotherapy having consistently higher IRs than TCS combination therapy for abdominal pain upper. Abdominal pain is currently included as an ADR to the SmPC.

For study Jahn, common TEAEs, occurring in 2% or more of patients in any treatment group, are summarized in Table 286.

Table 44 ***Summary of TEAEs from Week 0 to Week 52 by SOC and PT: 2% or More in Any Treatment Group***

SOC *Preferred Term*	PBO N=86 n (%)	BARI 1-mg N=45 n (%)	BARI 2-mg N=759[a] n (%)	BARI 4-mg N=730 n (%)	Combined BARI Group N=1534 n (%)
Infections and Infestations	**28 (32.6)**	**17 (37.8)**	**325 (42.8)**	**343 (47.0)**	**685 (44.7)**
Nasopharyngitis	8 (9.3)	9 (20.0)	96 (12.6)	114 (15.6)	219 (14.3)
Upper respiratory tract infection	1 (1.2)	0	36 (4.7)	39 (5.3)	75 (4.9)
Oral herpes	2 (2.3)	0	32 (4.2)	36 (4.9)	68 (4.4)
Herpes simplex	2 (2.3)	1 (2.2)	18 (2.4)	31 (4.2)	50 (3.3)
Influenza	2 (2.3)	0	30 (4.0)	20 (2.7)	50 (3.3)
Pharyngitis	3 (3.5)	0	18 (2.4)	14 (1.9)	32 (2.1)
Gastroenteritis	0	2 (4.4)	13 (1.7)	16 (2.2)	31 (2.0)
Bronchitis	1 (1.2)	0	6 (0.8)	24 (3.3)	30 (2.0)
Herpes zoster	1 (1.2)	0	10 (1.3)	18 (2.5)	28 (1.8)
Folliculitis	1 (1.2)	0	15 (2.0)	12 (1.6)	27 (1.8)
Conjunctivitis	1 (1.2)	1 (2.2)	10 (1.3)	9 (1.2)	20 (1.3)
Urinary tract infection	0	1 (2.2)	16 (2.1)	4 (0.5)	21 (1.4)
Impetigo	0	1 (2.2)	8 (1.1)	6 (0.8)	15 (1.0)
Rhinitis	1 (1.2)	1 (2.2)	8 (1.1)	6 (0.8)	15 (1.0)
Cystitis	0	2 (4.4)	3 (0.4)	8 (1.1)	13 (0.8)
Gastroenteritis viral	0	1 (2.2)	2 (0.3)	4 (0.5)	7 (0.5)
Skin bacterial infection	1 (1.2)	1 (2.2)	5 (0.7)	1 (0.1)	7 (0.5)
Tinea pedis	0	1 (2.2)	1 (0.1)	1 (0.1)	3 (0.2)
Appendicitis	0	1 (2.2)	0	0	1 (0.1)
Vaginal infection[b]	1 (2.4)	0	0	0	0
Skin and subcutaneous tissue disorders	**4 (4.7)**	**4 (8.9)**	**74 (9.7)**	**75 (10.3)**	**153 (10.0)**
Acne	0	1 (2.2)	12 (1.6)	18 (2.5)	31 (2.0)
Dermatitis contact	1 (1.2)	1 (2.2)	2 (0.3)	3 (0.4)	6 (0.4)
Alopecia	0	1 (2.2)	1 (0.1)	1 (0.1)	3 (0.2)
Erythema	0	1 (2.2)	0	1 (0.1)	2 (0.1)
Skin exfoliation	0	1 (2.2)	0	0	1 (0.1)
Gastrointestinal disorders	**6 (7.0)**	**2 (4.4)**	**72 (9.5)**	**54 (7.4)**	**128 (8.3)**
Diarrhoea	2 (2.3)	0	12 (1.6)	13 (1.8)	25 (1.6)
Abdominal pain	0	1 (2.2)	5 (0.7)	3 (0.4)	9 (0.6)
Anal fistula	0	1 (2.2)	0	0	1 (0.1)
Gastritis	2 (2.3)	0	5 (0.7)	3 (0.4)	8 (0.5)
Haemorrhoids	0	1 (2.2)	2 (0.3)	1 (0.1)	4 (0.3)
Nervous system disorders	**9 (10.5)**	**1 (2.2)**	**57 (7.5)**	**34 (4.7)**	**92 (6.0)**
Headache	6 (7.0)	1 (2.2)	44 (5.8)	19 (2.6)	64 (4.2)
Musculoskeletal and connective tissue disorders	**2 (2.3)**	**1 (2.2)**	**44 (5.8)**	**38 (5.2)**	**83 (5.4)**
Back pain	1 (1.2)	1 (2.2)	8 (1.1)	6 (0.8)	15 (1.0)

Respiratory, thoracic and mediastinal disorders	**1 (1.2)**	**2 (4.4)**	**39 (5.1)**	**36 (4.9)**	**77 (5.0)**
Cough	0	2 (4.4)	9 (1.2)	10 (1.4)	21 (1.4)
Asthma	0	1 (2.2)	9 (1.2)	5 (0.7)	15 (1.0)
Investigations	**1 (1.2)**	**2 (4.4)**	**30 (4.0)**	**43 (5.9)**	**75 (4.9)**
Blood creatine phosphokinase abnormal	0	1 (2.2)	0	0	1 (0.1)
Blood creatine phosphokinase increased	0	1 (2.2)	8 (1.1)	17 (2.3)	26 (1.7)
Injury, poisoning and procedural complications	**0**	**2 (4.4)**	**37 (4.9)**	**32 (4.4)**	**71 (4.6)**
Contusion	0	1 (2.2)	1 (0.1)	6 (0.8)	8 (0.5)
Foot fracture	0	1 (2.2)	1 (0.1)	2 (0.3)	4 (0.3)
General disorders and administration site conditions	**1 (1.2)**	**2 (4.4)**	**31 (4.1)**	**34 (4.7)**	**67 (4.4)**
Pyrexia	0	2 (4.4)	12 (1.6)	15 (2.1)	29 (1.9)
Eye disorders	**2 (2.3)**	**0**	**16 (2.1)**	**34 (4.7)**	**50 (3.3)**
Conjunctivitis allergic	2 (2.3)	0	5 (0.7)	16 (2.2)	21 (1.4)
Surgical and medical procedures	**4 (4.7)**	**1 (2.2)**	**23 (3.0)**	**17 (2.3)**	**41 (2.7)**
Myopia correction	0	1 (2.2)	0	0	1 (0.1)
Uterine dilation and curettage[b]	1 (2.4)	0	0	0	1 (0.1)
Metabolism and nutrition disorders	**0**	**1 (2.2)**	**12 (1.6)**	**26 (3.6)**	**39 (2.5)**
Hyperuricaemia	0	1 (2.2)	1 (0.1)	3 (0.4)	5 (0.3)
Psychiatric disorders	**1 (1.2)**	**1 (2.2)**	**18 (2.4)**	**19 (2.6)**	**38 (2.5)**
Depression	0	1 (2.2)	4 (0.5)	4 (0.5)	9 (0.6)
Vascular disorders	**0**	**0**	**14 (1.8)**	**16 (2.2)**	**30 (2.0)**
Blood and lymphatic system disorders	**0**	**1 (2.2)**	**9 (1.2)**	**13 (1.8)**	**23 (1.5)**
Anaemia	0	1 (2.2)	2 (0.3)	3 (0.4)	6 (0.4)
Immune system disorders	**0**	**1 (2.2)**	**3 (0.4)**	**10 (1.4)**	**14 (0.9)**
Mite allergy	0	1 (2.2)	0	1 (0.1)	2 (0.1)
Reproductive system and breast disorders	**1 (1.2)**	**0**	**7 (0.9)**	**5 (0.7)**	**12 (0.8)**
Uterine haemorrhage[b]	1 (2.4)	0	0	0	0

Abbreviations: BARI = baricitinib; N = number of patients in the safety population; n = number of patients in the specified category; PBO = placebo; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

[a] Includes patients enrolled under the baricitinib 2-mg open-label addendum.

[b] Denominator adjusted because gender-specific event for females: N=41 (PBO), N=16 (BARI 1-mg), N=316 (BARI 2-mg), N=237 (BARI4-mg), N=569 (Combined BARI Group).

An overview of the common TEAEs in all sets are presented in Table 45.

Table 45 ***Summary of common Treatment Emergent Adverse Events***

	16-Week Placebo-Controlled Analysis Set						Ext 2-mg and 4-mg Analysis Set				All BARI AD	
	PBO		2 mg		4 mg		2 mg		4 mg			
	Mono IR (PYR)	TCS IR (PYR)	Mono IR (PYR)	TCS IR (PYR)	Mono IR (PYR)	TCS IR (PYR)	Mono IR (PYR)	TCS IR (PYR)	Mono IR (PYR)	TCS IR (PYR)	Mono IR (PYR)	TCS IR (PYR)
Infections and infestations IR (PYR)	121.3 (54.4)	116.9 (133.4)	161.7 (35.3)	152.3 (103.7)	142.9 (41.3)	162.6 (79.3)	130.1 (60.7)	103.7 (227.5)	100.1 (82.9)	102.6 (264.1)	94.7 (283.1)	94.8 (991.7)
Nasopharyngitis	42.6 (58.7)	39.1 (148.4)	46.8 (40.6)	38.8 (123.6)	31.0 (48.4)	56.1 (92.6)	40.1 (79.8)	23.8 (323.5)	28.3 (106.0)	25.9 (378.5)	29.9 (354.2)	22.2 (1416.6)
Herpes simplex	1.6 (62.0)	4.4 (157.8)	14.2 (42.3)	5.4 (130.5)	10.0 (50.2)	10.1 (99.4)	6.6 (91.1)	3.7 (354.9)	4.9 (121.2)	5.7 (424.1)	4.5 (403.3)	4.6 (1574.3)
URTI	6.5 (61.6)	6.4 (157.1)	9.5 (42.2)	14.8 (128.8)	10.0 (50.1)	10.0 (99.9)	5.6 (89.8)	7.8 (345.5)	7.7 (117.3)	7.9 (418.6)	5.5 (396.9)	6.6 (1548.9)
UTI	4.9 (61.8)	3.2 (157.9)	4.7 (42.6)	5.4 (130.3)	10.0 (50.2)	6.0 (100.2)	4.4 (90.9)	3.1 (355.5)	4.2 (118.7)	2.3 (432.3)	4.5 (398.9)	2.1 (1597.4)
Folliculitis	3.2 (62.0)	5.7 (157.4)	7.1 (42.3)	8.5 (130.2)	8.0 (50.1)	6.0 (100.0)	3.3 (89.9)	4.5 (353.3)	4.2 (119.6)	2.8 (429.5)	2.2 (402.2)	3.7 (1575.3)
Influenza	3.2 (61.8)	3.8 (157.6)	9.5 (42.2)	6.9 (130.4)	6.0 50.3	9 (99.9)	4.5 (89.5)	5.7 (350.9)	4.1 (120.6)	6.2 (420.6)	3.0 (403.2)	5.4 (1561.8)
Oral herpes	4.9 (61.5)	3.8 (157.4)	4.7 (42.7)	6.1 (130.2)	3.9 (50.7)	10.1 (99.3)	4.5 (89.0)	4.0 (354.0)	2.5 (121.8)	7.2 (417.8)	4.8 (399.1)	5.3 (1564.0)
Pharyngitis	1.6 (62.1)	5.1 (157.6)	9.5 (42.0)	3.8 (130.7)	2.0 (50.7)	4.0 (100.6)	6.8 (88.2)	3.4 (355.4)	2.5 (120.8)	1.9 (431.5)	3.8 (399.1)	2.6 (1589.7)
Bronchitis	0.0 (62.1)	2.5 (157.8)	0.0 (42.9)	5.4 (130.8)	2.0 (50.9)	2.0 (100.8)	0.0 (91.9)	3.9 (354.9)	3.3 (121.1)	2.5 (432.2)	1.2 (405.7)	3.0 (1588.0)
Herpes zoster	1.6 (62.1)	1.3 (158.5)	0.0 (42.9)	4.6 (130.9)	0.0 (50.9)	0.0 (101.1)	1.1 (91.8)	4.2 (355.4)	1.6 (121.8)	2.1 (433.5)	2.0 (405.8)	2.6 (1595.3)
Gastrointestinal disorders IR (PYR)	43.5 (59.8)	26.5 (150.9)	52.5 (40.0)	31.5 (124.0)	35.4 (48.0)	38.4 (93.7)	30.9 (81.0)	17.1 (332.4)	18.7 (112.6)	16.2 (394.5)	21.6 (370.5)	14.4 (1481.0)
Abdominal pain upper	9.7 (61.7)	2.5 (157.6)	14.3 (42.1)	3.1 (131.0)	12.0 (49.9)	8.0 (99.6)	8.0 (87.6)	2.0 (358.7)	5.8 (119.9)	1.9 (431.8)	4.5 (399.6)	1.4 (1600.4)
Diarrhoea	8.1 (61.5)	6.4 (156.4)	7.1 (42.5)	5.4 (130.5)	12.1 (49.8)	9.1 (98.8)	5.6 (90.1)	2.8 (356.3)	5.8 (120.1)	3.3 (428.1)	5.8 (397.5)	2.6 (1588.1)

Nausea	9.8 (61.5)	1.3 (158.1)	7.1 (42.5)	8.5 (129.5)	3.9 (50.8)	2.0 (100.8)	4.4 (91.0)	3.4 (354.4)	3.3 (122.3)	1.4 (434.1)	2.5 (407.1)	1.8 (1597.8)
Nervous system disorders IR (PYR)	26.8 (59.8)	19.0 (152.9)	61.8 (38.8)	26.2 (125.9)	35.6 (47.8)	21.6 (97.0)	33.3 (81.1)	13.0 (337.3)	18.6 (113.2)	9.9 (414.6)	17.6 (380.2)	10.0 (1521.3)
Headache	15.0 (60.2)	12.2 (155.2)	50.3 (39.8)	13.2 (128.6)	35.5 (47.9)	18.4 (97.6)	23.6 (84.6)	6.6 (349.2)	15.7 (114.3)	7.4 (420.5)	13.7 (385.6)	6.6 (1552.7)
Investigations IR (PYR)	8.1 (61.6)	14.8 (155.0)	4.7 (42.7)	18.5 (129.5)	32.9 (48.6)	23.7 (97.2)	3.3 (90.7)	8.9 (347.7)	18.4 (108.9)	11.1 (415.5)	8.2 (388.4)	9.0 (1544.6)
Blood CPK increased	0.0 (62.1)	3.8 (157.7)	2.3 (42.9)	5.4 (130.8)	16.2 (49.4)	9.1 (99.3)	1.1 (91.8)	2.2 (358.4)	8.7 (115.2)	3.7 (430.3)	3.8 (397.4)	2.7 (1595.3)
Skin and subcutaneous tissue disorders IR (PYR)	39.6 (60.7)	27.7 (151.4)	23.7 (42.3)	32.0 (125.0)	31.0 (48.3)	39.8 (95.4)	21.4 (84.2)	17.5 (330.5)	25.2 (107.3)	21.5 (395.0)	18.9 (376.5)	17.6 (1462.7)
Dermatitis atopic	1.6 (62.0)	6.4 (157.0)	2.3 (42.9)	5.3 (131.2)	2.0 (50.9)	4.0 (100.9)	1.1 (91.9)	1.9 (360.2)	3.3 (122.5)	2.1 (436.6)	2.0 (408.1)	2.0 (1610.7)
Acne	3.2 (62.0)	3.2 (157.6)	7.0 (42.8)	3.8 (130.7)	2.0 (50.8)	8.0 (99.6)	4.5 (89.0)	3.1 (355.9)	2.5 (120.5)	4.0 (426.2)	3.0 (400.7)	3.4 (1577.6)
General disorders IR (PYR)	29.8 (60.5)	14.9 (154.3)	24.0 (41.6)	14.8 (128.6)	18.2 (49.5)	18.5 (97.4)	12.6 (87.2)	9.2 (347.5)	12.0 (116.9)	9.4 (414.0)	9.4 (394.5)	8.2 (1544.0)
Pyrexia	6.5 (61.6)	4.4 (157.3)	7.0 (42.6)	1.5 (131.4)	3.9 (50.7)	2.0 (100.6)	3.3 (91.2)	2.2 (358.1)	5.0 (120.4)	2.1 (433.1)	3.2 (404.4)	2.1 (1596.2)
Respiratory, thoracic and mediastinal disorders IR (PYR)	9.7 (61.9)	18.9 (153.2)	24.2 (41.3)	21.2 (127.2)	14.1 (49.8)	15.2 (98.6)	13.8 (86.7)	13.0 (339.5)	12.9 (116.0)	9.9 (414.2)	12.5 (391.3)	9.2 (1528.9)
Cough	1.6 (61.9)	2.5 (158.0)	4.7 (42.4)	6.9 (130.4)	10.0 (50.1)	1.0 (100.9)	2.2 (90.9)	3.9 (355.5)	5.9 (118.7)	1.6 (432.0)	3.2 (401.2)	2.3 (1594.1)
Oropharyngeal pain	3.2 (62.1)	3.8 (157.5)	2.3 (42.7)	6.9 (129.9)	0.0 (50.9)	4.0 (100.2)	1.1 (91.1)	4.0 (354.3)	1.6 (122.1)	1.9 (432.2)	1.5 (406.9)	2.2 (1591.9)
Musculoskeletal and connective tissue disorders IR (PYR)	8.1 (61.5)	14.9 (154.5)	4.7 (42.8)	21.3 (126.5)	10.0 (49.8)	19.4 (98.1)	6.8 (88.3)	12.8 (334.8)	5.0 (120.0)	10.7 (409.7)	6.4 (392.8)	11.5 (1498.7)
Back pain	4.9 (61.8)	2.5 (157.6)	2.3 (42.8)	3.8 (130.4)	0.0 (50.9)	7.0 (99.9)	2.2 (90.9)	2.5 (357.1)	0.0 (122.7)	2.6 (429.5)	0.7 (406.1)	2.5 (1591.1)
Injury, poisoning and procedural complications IR (PYR)	13.1 (61.0)	13.6 (154.9)	11.8 (42.3)	13.2 (128.5)	10.0 (50.2)	14.3 (98.1)	8.0 (87.7)	7.2 (347.7)	5.8 (119.8)	7.6 (422.1)	6.4 (393.7)	7.4 (1550.2)
Renal and urinary disorders IR (PYR)	0.0 (62.1)	1.9 (158.1)	0.0 (42.9)	1.5 (131.6)	10.0 (49.9)	4.0 (100.3)	3.3 (90.4)	1.7 (358.8)	4.1 (120.8)	1.6 (431.7)	2.5 (404.3)	1.6 (1599.5)

Blood and lymphatic system disorders IR (PYR)	9.8 (61.0)	4.4 (157.4)	0.0 (42.9)	6.1 (130.9)	7.9 (50.5)	8.0 (99.9)	1.1 (91.6)	3.4 (357.1)	5.0 (120.0)	3.5 (430.9)	2.0 (404.7)	2.8 (1594.1)
Metabolism and nutrition disorders IR (PYR)	11.5 (61.1)	5.1 (157.5)	11.9 (41.9)	7.7 (130.2)	7.9 (50.6)	5.0 (100.6)	5.8 (86.9)	3.7 (353.6)	8.5 (118.2)	4.2 (425.4)	6.1 (393.8)	3.6 (1578.0)
Vascular disorders IR (PYR)	4.9 (61.8)	3.8 (157.6)	7.1 (42.3)	5.4 (130.4)	7.9 (50.5)	4.0 (100.5)	6.8 (88.4)	3.9 (355.8)	4.1 (120.6)	4.2 (427.9)	3.7 (400.9)	3.2 (1587.3)
Hypertension	4.9 (61.8)	3.2 (157.6)	4.7 (42.6)	5.4 (130.4)	3.9 (50.8)	1.0 (101.1)	3.3 (89.9)	3.1 (356.7)	2.5 (121.8)	2.3 (431.2)	2.2 (403.7)	2.1 (1593.4)
Psychiatric disorders IR (PYR)	19.8 (60.7)	5.1 (157.2)	4.7 (42.8)	10.0 (129.5)	5.9 (50.4)	8.0 (100.3)	3.3 (91.5)	6.0 (351.8)	4.2 (119.4)	5.2 (426.6)	4.0 (402.4)	4.6 (1577.1)
Cardiac disorders IR (PYR)	0.0 (62.1)	0.6 (158.5)	0.0 (42.9)	2.3 (131.2)	2.0 (50.7)	2.0 (100.8)	0.0 (91.9)	2.0 (358.4)	0.8 (122.5)	0.7 (436.5)	0.5 (408.2)	1.0 (1609.0)
Ear and labyrinth disorders IR (PYR)	3.2 (61.6)	7.0 (157.0)	2.3 (42.9)	2.3 (131.4)	2.0 (50.6)	1.0 (101.0)	2.2 (91.5)	1.4 (358.9)	2.5 (121.2)	1.4 (434.1)	1.5 (405.4)	1.7 (1600.4)
Eye disorders IR (PYR)	8.1 (61.8)	8.3 (156.6)	4.7 (42.9)	7.7 (129.7)	2.0 (50.8)	14.2 (98.6)	2.2 (91.5)	6.0 (352.9)	4.2 (120.2)	7.7 (417.5)	3.7 (402.3)	5.6 (1563.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) IR (PYR)	1.6 (62.0)	3.2 (158.1)	2.3 (42.8)	3.8 (131.0)	2.0 (50.9)	4.0 (100.3)	1.1 (91.7)	2.2 (355.6)	1.6 (122.1)	2.6 (427.8)	1.7 (406.9)	2.3 (1587.7)
Reproductive system and breast disorders IR (PYR)	1.6 (61.9)	3.2 (157.8)	2.3 (42.7)	2.3 (131.1)	2.0 (50.7)	1.0 (100.9)	1.1 (91.6)	2.3 (355.5)	1.6 (121.6)	0.9 (434.9)	0.7 (407.0)	1.6 (1594.9)
Surgical and medical procedures IR (PYR)	6.5 (61.4)	6.4 (156.6)	4.7 (42.7)	5.4 (130.6)	2.0 (50.7)	4.0 (100.9)	3.3 (90.7)	5.7 (351.0)	2.5 (121.5)	3.5 (429.8)	2.5 (405.2)	4.1 (1581.6)
Congenital, familial and genetic disorders IR (PYR)	1.6 (62.0)	0.0 (158.6)	0.0 (42.9)	0.0 (131.8)	0.0 (50.9)	0.0 (101.1)	0.0 (91.9)	0.3 (361.2)	0.0 (122.7)	0.0 (437.2)	0.0 (408.5)	0.1 (1614.7)
Hepatobiliary disorders IR (PYR)	1.6 (61.9)	0.6 (158.6)	2.3 (42.7)	0.8 (131.5)	0.0 (50.9)	1.0 (100.9)	1.1 (91.7)	0.8 (361.0)	0.0 (122.7)	1.6 (432.9)	1.2 (406.2)	0.8 (1608.5)
Immune system disorders IR (PYR)	1.6 (61.8)	1.3 (158.5)	0.0 (42.9)	3.1 (131.1)	0.0 (50.9)	1.0 (100.8)	0.0 (91.9)	2.0 (358.4)	0.8 (122.4)	1.2 (434.6)	0.5 (407.4)	1.4 (1603.8)

Abbreviations: AD = atopic dermatitis; CPK = creatine phosphokinase; Ext = extended; IR = incidence rate; Mono = monotherapy; PYR = patient years at risk; TCS = topical corticosteroids; URTI = upper respiratory tract infection; UTI = urinary tract infection.

Note: Interpretation of the results in this table is challenging and has similar limitations to observational data. Using this table to assess a potential dose relationship is problematic due to study and treatment being confounded and risk over time changes due to reasons other than treatment exposure to dose.

Serious adverse event/deaths/other significant events

One death occurred, in a patient originally randomised to baricitinib 1 mg, who was re-randomised to 4 mg in study JAHN but received 2 mg because of a GFR<60ml/min/1.73m^2. The cause of death was a GI bleed, more than 12 months after start of baricitinib and while being on 2 mg for 9 months. The patient had no known risk factors for GI bleed, but had a low haematocrit and a low erythrocyte count at baseline, which may point to a possible earlier bleed.

Overall, the SAE IRs appear to be consistently higher for TCS combination therapy versus monotherapy and numerical differences between doses were also observed. the most commonly reported AE accounting for the higher rate of SAEs in 4 mg relative to 2 mg is worsening of AD.

In the 16-week placebo controlled treatment period, the proportion of patients with at least one SAE was higher in the placebo group (2.9%) as compared to the baricitinib 2 mg (1.6%) and 4 mg (1.8%) groups. Most SAEs occurred in the SOCs of skin and subcutaneous disorders, and infections and infestations. The corresponding SAEs in the placebo group were: atopic dermatitis (n=5), exfoliative dermatitis (n=1), eczema herpeticum (n=2), eye infection (n=1), post-operative abcess (n=1). In the baricitinib 2 mg group these were: atopic dermatitis (n=2), eczema (n=1), and single occurrences of bronchitis, cellulitis, staphylococcal infection. In the baricitinib 4 mg group these were: atopic dermatitis (n=1), tonsilitis (n=1).

In infections there was a tendency towards more serious infections in TCS, but the number of reports of each event was small, with most events having only 1 report. The exception to this pattern continues to be eczema herpeticum, which was reported as an SAE for 3 patients treated with 4 mg (IR = 0.6) and for 1 patient (IR = 0.2) treated with 2 mg. In addition, serious skin infections were reported more frequently with 4 mg (n = 6, IR = 1.3) compared with 2 mg (n = 2, IR = 0.5). These skin infections included 2 cases of cellulitis in patients treated with either 2 mg or 4 mg, unspecified staphylococcal infection of the skin (1 each in 2 mg and 4 mg), and a single case each of skin bacterial infection, staphylococcal skin infection, and erysipelas reported in the 4-mg group. In addition, there were 2 cases of toxic skin eruption in the baricitinib 4 mg group, both were considered to be related to the study drug by the investigator and study drug was discontinued.

Table 46 ***Serious Adverse Events by System Organ Class "As-Treated"***

	16-Week Placebo-Controlled Analysis Set						Ext 2-mg and 4-mg Analysis Set				All BARI AD	
	PBO		2 mg		4 mg		2 mg		4 mg			
	Mono IR (PYR)	TCS IR (PYR)	Mono IR (PYR)	TCS IR (PYR)	Mono IR (PYR)	TCS IR (PYR)	Mono IR (PYR)	TCS IR (PYR)	Mono IR (PYR)	TCS IR (PYR)	Mono IR (PYR)	TCS IR (PYR)
All Serious Adverse Events	9.7 (61.7)	9.6 (156.5)	2.3 (42.8)	6.9 (131.2)	3.9 (50.8)	12.0 (99.6)	2.2 (91.4)	4.2 (359.0)	6.6 (121.4)	8.0 (426.7)	4.2 (405.4)	6.7 (1581.9)
Infections and infestations IR (PYR)	1.6 (62.1)	2.5 (158.3)	0.0 (42.9)	2.3 (131.6)	2.0 (50.9)	2.0 (101.0)	1.1 (91.5)	1.9 (361.2)	2.4 (122.5)	2.3 (434.8)	1.7 (406.9)	2.3 (1607.0)
Gastrointestinal disorders IR (PYR)	0.0 (62.1)	0.6 (158.4)	0.0 (42.9)	0.0 (131.8)	0.0 (50.9)	1.0 (100.8)	0.0 (91.9)	0.0 (361.9)	0.0 (122.7)	0.2 (436.9)	0.0 (408.5)	0.5 (1613.4)
Nervous system disorders IR (PYR)	-	-	-	-	-	-	0.0 (91.9)	0.0 (361.9)	0.0 (122.7)	0.2 (437.0)	0.0 (408.5)	0.1 (1615.3)
Skin and subcutaneous tissue disorders IR (PYR)	3.2 (61.9)	3.2 (157.8)	0.0 (42.9)	3.8 (131.4)	0.0 (50.9)	3.0 (100.9)	0.0 (91.9)	1.4 (361.2)	2.4 (122.5)	2.1 (436.6)	1.7 (408.1)	1.9 (1610.2)
General disorders IR (PYR)	0.0 (62.1)	0.0 (158.6)	0.0 (42.9)	0.0 (131.8)	0.0 (50.9)	1.0 (101.0)	0.0 (91.9)	0.0 (361.9)	0.0 (122.7)	0.2 (436.7)	0.0 (408.5)	0.1 (1614.7)
Respiratory, thoracic and mediastinal disorders IR (PYR)	0.0 (62.1)	0.0 (158.6)	0.0 (42.9)	0.0 (131.8)	0.0 (50.9)	2.0 (100.9)	0.0 (91.9)	0.0 (361.9)	0.0 (122.7)	0.9 (435.1)	0.0 (408.5)	0.4 (1612.6)
Musculoskeletal and connective tissue disorders IR (PYR)	0.0 (62.1)	1.3 (158.3)	0.0 (42.9)	0.0 (131.8)	0.0 (50.9)	1.0 (101.0)	0.0 (91.9)	0.0 (361.9)	0.0 (122.7)	0.5 (436.1)	0.0 (408.5)	0.6 (1609.8)
Injury, poisoning and procedural complications IR (PYR)	1.6 (62.1)	0.0 (158.6)	0.0 (42.9)	0.8 (131.7)	2.0 (50.8)	1.0 (101.1)	0.0 (91.9)	0.3 (361.4)	0.8 (122.4)	0.5 (436.5)	0.2 (408.1)	0.5 (1611.9)
Renal and urinary disorders IR (PYR)	-	-	-	-	-	-	0.0 (91.9)	0.0 (361.9)	0.0 (122.7)	0.0 (437.2)	0.0 (408.5)	0.1 (1614.6)
Blood and lymphatic system disorders IR (PYR)	-	-	-	-	-	-	0.0 (91.9)	0.0 (361.9)	0.0 (122.7)	0.0 (437.2)	0.0 (408.5)	0.1 (1615.3)
Metabolism and nutrition disorders IR (PYR)	-	-	-	-	-	-	0.0 (91.9)	0.0 (361.9)	0.0 (122.7)	0.0 (437.2)	0.0 (408.5)	0.1 (1614.5)
Vascular disorders IR (PYR)	0.0 (62.1)	0.6 (158.6)	0.0 (42.9)	0.0 (131.8)	0.0 (50.9)	0.0 (101.1)	0.0 (91.9)	0.0 (361.9)	0.0 (122.7)	0.7 (437.0)	0.0 (408.5)	0.2 (1615.2)
Psychiatric disorders IR (PYR)	1.6 (62.0)	0.0 (158.6)	2.3 (42.8)	0.8 (131.7)	0.0 (50.9)	0.0 (101.1)	1.1 (91.8)	0.3 (361.8)	0.0 (122.7)	0.0 (437.2)	0.2 (408.4)	0.1 (1615.4)
Cardiac disorders IR (PYR)	0.0 (62.1)	0.0 (158.6)	0.0 (42.9)	0.8 (131.8)	0.0 (50.9)	0.0 (101.1)	0.0 (91.9)	0.8 (360.6)	0.0 (122.7)	0.0 (437.2)	0.0 (408.5)	0.3 (1613.7)
Ear and labyrinth disorders IR (PYR)	-	-	-	-	-	-	0.0 (91.9)	0.0 (361.9)	0.8 (122.1)	0.0 (437.2)	0.2 (407.8)	0.0 (1615.4)

Eye disorders IR (PYR)	0.0 (62.1)	0.6 (158.2)	0.0 (42.9)	0.0 (131.8)	0.0 (50.9)	2.0 (100.8)	0.0 (91.9)	0.0 (361.9)	0.0 (122.7)	0.9 (435.8)	0.0 (408.5)	0.3 (1612.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) IR (PYR)	1.6 (62.0)	1.3 (158.5)	0.0 (42.9)	0.0 (131.8)	0.0 (50.9)	0.0 (101.1)	0.0 (91.9)	0.0 (361.9)	0.0 (122.7)	0.0 (437.2)	0.0 (408.5)	0.2 (1614.2)
Reproductive system and breast disorders IR (PYR)	-	-	-	-	-	-	0.0 (91.9)	0.0 (361.9)	0.0 (122.7)	0.2 (436.9)	0.0 (408.5)	0.1 (1615.1)
Hepatobiliary disorders IR (PYR)	-	-	-	-	-	-	0.0 (91.9)	0.0 (361.9)	0.0 (122.7)	0.2 (436.3)	0.0 (408.5)	0.1 (1614.4)

Abbreviations: - = there were no reports in any treatment group for that analysis set; AD = atopic dermatitis; Ext = extended; IR = incidence rate; Mono = monotherapy; PT = preferred term; PYR = patient years at risk; TCS = topical corticosteroids.

Note: Interpretation of the results in this table is challenging and has similar limitations to observational data. Using this table to assess a potential dose relationship is problematic due to study and treatment being confounded and risk over time changes due to reasons other than treatment exposure to dose.

In addition, there were 2 cases of toxic skin eruption in the baricitinib 4 mg group, both were considered to be related to the study drug by the investigator and study drug was discontinued.

In the updated database, the frequency and IR of SAEs in the updated database had small changes, with a decrease in the rate for PBO and 2 mg, and an increase in the rate for 4 mg. The rates for 2 mg and 4 mg were both lower than PBO during the PC period. As in the original database, frequency and IR of SAEs was higher for baricitinib 4 mg than for baricitinib 2 mg during the extension period (in the Ext BARI 2-mg and 4-mg analysis set).

In the updated analysis of those patients treated with 2 mg in the open-label addendum, a total of 11 patients (4.5%) reported SAEs and the IR was 7.4. Although this IR is less than that observed in the original submission (10.6) for this addendum, the IR for the 2-mg group remains higher than that observed in the updated Ext BARI 2-mg and 4-mg dataset for 2 mg (3.5), and both IRs are lower than the IR observed for PBO (8.0) in the updated PC database. Although the rates are lower than PBO, there was still a higher IR for SAEs for 4-mg compared to 2-mg in the extended period.

Table 47 ***Serious Adverse Event Frequencies and Incidence Rates (Original and Updated Databases)***

Analysis Set	16-Week Placebo-Controlled Period			Ext BARI 2 mg and 4 mg AD		All BARI AD
Treatment Period	Weeks 0–16			From Week 0		
Database	PBO N n (adj%) [adjIR]	BARI 2 mg N n (adj%) [adjIR]	BARI 4 mg N n (adj%) [adjIR]	BARI 2 mg N n (adj%) [adjIR]	BARI 4 mg N n (adj%) [adjIR]	All Doses N n (adj%) [adjIR]
Original	650 19 (2.9) [10.1]	392 7 (1.6) [5.3]	397 8 (1.8) [5.7]	392 7 (1.6) [2.7]	397 25 (6.8) [8.5]	1646 79 (4.8) [6.7]
Updated	743 21 (2.3) [8.0]	576 10 (1.4) [4.4]	489 14 (2.3) [7.7]	576 17 (2.2) [3.5]	489 40 (7.3) [9.1]	2531 138 (5.5) [6.1]

Abbreviations: AD = atopic dermatitis; Ext = extended; IR = incidence rate; N = number of patients in the safety analysis set; n = number of patients in the specified category; SCS = Summary of Clinical Safety.

Further analysis of the nature of the SAEs in patients treated with baricitinib 4 mg compared with 2 mg has been conducted to characterise the clinical significance of the observed difference in SAE incidence. Overall, there has been a minimal change compared with these SAEs in the original submission. Most of the SAEs continue to be reported only once. The most common event accounting for the higher rate of SAEs in the 4 mg relative to the 2 mg group is worsening of AD, the underlying

condition. Flares of AD are common in patients with moderate to severe disease and are mostly not related to baricitinib but rather to failure of treatment (Table 48).

Table 48 ***Serious Adverse Event Frequency and Incidence Rates for Baricitinib 2 mg and 4 mg for Patients with ≥2 SAE (Updated Databases)***

	Updated Ext BARI 2 mg and 4 mg AD	
	BARI 2 mg (N = 576) n (adj %) [adj IR]	**BARI 4 mg (N = 489) n (adj %) [adj IR]**
Infections and infestations	**8 (0.9) [1.5]**	**13 (2.5) [3.0]**
Eczema herpeticum	**1 (0.1) [0.2]**	3 (0.6) [0.6]
Cellulitis	**2 (0.2) [0.4]**	**2 (0.4) [0.4]**
Skin and subcutaneous tissue disorders	**5 (0.6) [1.0]**	**10 (1.9) [2.3]**
Dermatitis atopic	**3 (0.4) [0.7]**	**9 (1.7) [2.0]**
Respiratory, thoracic, and mediastinal disorders	0 [0.0]	4 (0.6) [0.8]
Pulmonary embolism	0 [0.0]	2 (0.3) [0.4]
Vascular disorders	0 [0.0]	**3 (0.6) [0.6]**
Thrombophlebitis	0 [0.0]	2 (0.4) [0.4]

Abbreviations: adj % = study-size-adjusted percentage; adj IR = study-size-adjusted incidence rate (per 100 patient-years); N = number of patients in the safety analysis set; n = number of patients in the specified category; SCS = Summary of Clinical Safety.

Note: Bold type for n, adj %, and adj IR in the columns for the updated database indicates changes from the original database.

At the CHMP's request, the MAH submitted Updated Incidence Rates of Serious Adverse Events by System Organ Class. Overall, the SAE IRs were numerically higher at 4 mg compared to 2 mg. Table below provides SAEs in decreasing frequency according to 4-mg dose in the Extended period.

Table 49 ***Updated Incidence Rates of Serious Adverse Events by System Organ Class***

	16-Week Placebo-Controlled 'as-randomised' Analysis Set[a]			Ext 2 mg and 4 mg 'as-treated' Analysis Set	
	PBO adj % (adj IR) [PYR]	2 mg adj % (adj IR) [PYR]	4 mg adj % (adj IR) [PYR]	2 mg (IR) [PYR]	4 mg (IR) [PYR]
Patients with ≥1 SAE	2.3 (8.0) [218.0]	1.4 (4.4) [173.9]	2.3 (7.7) [150.3]	(3.8) [449.9]	(7.7) [557.5]
Infections and infestations	0.6 (2.1) [220.1]	0.4 (1.0) [174.5]	0.6 (1.9) [151.7]	(1.8) [452.7]	(2.5) [567.1]
Skin and subcutaneous tissue disorders	0.8 (2.7) [219.7]	0.6 (2.0) [174.3]	0.6 (1.9) [151.8]	(1.1) [453.1]	(2.1) [569.6]
Respiratory, thoracic and mediastinal disorders	0 0 [220.7]	0 0 [174.7]	0.2 (0.8) [151.9]	0 [453.7]	(0.7) [568.3]
Eye disorders	0.1 (0.3) [220.3]	0 0 [174.7]	0.3 (1.0) [151.7]	0 [453.7]	(0.7) [569.1]
Injury, poisoning and procedural complications	0.1 (0.3) [220.7]	0.1 (0.4) [174.7]	0.4 (1.3) [151.9]	(0.2) [453.3]	(0.5) [569.4]
Musculoskeletal and connective tissue disorders	0.2 (0.7) [220.3]	0 0 [174.7]	0.1 (0.4) [151.9]	0 [453.7]	(0.5) [569.2]
Vascular disorders	0.1 (0.3) [220.7]	0 0 [174.7]	0 0 [152.1]	0 [453.7]	(0.5) [570.2]
Gastrointestinal disorders	0.1 (0.4) [220.5]	0 0 [174.7]	0.1 (0.4) [151.7]	0 [453.7]	(0.2) [570.1]
General disorders and administration site conditions	0 0 [220.7]	0 0 [174.7]	0.2 (0.6) [152.0]	0 [453.7]	(0.2) [570.0]
Hepatobiliary disorders	--	--	--	0 [453.7]	(0.2) [569.6]
Ear and labyrinth disorders	--	--	--	0 [453.7]	(0.2) [569.5]
Nervous system disorders	--	--	--	0 [453.7]	(0.2) [570.3]
Reproductive system and breast disorders	--	--	--	0 [453.7]	(0.2) [570.2]
Cardiac disorders	0 0 [220.7]	0.1 (0.3) [174.7]	0 0 [152.1]	(0.7) [452.5]	0 [570.5]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0.4 (1.3) [220.5]	0 0 [174.7]	0 0 [152.1]	0 [453.7]	0 [570.5]

	16-Week Placebo-Controlled 'as-randomised' Analysis Set[a]			Ext 2 mg and 4 mg 'as-treated' Analysis Set	
	PBO adj % (adj IR) [PYR]	2 mg adj % (adj IR) [PYR]	4 mg adj % (adj IR) [PYR]	2 mg (IR) [PYR]	4 mg (IR) [PYR]
Psychiatric disorders	0.1 (0.3) [220.6]	0.4 (1.3) [174.4]	0 0 [152.1]	(0.4) [453.2]	0 [570.5]
Renal and urinary disorders	--	--	--	0 [453.7]	(0.0) [570.5]
Blood and lymphatic system disorders	--	--	--	0 [453.7]	0 [570.5]
Metabolism and nutrition disorders	--	--	--	0 [453.7]	0 [570.5]

Abbreviations: - = there were no reports in any treatment group for that analysis set; adj = adjusted; Ext = extended; incl = including; IR = incidence rate; PYR = patient-years at risk; SAE = serious adverse event.

[a] Data from the 16-week placebo-controlled period are 'as-randomised' and from the updated data analysis set.

AESI's were selected based on the established safety profile of baricitinib based on data in RA, on the 'phase 2' dose-finding study in AD, the mechanism of action of baricitinib and information from the literature.

- Infections, including potential opportunistic infections
- Hematologic changes
- Lipid increases
- Major adverse cardiovascular event (MACE)
- VTE
- Arterial thromboembolic event (ATE)
- CPK increases and muscle-related symptoms
- Non-melanoma skin cancer (NMSC) and malignancy other than NMSC
- Abnormal hepatic tests
- Renal function
- GI perforation
- Depression and suicidality
- Allergic reactions or hypersensitivity, and photosensitivity reactions.

In the AD data, MACE events, arterial thrombotic events, GI perforation, did not occur up to now. There was no completed suicide and few cases of suicidal ideation or behaviour not concentrated in the baricitinib groups. If changes occurred in creatinine, these were small. There were 5 cases of malignancy in the long-term use data set: anaplastic large cell lymphoma, and 4 NMSC cases: 2 cases of Bowen's disease, basal cell carcinoma, and keratoacanthoma. Few cases of hypersensitivity (including severe angioedema, exfoliative dermatitis, toxic skin eruption) occurred. There were 7 cases of photosensitivity reported while on baricitinib.

Infections

Through inhibition of the JAK-STAT pathway, baricitinib is supposed to increase the risk for infections. The occurrence of infections was raised in both baricitinib dose groups as compared to placebo (Table 50) and over time was slightly larger in the higher dose group. Serious infections were few. Part of the increased occurrence of infections can be attributed to herpes simplex and oral herpes.

Herpes zoster and herpes simplex (including eczema herpeticum, herpes simplex, ophthalmic herpes simplex, and oral herpes) are recognized as common ADRs in the EU SmPC. Upper respiratory tract infections are recognized as very common ADRs in the EU SmPC. Other infections listed in the EU SmPC include gastroenteritis, urinary tract infections, and pneumonia (all common). Serious and Opportunistic infections are important potential risks in the RMP. The current SmPC for RA includes warnings: to be cautious in patients with clinically important chronic or active infections; not to use baricitinib in case of active TB; that viral reactivation (including herpes zoster and hepatitis B and C) is possible; perform screening for viral hepatitis. Since infections are the key identified risks for baricitinib, the posology section of the SmPC indicates that a lower dose (2-mg) may be appropriate for patients with a history of chronic or recurrent infections. No changes for the SmPC regarding infections are proposed with the present application.

In the updated database, the highest IRs were seen in the baricitinib doses compared to PBO in the PC period, and there were no dose differences in the PC and extended periods. There were no clinically relevant differences between monotherapy and TCS as the IR was higher in the baricitinib 2-mg monotherapy group than TCS in the extended period, but IRs were similar in the baricitinib 4-mg extended and All BARI AD groups.

All opportunistic infections were reported in TCS-treated patients. There was 1 toxoplasmosis in the eye reported in a patient receiving PBO. There were 3 multi-dermatomal herpes zoster events reported in baricitinib-treated patients, 2 on baricitinib 2 mg and 1 on baricitinib 4 mg. None of these were reported as serious infections or led to study drug interruption. Herpes simplex was reported more frequently in the baricitinib 4-mg dose for both monotherapy and TCS in the PC period.

Table 50 ***Overview of infections***

	16-Week Placebo-Controlled Analysis Set						Ext 2-mg and 4-mg Analysis Set				All BARI AD	
	PBO		2 mg		4 mg		2 mg		4 mg			
	Mono	TCS	Mono	TCS	Mono	TCS	Mono	TCS	Mono	TCS	Mono	TCS
Patients with ≥1 TEAE	121.3 (54.4)	116.9 (133.4)	161.7 (35.3)	152.3 (103.7)	142.9 (41.3)	162.6 (79.3)	130.1 (60.7)	103.7 (227.5)	100.1 (82.9)	102.6 (264.1)	94.7 (283.1)	94.8 (991.7)
SAE IR (PYR)	1.6 (62.1)	2.5 (158.3)	0.0 (42.9)	2.3 (131.6)	2.0 (50.9)	2.0 (101.0)	1.1 (91.5)	1.9 (361.2)	2.4 (122.5)	2.3 (434.8)	1.7 (406.9)	2.3 (1607.0)
AEs that led to: IR (PYR)												
Permanent DC from Study Drug	0.0 (62.1)	1.3 (158.4)	2.3 (42.8)	0.8 (131.8)	0.0 (50.9)	2.0 (101.0)	1.1 (91.8)	1.1 (361.5)	0.8 (122.7)	1.1 (436.9)	0.5 (408.4)	0.9 (1614.2)
Temporary Interruption from Study Drug	4.8 (61.9)	0.6 (158.4)	4.7 (42.7)	11.6 (129.5)	12.0 (50.1)	9.1 (99.4)	3.3 (91.5)	8.4 (347.3)	7.5 (119.7)	7.1 (423.1)	5.0 (401.3)	6.9 (1557.5)
TE Opportunistic Infection	0.0 (62.1)	0.6 (158.3)	0.0 (42.9)	0.8 (131.5)	0.0 (50.9)	0.0 (101.1)	0.0 (91.9)	0.3 (361.3)	0.0 (122.7)	0.2 (437.0)	0.0 (408.5)	0.2 (1614.2)
TE Herpes Zoster	1.6 (62.1)	1.3 (158.5)	0.0 (42.9)	4.6 (130.9)	0.0 (50.9)	0.0 (101.0)	1.1 (91.8)	4.2 (355.4)	1.6 (121.8)	2.1 (433.5)	2.0 (405.8)	2.6 (1595.3)
TE Herpes Simplex	9.8 (61.3)	10.2 (156.3)	19.0 (42.1)	13.2 (128.4)	18.1 (49.8)	28.0 (96.4)	11.3 (88.3)	9.3 (345.2)	10.0 (120.1)	14.5 (399.7)	10.2 (393.9)	11.6 (1511.3)
TE Tuberculosis	0 (62.1)	0 (158.6)	0 (42.9)	0 (131.8)	0 (50.9)	0 (101.1)	0 (91.9)	0 (361.9)	0 (122.7)	0 (437.2)	0 (408.5)	0 (1615.4)
TE Viral Hepatitis	0 (62.1)	0 (158.6)	0 (42.9)	0 (131.8)	0 (50.9)	0 (101.1)	0 (91.9)	0 (361.9)	0 (122.7)	0.2 (436.8)	0 (408.5)	0.1 (1615.1)
Patients with ≥1 skin infection requiring antibiotics	21.1 (61.5)	17.9 (139.8)	21.3 (42.2)	19.1 (115.3)	7.9 (50.3)	16.2 (86.3)	10.0 (89.8)	6.6 (335.1)	3.3 (121.3)	3.4 (414.1)	4.2 (403.2)	3.0 (1554.0)

Abbreviations: AD = atopic dermatitis; DC = discontinuation; Ext = extended; IR = incidence rate; Mono = monotherapy; PYR = patient years at risk; TE = treatment emergent; TCS = topical corticosteroids.

Note: Interpretation of the results in this table is challenging and has similar limitations to observational data. Using this table to assess a potential dose relationship is problematic due to study and treatment being confounded and risk over time changes due to reasons other than treatment exposure to dose.

Hematologic changes

The hematologic growth promoters are erythropoietin, G-CSF, GM-CSF, and thrombopoietin signal via JAK2 signaling. JAK2 inhibition could impair the production of erythrocytes, leukocytes, or platelets. Myelosuppression has been reported to varying degrees with other marketed JAK inhibitors, ruxolitinib and tofacitinib.

There were dose-dependent changes for baricitinib 2 mg and 4 mg, as compared to placebo, in neutrophils-low, haemoglobin-low, platelets-high. Changes only for the highest dose were in neutrophils-high, lymphocytes-low. Specifically, thrombocytosis (with a change to >400 x 109 cells/L) occurred in 3.5% of the patients of the placebo group, 9.3% in the baricitinib 2 mg group and 12.8% in the 4 mg group. In the extended data set, proportions of patients with hematologic changes increased, most notably for: neutrophils-high, neutrophils-low, lymphocytes-low, platelets-high (Table 51).

Table 51 ***Overview of haematological changes in the extended data set***

	Ext BARI 2-mg and 4-mg AD			ALL BARI AD
	BARI 2-mg (N = 392) %	BARI 4-mg (N = 397) %	BARI 4-mg vs 2-mg OR (p-value)	All Doses (1-mg, 2-mg, 4-mg) (N = 1646) %
Neutrophils, Segmented – Low (10^9 cells /L)	9.8	16.3	1.8 (0.007)	11.6
Neutrophils, Segmented – High (10^9 cells /L)	6.5	8.8	1.4 (0.226)	7.1
Lymphocytes – Low (10^9 cells /L)	12.2	12.0	1.0 (0.921)	11.2
Lymphocytes – High (10^9 cells /L)	2.6	5.7	2.2 (0.034)	4.6
Hemoglobin – Low (mmol/L-Fe)	5.6	8.5	1.6 (0.129)	5.8
Hemoglobin – High (mmol/L-Fe)	0.5	0.3	0.5 (0.533)	0.4
Platelets – Low (10^9 cells /L)	0.3	0.3	1.0 (0.975)	0.3
Platelets – High (10^9 cells /L)	5.2	9.3	1.9 (0.031)	6.6

Abbreviations: AD = atopic dermatitis; N = number of patients in the safety analysis set; OR = odds ratio.
Source tables are provided in the Appendix to the Summary of Clinical Safety: Table SCS APP 2.7.4.7.52 for the **Ext BARI 2-mg and 4-mg AD** and **All BARI AD** analysis sets.

Low neutrophils and thrombocytosis are listed as ADR in the SmPC. It is included in the warnings that treatment should not be initiated or it should temporarily be interrupted, in presence of absolute neutrophil counts < 1 x 109 cells/L, absolute lymphocyte counts < 0.5 x 109 cells/L, a haemoglobin level < 4.9 mmol/L-FE. No changes regarding haematological changes are proposed for the SmPC with the present application.

Blood lipid increases

Lipid changes such as increased LDL-C, HDL-C, and triglycerides are consistent with a pharmacologic effect of JAK inhibition, with hypercholesterolemia and hypertriglyceridemia recognized as ADRs for baricitinib. Lipid changes are also observed with tofacitinib.

Mean total cholesterol, LDL, and HDL were elevated for baricitinib-treated patients in the placebo-controlled period and continued to be elevated during the extended period (Figure below). At week 16 of the placebo-controlled period, increased total cholesterol was present in 9.6% of the placebo group, and 21.0% and 20.8% in the baricitinib 2 mg and 4 mg groups. Triglycerides did not show a mean change from baseline, although some patients did have clinically significant changes. A higher proportion of patients treated with baricitinib 4-mg compared to 2-mg had categorical increases in cholesterol, HDL, LDL, and triglycerides. The ratio of LDL/HDL cholesterol increased up to week 52, more for baricitinib 4 mg as for 2 mg. Results for total cholesterol are shown below.

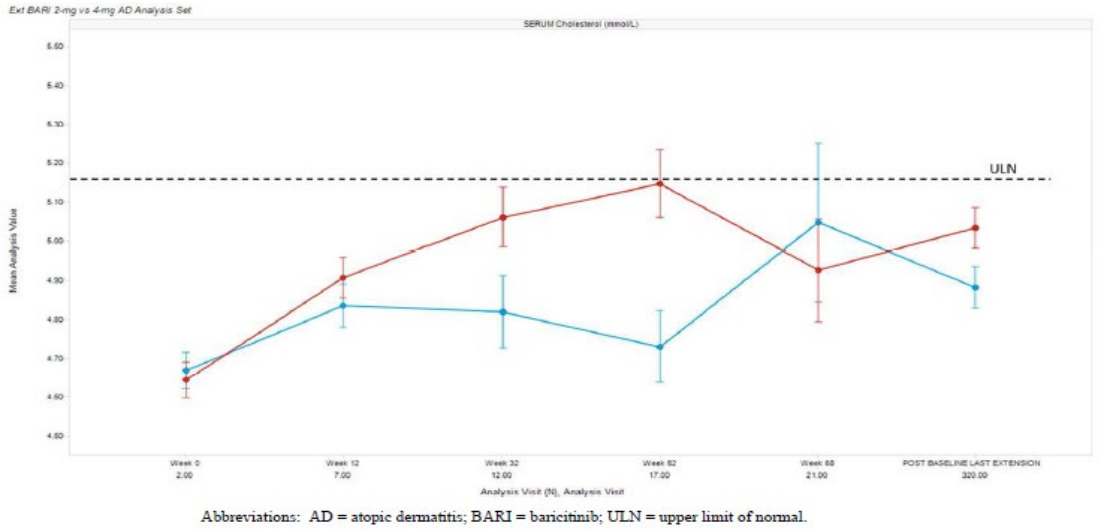


Figure 25 Mean change in cholesterol up to week 52 and beyond.

At the end of the 16-week placebo-controlled period, in the placebo group 9.6% were considered to have a high cholesterol level (maximum NCEP grade) compared to 21% in the baricitinib 2 mg and 21% in the 4 mg group. In the extended data set, 27% in the 2 mg group and 31% in the 4 mg group had a borderline high or high cholesterol (NCEP grade).

Hypercholesterolemia and hypertriglyceridemia are listed as very common and uncommon ADRs in the SmPC. It is included in the warnings that lipid parameters should be assessed approximately 12 weeks following initiation of baricitinib and then followed according to clinical guidelines for hyperlipidemia. The MAH considers the monitoring of lipids sufficient for the AD population.

In the updated database, among the patients with normal LDL cholesterol at baseline and available LDL measurements at Week 12, there were only 6 patients (0.6%) with high LDL cholesterol after Week 12. Furthermore, there were only 2 patients for whom additional lipid monitoring after Week 12 revealed high LDL cholesterol in patients without a history of hyperlipidaemia and with normal values at baseline and at Week 12. One of these patients could be considered at risk, as he was reported to be obese at baseline. The remaining 4 patients would have been subject to routine monitoring in accordance with prevailing guidelines and standard practice.

Venous Thrombolic Events

Venous thromboembolism, including PE and DVT, are listed as ADRs in the SmPC, and VTE is an important potential risk for baricitinib based on data from the RA population.

There was 1 case of PE in the baricitinib 4 mg group in the placebo-controlled period. In the extended data set another case of PE occurred in a patient treated with baricitinib 2 mg, and a case of peripheral venous thrombosis in another patient treated with 2 mg. None of these 3 patients with a VTE had a platelet count of 400 x 109 cells/L or greater at any time before the event. The patient with the peripheral venous thrombosis also had a Factor V-Leiden mutation.

The SmPC includes a warning for the occurrence of VTE: 'Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) 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 treatment should be discontinued and patients should be evaluated promptly, followed by appropriate treatment.'

The MAH proposed to add information on the signs and symptoms of a possible PE and DVT in the Patient Alert Card and the Healthcare Professional training materials. A postauthorization study is proposed to further assess the long-term safety profile in AD, including the risk of VTE.

Creatine phosphokinase changes

Increases in CPK were observed in the baricitinib RA clinical studies and have been described in association with other JAK inhibitors.

In both baricitinib 2-mg and 4-mg groups, elevations of mean CPK were observed at 4 to 8 weeks and remained stable at a higher value than baseline thereafter, including in the extended period. Dose-related increases in mean changes were seen throughout the placebo-controlled period and extended period.

Table 52 ***Shifts to maximum CTCAE grades for CPK in the placebo-controlled period***

	16-Week Placebo-Controlled Period					
	PBO (N = 650) %	BARI 2-mg (N = 392) %	BARI 4-mg (N = 397) %	BARI 4-mg vs PBO OR (p-value)	BARI 2-mg vs PBO OR (p-value)	BARI 4-mg vs BARI 2-mg OR (p-value)
Any CTCAE Grade Shift	10.1	20.1	24.2	2.9 (<0.001)	2.3 (<0.001)	1.3 (0.159)
Increase to Grade ≥1	10.4	20.1	24.8	2.9 (<0.001)	2.2 (<0.001)	1.3 (0.131)
Increase to Grade ≥2	3.0	5.3	7.0	2.5 (0.002)	1.8 (0.074)	1.4 (0.313)
Increase to Grade ≥3	1.9	2.6	3.8	2.0 (0.071)	1.4 (0.471)	1.5 (0.349)
Increase to Grade ≥4	1.1	1.0	1.8	1.9 (0.264)	1.1 (0.920)	1.7 (0.386)

Abbreviations: AD = atopic dermatitis; CPK = creatine phosphokinase; CTCAE = Common Terminology Criteria for Adverse Events; N = number of patients in the safety analysis set; OR = odds ratio.

Table SCS APP 2.7.4.7.192 in the Appendix to the Summary of Clinical Safety provides the CTCAE related to elevations in CPK.

Source tables are provided in the Appendix to the Summary of Clinical Safety: Table SCS APP 2.7.4.7.106 for the **BARI 2-mg AD PC** analysis set; Table SCS APP 2.7.4.7.107 for the **BARI 4-mg AD PC** and **BARI 2-mg AD PC vs 4-mg AD PC** analysis sets.

In the extended data set, there were more patients on 4 mg than on 2 mg with a shift, an increase grade ≥3 was seen in 3.1% on baricitinib 2 mg and 4.8% on 4 mg. In the extended data set, no patients reported AEs related to muscle symptoms in the 2 mg baricitinib group. In the 4 mg group there were 3 patients with myalgia, 2 of them had raised CPK.

Abnormal hepatic tests

While baricitinib elimination occurs primarily by renal clearance, tofacitinib and ruxolitinib (other JAK inhibitors) are mainly eliminated by hepatic metabolism. Increases in ALT and AST values have been noted with the JAK inhibitors, tofacitinib and ruxolitinib.

Treatment with baricitinib was associated with dose-dependent increases in ALT and AST. Most cases of hepatic transaminase elevations were asymptomatic and transient. In the placebo-controlled period, ALT and AST did not appear to occur more often with baricitinib as with placebo. The proportion of patients with ALT increased > 3 xULN were 0.9% in the placebo group, and 0.5% and 0.3% in the baricitinib 2 mg and 4 mg groups. In the extended period, ALT≥3 x ULN and AST ≥3 x ULN occurred in ~1% of patients on 2 mg and ~2% of patients on 4 mg. There was one occurrence of hepatic failure in a patient with multiple risk factors, and 5 cases where treatment was stopped due to hepatic-related AEs.

Discontinuation due to adverse events

In the extended period, relatively more patients in the baricitinib 4 mg group (n=21; 5.0%) than in the 2 mg group (n=9; 2.4%) permanently discontinued study drug due to adverse events.

The most frequently reported event leading to study discontinuation was dermatitis atopic (n=14). In general, the IR for AD was similar between monotherapy and TCS groups.

Temporary drug discontinuations occurred more often in the baricitinib 4 mg group (Table 53) and were usually due to adverse events (infections) and infrequently due to abnormal laboratory values.

Table 53 ***Summary of Adverse Events Leading to Permanent Discontinuation of the Study Drug in the Placebo-Controlled Period (Updated Database)***

	16-Week Placebo-Controlled Period[a]					
Preferred Term	**PBO (N = 743) n (adj %) [adj IR]**	**BARI 2 mg (N = 576) n (adj %) [adj IR]**	**BARI 4 mg (N = 489) n (adj %) [adj IR]**	**BARI 2 mg vs. PBO OR[b] (95% CI)**	**BARI 4-mg vs. PBO OR[b] (95% CI)**	**BARI 4 mg vs. BARI 2 mg OR[b] (95% CI)**
Patients with ≥1 adverse event	13 (1.4) [4.6]	10 (1.5) [4.7]	15 (2.1) [6.5]	1.0 (0.5, 2.1)	1.7 (0.8, 3.6)	1.7 (0.7, 4.0)
Toxic skin eruption	0 [0.0]	0 [0.0]	2 (0.2) [0.8]	NA	NA	NA
White blood cell count decreased	0 [0.0]	0 [0.0]	2 (0.3) [0.7]	NA	NA	NA
Abdominal pain	0 [0.0]	1 (0.1) [0.3]	1 (0.1) [0.4]	NA	NA	1.5
Asthma	0 [0.0]	0 [0.0]	1 (0.1) [0.4]	NA	NA	NA
Dermatitis atopic	1 (0.1) [0.3]	2 (0.2) [0.7]	1 (0.1) [0.3]	2.1	1.3	0.6
Eczema	1 (0.1) [0.3]	0 [0.0]	1 (0.1) [0.3]	0.0	1.3	NA
Haematuria	0 [0.0]	0 [0.0]	1 (0.2) [0.6]	NA	NA	NA
Headache	0 [0.0]	0 [0.0]	1 (0.1) [0.3]	NA	NA	NA
Lymphocyte count abnormal	0 [0.0]	0 [0.0]	1 (0.1) [0.3]	NA	NA	NA
Pulmonary embolism	0 [0.0]	0 [0.0]	1 (0.1) [0.4]	NA	NA	NA
Skin infection	0 [0.0]	0 [0.0]	1 (0.2) [0.6]	NA	NA	NA
Skin ulcer	0 [0.0]	0 [0.0]	1 (0.2) [0.6]	NA	NA	NA

Upper respiratory tract infection	0 [0.0]	0 [0.0]	1 (0.2) [0.6]	NA	NA	NA
Blood alkaline phosphatase increased	1 (0.2) [0.7]	0 [0.0]	0 [0.0]	0.0	0.0	NA
Breast cancer	1 (0.1) [0.3]	0 [0.0]	0 [0.0]	0.0	0.0	NA
Conjunctivitis allergic	0 [0.0]	1 (0.2) [0.7]	0 [0.0]	NA	NA	0.0
Dermatitis exfoliative generalised	1 (0.1) [0.3]	0 [0.0]	0 [0.0]	0.0	0.0	NA
Dizziness	2 (0.2) [0,7]	0 [0.0]	0 [0.0]	0.0	0.0	NA
Fatigue	0 [0.0]	1 (0.1) [0.3]	0 [0.0]	NA	NA	0.0
Lymphopenia	3 (0.3) [0.9]	0 [0.0]	0 [0.0]	0.0	0.0	NA
Nasopharyngitis	0 [0.0]	1 (0.2) [0.7]	0 [0.0]	NA	NA	0.0
Neutropenia	0 [0.0]	1 (0.1) [0.4]	0 [0.0]	NA	NA	0.0
Panic attack	0 [0.0]	1 (0.2) [0.7]	0 [0.0]	NA	NA	0.0
Papillary thyroid cancer	1 (0.1) [0.3]	0 [0.0]	0 [0.0]	0.0	0.0	NA
Pneumonia	1 (0.1) [0.3]	0 [0.0]	0 [0.0]	0.0	0.0	NA
Postoperative abscess	1 (0.1) [0.4]	0 [0.0]	0 [0.0]	0.0	0.0	NA
Staphylococcal infection	0 [0.0]	1 (0.1) [0.4]	0 [0.0]	NA	NA	0.0
Weight increased	0 [0.0]	1 (0.2) [0.7]	0 [0.0]	NA	NA	0.0

Abbreviations: AD = atopic dermatitis; adj % = study-size-adjusted percentage; adj IR = study-size-adjusted incidence rate (per 100 patient-years); N = number of patients in the safety analysis set; n = number of patients in the specified category; NA = not applicable; OR = Mantel-Haenszel odds ratio; vs. = versus.

[a] Study JAIW compared PBO with BARI 1 mg and 2 mg and did not include BARI 4 mg. Therefore, JAIW data are included only in the Updated BARI 2-mg versus PBO and Updated All BARI AD datasets, and are counted in this table only in the BARI 2-mg vs. PBO column. The updated database is described in Section 4.1.1.2.2.

[b] Mantel-Haenszel odds ratio stratified by study and 95% CI (calculated if ≥4 events are present in the numerator and ≥1 in the denominator). Comparator is the denominator.

Note: IR is 100 times the number of patients experiencing the AE divided by the event-specific exposure to treatment (exposure time up to the event for patients with the event and exposure time to the end of the period for patients without the event, in years). Mantel-Haenszel odds ratio stratified by study and 95% CI (calculated if ≥4 events are present in the numerator and ≥1 in the denominator). Comparator is the denominator. Preferred terms are sorted in decreasing frequency in the BARI 4-mg group.

Post marketing experience

The first marketing authorization for baricitinib occurred on 13 February 2017, for the treatment of moderate-to-severe active RA in adults. Baricitinib is currently approved for the treatment of RA in over 60 countries including in the EU, US, and Japan. The use of baricitinib in AD has not been approved, and therefore, no postmarketing data are available for patients with AD.

Since the first marketing approval for baricitinib, based on findings from postmarketing spontaneous reports, and mechanistic plausibility, 6 MedDRA PTs were added in the section 4.8 of the SmPC:

- pneumonia
- swelling face
- urticaria
- rash
- deep vein thrombosis
- pulmonary embolism

In addition, section 4.4 of the SmPC has been updated to include hypersensitivity.

2.5.1. Discussion on clinical safety

In the updated safety database, all patients from the 5 studies are included as currently Study JAIY is also included. A total of 2531 patients with AD were exposed to baricitinib at any dose (1 mg, 2 mg, 4 mg) across the entire AD baricitinib development programme (safety population). Overall exposure was 2247.4 patient-years. A total of 1106 patients had an exposure off ≥52 weeks (i.e. 43%), which is considered enough to the CHMP. Subgroup analysis by concomitant TCS (yes/no) was provided by the MAH to inform assessment of benefit/risk. Also, data were presented in which patients were followed after dose change, thus patients could provide observation time to multiple doses, all observation time on dose was accounted for.

Baseline characteristics were as expected and similar for the treatment groups. Average age and average disease duration are in line with the natural course of AD. The treatment history is in line with the intended indication.

In the 16-week placebo-controlled treatment period of pooled studies JAHG, JAHL, JAHM and JAIY, the occurrences of treatment-emergent adverse events were similar in the baricitinib 2 mg and 4 mg groups which were higher as compared to the placebo group. Adverse events were usually mild or moderate, the occurrence of severe adverse events was similar in the placebo group as compared to baricitinib 2 mg and 4 mg groups. Serious adverse events occurred more frequently in the placebo group as compared to the baricitinib 2 mg and 4 mg groups. Discontinuation from the study or the study drug due to adverse events did not occur often, but most frequently in the baricitinib 4 mg group.

In the extended treatment period, notably serious adverse events and permanent discontinuations, occurred more frequently in the baricitinib 4 mg group as compared to the 2 mg group. One death occurred in a patient who was treated with a 2 mg dose. See description below.

The most frequently reported event leading to study discontinuation was dermatitis atopic (n=14). The IR for AD was similar between monotherapy and TCS groups in the All BARI AD group. Discontinuations was higher in the 4 mg group but mostly attributed as a flare of AD.

Common adverse events

In the 16-week placebo controlled treatment period, common adverse events that occurred more frequently in baricitinib 4 mg and 2 mg treated patients, as compared to placebo, were: headache, upper respiratory tract infection, oral herpes, herpes simplex, influenza, blood CPK increased, folliculitis, upper abdominal pain. Common adverse events that appeared to occur more frequently for baricitinib 4 mg only, versus placebo, were: diarrhoea, urinary tract infection, ALT increased, and AST increased.

In the extended treatment period, common treatment-emergent adverse events overall occurred more frequently in the baricitinib 4 mg group as compared to the 2 mg group. This includes the occurrence of infections (nasopharyngitis, upper respiratory tract infections, oral herpes, herpes simplex, bronchitis) and the occurrence of abnormalities in laboratory values (blood CPK increased).

Serious adverse events and deaths

One death occurred, in a patient originally randomised to baricitinib 1 mg, who was re-randomised to 4 mg in study JAHN but received 2 mg because of a GFR<60ml/min/1.73m2. The cause of death was a GI bleed, more than 12 months after start of baricitinib and while being on 2 mg for 9 months. The

patient had no known risk factors for GI bleed, but had a low haematocrit and a low erythrocyte count at baseline, which may point to a possible earlier bleed.

In the 16-week placebo-controlled treatment period, the proportion of patients with at least one SAE was higher in the placebo group as compared to the baricitinib 2 mg and 4 mg groups. Most SAEs occurred in the SOCs of skin and subcutaneous disorders, and infections and infestations. The corresponding SAEs in the placebo group were: atopic dermatitis (n=5), exfoliative dermatitis (n=1), eczema herpeticum (n=2), eye infection (n=1), post-operative abcess (n=1). In the baricitinib 2 mg group these were: atopic dermatitis (n=2), eczema (n=1), and single occurrences of bronchitis, cellulitis, staphylococcal infection. In the baricitinib 4 mg group these were: atopic dermatitis (n=1), tonsilitis (n=1). In the higher number of SAE in the 4 mg in the extended phase were mostly of SAEs were AD, suggestive treatment failure rather than to baricitinib.

In the extended treatment period, there were 17 (IR 2.2) patients with at least one SAE in the baricitinib 2 mg group and 40 (IR 7.3) in the baricitinib 4 mg group. In the baricitinib 4 mg group there were cases of: atopic dermatitis (n=9), eczema herpeticum (n=3), pulmonary embolism (n=2), thrombophlebitis (n=2), infections (n=13), and further single occurrences.

There were no obvious differences between the two doses. Over time, the occurrence of adverse events of all kinds appears to be slightly higher with the 4 mg dose as compared to the 2 mg dose. The CHMP considered that these events are addressed in the SmPC and RMP and can be well managed in the clinic. In addition, the SmPC allows for down titration to 2mg dose if a desirable target level of AD is reached. Discontinuations due to AE were more frequent with 4 mg but mostly attributed as a flare of AD.

There were no clear clinically relevant differences in the safety profile of baricitinib either taken as monotherapy or used in combination with TCS, despite differences in SAEs and discontinuations. However, these differences are small and not consistent for the doses. Altogether, it can be concluded that the available data provide reassurance that baricitinib can be used in combination with TCS. The data presented as subgroup analysis by concomitant TCS (yes/no), does not give rise to new safety issues.

Discontinuations

The most frequently reported event leading to study discontinuation was dermatitis atopic (n=14). The IR for AD was similar between monotherapy and TCS groups in the All BARI AD group. Discontinuations was higher in the 4 mg group but mostly attributed as a flare of AD.

AE of special interest

Infections and infestations did occur more frequently in baricitinib treated patients compared to patients on placebo. There were no dose differences in the placebo-controlled phase and in the extended periods. There were no clinically relevant differences between monotherapy and TCS.

Based on the initial submission data and data updated to better attribute events to dose, serious infections infrequently occurred in the placebo-controlled period, 4 in the placebo group, 2 in the 2 mg and 1 in the 4 mg group. Herpes zoster did not appear to occur more frequently in baricitinib treated patients.

Since infections are the key identified risks for baricitinib, the posology section of the SmPC indicates that a lower dose (2-mg) may be appropriate for patients with a history of chronic or recurrent infections. No changes for the SmPC regarding infections are proposed with the current application which was endorsed by the CHMP.

The risk for VTE remains a concern for JAK inhibitors such as baricitinib. PE/DVT is listed as ADR and the SmPC includes precautions (section 4.4). The MAH proposed to add information on the signs and symptoms of a possible PE and DVT in the Patient Alert Card and the Healthcare Professional training materials; this proposal was endorsed by the PRAC / CHMP. A post authorisation study was proposed to further assess the long-term safety profile in AD, including the risk of VTE which was endorsed by the PRAC / CHMP. Cf RMP Section 2.6.

The adverse events of special interest generally occurred in similar patterns as is known from RA. In AD, no MACE or cardiac events occurred but the AD population is relatively young and the study population was on average 35 years. The effect of a prolonged high level of lipids due to baricitinib in AD is uncertain. According to the current SmPC, lipid parameters should be monitored 12 weeks after initiation of treatment and thereafter according to international clinical guidelines for hyperlipidaemia. In the updated database, there were only 6 new patients (0.6%) with high LDL cholesterol after Week 12. Only two out of these 6 patients did not have a history of hyperlipidaemia. The current warning in the SmPC is considered adequate by the CHMP.

Blood lipid changes were present in baricitinib treated patients as compared to placebo. Mean total cholesterol, LDL and HDL were elevated in baricitinib treated patients in the placebo-controlled period, which remained in the extended treatment period in both dose groups. Increase in cholesterol occurred earlier in the 4 mg group. After 16 weeks of treatment, 21% of baricitinib 2 mg and also 21% of patients on 2 mg had an increase to borderline or high cholesterol, as compared to 10% in placebo treated patients.

Lipid AEs as well as MACE will be closely followed in the post authorisation setting.

The data in the AD clinical program indicate that CPK increases greater than 5 times the ULN is a common ADR. Therefore, the MAH proposed that the frequency for this ADR in the EU SmPC is changed from uncommon to common. This proposal was endorsed by the CHMP. In AD patients, a dose relationship was seen following extended exposure; however, the majority of cases were transitory, did not result in treatment discontinuation, and were largely asymptomatic, with no reports of rhabdomyolysis. A post-authorization study has been proposed by the MAH to further assess the long-term safety profile in AD, including the risk of rhabdomyolysis. This is endorsed by PRAC/CHMP. Cf RMP Section 2.6.

Elevations of 3 or more times the ULN for ALT and AST are respectively considered common and uncommon ADRs in the established safety profile and are included in the SmPC. Monitoring of hepatic transaminases is recommended before initiation of treatment and thereafter. No changes were proposed to the SmPC. The MAH proposed to follow the risk for drug-induced liver injury in a post-marketing study which was endorsed by the PRAC / CHMP.

Malignancies occurred in 2 cases in the placebo group during the placebo-controlled phase. In the all-exposed population, 4 cases of malignancies occurred (2 cases of Bowen’s disease, basal cell carcinoma, keratoacanthoma).

The safety data from the AD and RA studies have been integrated to provide the frequencies of adverse drug reactions (ADRs) for inclusion in Section 4.8 of the SmPC. In addition, the MAH committed to further shorten section 4.8 (both the AD and RA indications) of the SmPC. Considering the consistent safety profile for the RA and AD indications, the MAH should make an integrated proposal for both AD and RA indications for the purpose of readability and ease of use of Section 4.8 of the SmPC and Section 4 of the PL. The MAH should submit the revised product information at the earliest regulatory opportunity.

Headache was added to the SOC "Nervous system disorders" with a frequency "commun". Abdominal pain was added to the SOC "Gastrointestinal disorders" with a frequency "commun". The frequency of the ADR "Acne" and "Creatine phosphokinase increased > 5 x ULN" were changed from uncommon to common. Those changes were endorsed by the CHMP.

2.5.2. Conclusions on clinical safety

In placebo-controlled atopic dermatitis clinical trials, for up to 16 weeks, the most commonly reported ADRs occurring in ⩾ 2 % of patients treated with Olumiant monotherapy or in combination with topical corticosteroids were similar to those observed in rheumatoid arthritis, except for increased LDL cholesterol (13.2 % versus 33.6 % in RA) and herpes simplex (6.1 %). In patients treated with baricitinib in the atopic dermatitis clinical trials, the frequency of herpes zoster was very rare (1.4% in RA).

The pattern of AEs in AD is in line with what can be expected with baricitinib treatment based on the RA experience. SAEs and discontinuations due to AEs were infrequent. The dataset did not reveal new safety signals in comparison to previous assessment and already known safety profile from the patients with RA treated with baricitinib. There were more discontinuations with 4mg but mostly attributed as a flare of AD.

There were no clear clinically relevant differences in the safety profile of baricitinib either taken as monotherapy or used in combination with TCS, despite differences in SAEs and discontinuations. However, these differences are small and not consistent for the doses.

There were no obvious differences between the two doses. Over time, the occurrence of adverse events of all kinds appears to be slightly higher with the 4 mg dose as compared to the 2 mg dose. The CHMP considered that these events are addressed in the SmPC and RMP and can be well managed in the clinic. In addition, the SmPC allows for down titration to 2mg dose if a desirable target level of AD is reached.

In conclusion, the CHMP considers that the safety of baricitinib in the claimed indication is supported by the data submitted.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 8.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 8.1 with the following content:

Safety concerns

Important identified risks	• Herpes zoster
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 • VTE
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

Pharmacovigilance plan

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 1 - Imposed mandatory additional PV activities that are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional PV 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 PV 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	Important Identified Risks: • Herpes zoster Important potential risks: • Serious and opportunistic infections (including tuberculosis, *Candida* infections, PML)	Study progress reports	Annually in PBRER/PSUR submitted in April of each year after start of data collection
			Final study report	*31 December 2031*

	(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: 3) Describe the incidence of the above outcomes in very elderly patients (aged ≥75 years).	• MACE as an outcome of hyperlipidaemia • Malignancies (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers) • Potential for DILI • VTE • Myelosuppression (agranulocytosis) • Myopathy including rhabdomyolysis • GI perforation Missing information: • Long-term safety • Use in very elderly (≥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	Important Identified Risks • Herpes zoster Important potential risks: • Serious and opportunistic infections (including tuberculosis, *Candida* infections, PML) • MACE as an outcome of hyperlipidaemia	*Study progress reports* *Final Study Report*	Annually in PBRER/PSUR submitted in April of each year after start of data collection *30 June 2030*

	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 elderly patients (aged ≥75 years old).	• Malignancies (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers) • Potential for DILI • VTE • Myelosuppression (agranulocytosis) • Myopathy including rhabdomyolysis • GI perforation Missing information: • Long-term safety • Use in very elderly (≥75 years)		
I4V-MC-B010 Assessment of the Effectiveness of the PAC and HCP Educational Material (Ongoing)	**Cross-sectional survey:** Primary Objective: 1) 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 HCPs, regarding: • Use in pregnancy • Infections • Lipids	Important Identified Risks • Herpes zoster Important Potential Risks: • Serious and opportunistic infections (including tuberculosis, *Candida* infections, PML) • MACE as an outcome of hyperlipidaemia • Foetal malformation following exposure in utero Missing Information	*Final Study Report*	31 July 2020

		• Use in pregnancy and breastfeeding		
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: 3) To monitor the incidence rates of the aggregate outcomes	Important identified risks: • Herpes zoster 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 • VTE • 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 2027

	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), and VTE among patients with long-term exposure to baricitinib	Important identified Risks: • Herpes zoster 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*	Study progress reports Final study report	Annually in PBRER/ PSUR submitted in April of each year 31 March 2024

	compared to patients with long-term exposure to other medications used for moderate-to-severe RA, as possible given the data available in the BSRBR, RABBIT, and ARTIS registries. 2) To describe the occurrence of the following individual outcomes: lymphoma, herpes zoster, opportunistic infections, rhabdomyolysis, agranulocytosis, PML, GI perforations, and evidence of DILI.	infections, PML), • Myelosuppression (agranulocytosis) • Myopathy including rhabdomyolysis • Potential for drug-induced liver injury • GI perforation • MACE as an outcome of hyperlipidaemia • VTE		
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

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 Important Potential Risks: • Serious and opportunistic infections (including tuberculosis, *Candida* infections, PML) • MACE as an outcome of hyperlipidaemia • Foetal malformation following exposure in utero • VTE	Final study report	30 September 2023

Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Herpes zoster	[Routine risk minimisation measures:] SmPC Section 4.8 • SmPC section 4.4 recommends that if an infection develops, the patient should be monitored carefully, and Olumiant should be temporarily interrupted and not be resumed until the infection resolves. There is a further recommendation that, prior to starting treatment, all patients 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	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection • Herpes zoster follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to monitor the incidence of herpes zoster in patients exposed to baricitinib RA: • 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 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	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *Candida* infection follow-up form • Pneumonia follow-up form • Viral reactivation follow-up form • Unspecified infection follow-up form • Extrapulmonary TB follow-up form • Pulmonary TB follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to compare the incidence of serious and opportunistic infections (including TB, *Candida*, and PML) in patients exposed to baricitinib with patients exposed to other medications used for moderate-to-severe: RA: • National RA registries, such as Corrona • EU registries • An observational database study • Nordic healthcare study AD: • Nordic healthcare study

	their doctor or pharmacist before and during treatment with Olumiant if they have an infection or if they often get infections. It also advises patents that they should tell their doctor if they get signs of TB, herpes zoster or have, or have previously had, hepatitis B or C. [Additional risk minimisation measures:] • Healthcare Professional Educational Material • Patient Alert Card	
Myelosuppression (agranulocytosis)	[Routine risk minimisation measures:] SmPC Sections 4.2,4.4, 4.8, and 5.3 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	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Cardiac disorders follow-up form • Cerebrovascular accident follow-up form • Mortality follow-up form

	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	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. 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 your doctor or pharmacist for advice before taking the medicine • States that patients should use an effective method of contraception to avoid becoming pregnant during	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Pregnancy data collection – maternal follow-up form • Pregnancy data collection – paternal follow-up form • Pregnancy outcome - maternal follow-up form • Pregnancy outcome - paternal follow-up form 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

	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	
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 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	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: • 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	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:

	malignancy and MACE. [Additional risk minimisation measures:] None.	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. [Additional risk minimisation measures:] None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Observational post-marketing safety studies to monitor the incidence of use in very elderly (≥75 years) in patients exposed to baricitinib: RA: • National RA registry, such as Corrona • 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	[Routine risk minimisation measures:] SmPC Section 4.4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

lymphoproliferative disease	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	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:] None	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)

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, 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

The guide for HCPs and the patient alert card in the Annex II were updated to reflect the risk of deep venous thrombosis (DVT) and pulmonary embolism (PE).

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s).

Minor editorial changes were brought to the Labelling. Furthermore, the Annex II is brought in line with the latest QRD template version 10.1.

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:

The new indication targets a similar patient demographic as the representative test population that was used for the user testing performed for the initial marketing authorisation application. The proposed text modifications resulting from the new indication are minor and do not include text that is significantly different from that already user tested.

3. Benefit-Risk Balance

3.1. Therapeutic Context

This variation application concerns baricitinib for a proposed new indication in AD:

"Olumiant is indicated for the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy."

3.1.1. Disease or condition

Atopic dermatitis (eczema) is a chronic relapsing, pruritic, inflammatory skin disease that occurs most frequently in children but also occurs in adults. While in children most cases of AD spontaneously resolve, AD can persist or start in adulthood (Thomsen 2014). It is estimated that in Europe, 2% to 7% of adults have AD and the proportion of adults with moderate to severe AD is estimated at 30%, with 1 in 4 adults with AD reporting adult-onset of the disease (Sacotte and Silverberg 2018; Diepgen et al. 2016; Bieber and Straeter 2015). The pathomechanism of AD includes skin barrier defects, immune dysregulation, and genetic predisposition (Boguniewicz and Leung 2011). The main manifestations of AD are eczematous skin lesions, itch, skin pain, sleep disturbances, it is associated with other atopic conditions such as asthma and allergic rhinitis (Silverberg 2018). Itch is the central and debilitating manifestation. AD may lead to difficult to control scratching and superimposed skin inflammation and infections, sleep disturbances, functional impairment and mental distress, feelings of anxiety and depression (Jeon et al. 2017, Yu et al. 2016, Thyssen et al. 2019, Boguniewicz et al. 2017, Thyssen et al. 2018, Ronnstad et al. 2018).

3.1.2. Available therapies and unmet medical need

The aim of medical treatment of AD is symptomatic, to bring signs and symptoms of AD under control (Wollenberg et al. 2018). Patients with mild disease are generally managed with emollients and mild-to moderate-potency topical corticosteroids (TCS). Topical calcineurin inhibitors are considered as an alternative or adjunct treatment to TCS, especially when treatment with TCS is either inadvisable or not possible and when steroid-sparing treatment is needed in sensitive areas, such as face and skin folds. However, patients with moderate to severe AD require additional therapies to control their skin inflammation and alleviate the most bothersome symptoms. These additional therapies include phototherapy, high-potency TCS, and, eventually when topical options fail to control the disease, systemic treatments.

Currently, 2 systemic therapies are approved for patients with moderate to severe AD: ciclosporin (oral systemic agent approved only for severe patients), and dupilumab (SC injection). Ciclosporin is only approved for patients with severe AD and due to its safety profile, it is recommended for intermittent use (Ciclosporin SmPC). Dupilumab is approved for patients with moderate and severe AD; the most

common side effects, when used in treatment of AD, are injection-site reactions (≥10%), conjunctivitis and blepharitis (Dupixent EPAR).

Staquis (an ointment with a PDE-4 inhibitor) was recently approved for treatment of mild to moderate atopic dermatitis in adults and paediatric patients from 2 years of age with ≤ 40% body surface area (BSA) affected.

Other therapies are not centrally authorised but are approved in individual member states and recommended by AD treatment guidelines (Wollenberg et al. 2018):

- Oral glucocorticosteroids is intended for severe AD (Wollenberg et al. 2018).
- PUVA is intended for severe AD (Wollenberg et al. 2018).

Non pharmacological approaches are recommended in moderate to severe AD according to AD treatment guidelines (Wollenberg et al. 2018).

In addition to approved therapies, current AD guidelines and expert advice recommend off-label use of other oral therapies, such as systemic corticosteroids, methotrexate, azathioprine, and mycophenolate mofetil (Wollenberg et al. 2018b).

For patients with moderate to severe AD for whom treatment with TCS and or TCIs and/or systemic therapies is insufficient, treatment options are limited and therefore there is a need for new treatment options. An advantage for patients with moderate to severe AD may be that baricitinib is taken orally once daily.

3.1.3. Main clinical studies

Baricitinib doses for the main clinical studies were primarily chosen based on the results of 'phase 2' study JAHG. The main clinical studies were randomised double-blinded controlled trials performed in adult patients with moderate to severe AD for whom previous topical treatment and/or systemic treatment was insufficient or not tolerated (Table 2). These studies were: two identical 16-week monotherapy studies comparing baricitininb 1 mg, 2 mg, 4 mg versus placebo (JAHL and JAHM); one 16-week 'add-on' combination therapy study comparing baricitinib 2mg +TCS and 4 mg +TCS versus placebo +TCS (JAIY); an ongoing 104-week extension study (JAHN) including dose continuation of 2 mg and 4 mg in responders and partial responders for in total 52 weeks, to be followed by a randomised down-titration/stop sub-study.

Study JAHN is ongoing, all patients coming from studies JAHL and JAHM reached week 52, but patients coming from study JAIY have not yet reached 52-weeks of follow-up, about 50% of them reached week 24.

Study JAIN is a supportive ongoing Phase 3 study investigating the efficacy and safety of baricitinib in patients who experienced failure with ciclosporin or are intolerant to or have a contraindication to ciclosporin. Final results of the 16-week placebo-controlled phase are available. Similar to Study JAIY, patients in Study JAIN are permitted to use low- and moderate-potency TCS as concomitant therapy throughout the study.

3.2. Favourable effects

In all three studies (JAHL, JAHM, JAIY), baricitinib 4 mg was statistically significant more effective than placebo in reaching IGA 0 or 1 at week 16 (with a ≥2 points improvement from baseline), while adjusting for multiplicity. Baricitinib 2 mg was more effective than placebo in reaching IGA 0 or 1 at

week 16 in the monotherapy studies, but not in the combination therapy study. The 1 mg dose was not more effective than placebo. The results were supported by sensitivity analyses.

In the monotherapy studies JAHL and JAHM, responses in primary and secondary outcomes were numerically higher when it was allowed for rescue treatment (usually TCS) in the analyses. Responses in IGA 0 or 1 were 6% to 8% higher if results were analysed while allowing for rescue treatment.

Response sizes of secondary outcomes (EASI75, improvement ≥4 points in the Itch NRS, change in ADSS item 2, SCORAD75, Skin pain NRS) were generally similar in the identical monotherapy studies JAHL and JAHM and usually numerically higher in the combination study JAIY. The statistical tests corrected for multiplicity in the main secondary outcomes were supportive for the baricitinib 4 mg dose in all three studies, the support for the 2 mg dose is less robust and it was not supported by the primary and secondary outcomes in the combination therapy study.

Treatment effects in subgroups (weight, age, gender, race, disease severity, and previous treatment, including immunosuppressants) were consistent with the results in the overall study population.

The effect after 16 weeks appears to be largely maintained over 52 weeks, similar in the patients continuing 2 mg and 4 mg, whether on monotherapy or on combination therapy.

Maintenance results on IGA 0 or 1 and the tendency for similar or larger responses in the 2 mg as compared to the 4 mg group are also reflected in EASI75 and in Itch-response.

Previous failure of ciclosporin did not seem to have a negative influence on the treatment effect, at least for the 4 mg dose. In case of previous use of TCI, the treatment effect may be somewhat smaller if on monotherapy with baricitinib. The number of patients having used dupilumab before was small, but there was no indication that treatment with baricitinib would be ineffective if patients had previously used dupilumab. The CHMP considered that these results have no further consequences for the SmPC yet, as treatment effects appear to be present across all subgroups. Study JAIN was specifically performed in patients with ciclosporin failure of for whom ciclosporin is contra-indicated, though this study standardly included concomitant TCS with baricitinib or placebo. Its results confirmed the efficacy of baricitinib in this subpopulation.

3.3. Uncertainties and limitations about favourable effects

The maintenance data are not complete for the patients coming from study JAIY, about 50% of the patients reached week 24. However, the patients from the monotherapy studies have completed 52 weeks of follow-up. In the patients from monotherapy as well as the patients from the combination therapy, it was shown in all main outcomes that effects are basically maintained, similarly for the 2 mg and 4 mg doses. The CHMP considered that more data of study JAIY are unlikely to change this assessment.

Though effects were small and TCS was much used as rescue treatment when baricitinib was used as monotherapy, the effects of baricitinib as monotherapy are considered of clinical relevance by the CHMP and in line with the proposed indication.

Because maintenance of effects in (partial) responders on 4 mg are well maintained with the 2 mg dose, the SmPC includes the opportunity to lower the dose to 2 mg if a desirable target level of AD is reached.

The effect of down-titration or stop is not yet known for baricitinib in the treatment of AD. This is studied in period 2 of study JAHN, which is ongoing. It is expected that these results will be used to update the information in section 5.1 of the SmPC, when final results are available in 2023.

3.4. Unfavourable effects

In the updated safety database patients from the 5 studies are included as currently Study JAIY is also included. A total of 2531 patients with AD were exposed to baricitinib at any dose (1 mg, 2 mg, 4 mg) across the entire AD baricitinib development programme (safety population). Overall exposure was 2247.4 patient-years. A total of 1106 patients had an exposure off ≥52 weeks (i.e. 43%), which is sufficient for assessing safety. Subgroup analysis by concomitant TCS (yes/no) is also provided. Data were analysed 'as randomised' and 'as treated' with observation time not being censored after a dose change. Thus, patients could contribute exposure time to more than one dose and consequently, all AEs occurring with 2 mg or 4 mg could be attributed to dose. The overall results of the 'as randomised' and the 'as treated' extended data sets pointed to the same results, though the overall incidence rate of AEs was lower for the 4 mg "as treated" group, versus those who received the 2 mg dose. However, the incidence of serious AEs and treatment withdrawal due to AEs was higher for the 4 mg dose.

Currently, the number of patients and duration of exposure were sufficient by the CHMP to assess long-term safety.

In placebo-controlled atopic dermatitis clinical trials, for up to 16 weeks, the most commonly reported ADRs occurring in ⩾ 2 % of patients treated with Olumiant monotherapy or in combination with topical corticosteroids were similar to those observed in rheumatoid arthritis, except for increased LDL cholesterol (13.2 % versus 33.6 % in RA) and herpes simplex (6.1 %). In patients treated with baricitinib in the atopic dermatitis clinical trials, the frequency of herpes zoster was very rare (1.4% in RA).

There were more discontinuations with 4mg but mostly attributed as a flare of AD.

The safety data from the AD and RA studies have been integrated to provide the frequencies of adverse drug reactions (ADRs) for inclusion in Section 4.8 of the SmPC.

Headache was added to the SOC "Nervous system disorders" with a frequency "common". Abdominal pain was added to the SOC "Gastrointestinal disorders" with a frequency "common". The frequency of the ADR "Acne" and "Creatine phosphokinase increased > 5 x ULN" were changed from uncommon to common. Those changes were endorsed by the CHMP.

The safety dataset did not reveal new safety signals in comparison to previous assessment and already known safety profile from the patients with RA treated with baricitinib.

There were no clear clinically relevant differences in the safety profile of baricitinib either taken as monotherapy or used in combination with TCS, despite differences in SAEs and discontinuations. However, these differences are small and not consistent for the doses.

The largest differences between baricitinib 4 mg and 2 mg versus placebo can be noted in infections (URTI, Herpes simplex) headache, blood CPK increased, and upper abdominal pain. Over time, the occurrence of serious adverse events like thrombotic events appears to be slightly higher with the 4 mg dose as compared to the 2 mg dose. The CHMP considered that these events are addressed in the SmPC and RMP and can be well managed in the clinic. In addition, the SmPC allows for down titration to 2mg dose if a desirable target level of AD is reached.

3.5. Uncertainties and limitations about unfavourable effects

Infections and infestations did occur more frequently in baricitinib treated patients compared to patients on placebo. There were no dose differences in the placebo-controlled phase and in the extended periods. There were no clinically relevant differences between monotherapy and TCS. Serious infections

infrequently occurred in the placebo-controlled period, 4 in the placebo group, 2 in the 2 mg and 1 in the 4 mg group. Herpes zoster did not appear to occur more frequently in baricitinib treated patients. Since infections are the key identified risks for baricitinib, the posology section of the SmPC indicates that a lower dose (2-mg) may be appropriate for patients with a history of chronic or recurrent infections. No changes for the SmPC regarding infections are proposed with the current application which was endorsed by the CHMP.

Malignancies occurred in 2 cases in the placebo group during the placebo-controlled phase. In the all-exposed population, 4 cases of malignancies occurred (2 cases of Bowen's disease, basal cell carcinoma, keratoacanthoma).

Venous thrombolic events occurred in three patients treated with baricitinib. There was one case of PE during the placebo-controlled period, in a patient treated with baricitinib 4 mg. In the extended period, an additional case of PE occurred in the 4 mg group and a case of DVT in the 2 mg group. A warning that baricitinib should be used with caution in patients at risk for VTE is already included in the SmPC. The MAH proposed to add information on the signs and symptoms of a possible PE and DVT in the Patient Alert Card and the Healthcare Professional training materials; this proposal was endorsed by the PRAC / CHMP. A post authorisation study was proposed to further assess the long-term safety profile in AD, including the risk of VTE which was endorsed by the PRAC / CHMP. Cf RMP Section 2.6.

MACE did not occur in the placebo-controlled period nor in the extended treatment period. There were few cases with hypertension as adverse events, not clearly different in occurrence for placebo and baricitinib treated groups. The effect of a prolonged high level of lipids due to baricitinib in AD is uncertain. According to the current SmPC, lipid parameters should be monitored 12 weeks after initiation of treatment and thereafter according to international clinical guidelines for hyperlipidaemia. In the updated database, there were only 6 new patients (0.6%) with high LDL cholesterol after Week 12. Only two out of these 6 patients did not have a history of hyperlipidaemia. The current warning in the SmPC is considered adequate by the CHMP.

Blood lipid changes were present in baricitinib treated patients as compared to placebo. Mean total cholesterol, LDL and HDL were elevated in baricitinib treated patients in the placebo-controlled period, which remained in the extended treatment period in both dose groups. Increase in cholesterol occurred earlier in the 4 mg group. After 16 weeks of treatment, 21% of baricitinib 2 mg and also 21% of patients on 2 mg had an increase to borderline or high cholesterol, as compared to 10% in placebo treated patients.

Lipid AEs as well as MACE will be closely followed in the post authorisation setting.

Increases in ALT and AST values (>3 times ULN) occurred in 3 and 4 cases on 4 mg in the placebo-controlled period, and did not occur in placebo or 2 mg groups. In the extended treatment period, there were few cases of ALT increased in the 2 mg group, and 9 cases of ALT increased and 8 cases of AST increased in the 4 mg group. Elevations of 3 or more times the ULN for ALT and AST are respectively considered common and uncommon ADRs in the established safety profile and are included in the SmPC. Monitoring of hepatic transaminases is recommended before initiation of treatment and thereafter. No changes were proposed to the SmPC. The MAH proposed to follow the risk for drug-induced liver injury in a post-marketing study which was endorsed by the PRAC / CHMP.

The data in the AD clinical program indicate that CPK increases greater than 5 times the ULN is a common ADR. Therefore, the MAH proposed that the frequency for this ADR in the EU SmPC is changed from uncommon to common. This proposal was endorsed by the CHMP. In AD patients, a dose relationship was seen following extended exposure; however, the majority of cases were transitory, did not result in treatment discontinuation, and were largely asymptomatic, with no reports

of rhabdomyolysis. A post-authorization study has been proposed by the MAH to further assess the long-term safety profile in AD, including the risk of rhabdomyolysis. Cf RMP Section 2.6.

There were no clear clinically relevant differences in the safety profile of baricitinib either taken as monotherapy or used in combination with TCS, despite differences in SAEs and discontinuations. However, these differences are small and not consistent for the doses.

Table 54 ***Effects table for Baricitinib 4 mg and 2 mg for the treatment of Atopic dermatitis in the 16-week placebo-controlled phase***

Effect	Short description	Unit	Regimen	Placebo	Bari 2 mg	Bari 4 mg	Uncertainties / Strength of evidence	References
Favourable Effects								
IGA 0/1	'Clear' or 'almost clear' according to Investigator's Global Assessment (and ≥2 points improvement)	%	Mono +TCS	4.7 14.7	11.0 23.9	15.3 30.6	Effects for 4 mg shown in 2 duplicate placebo-controlled monotherapy trials and one trial of bari add-on to TCS on similar set of outcomes	Tables 5.4.2.7 - 9
EASI75	≥75% improvement in EASI score from baseline	%	Mono +TCS	7.5 22.9	18.3 43.1	23.0 47.7	Rescue treatment with TCS was much used in the 'monotherapy' trials Responses in IGA 0/1 are numerically low, but results are robust over outcomes and trials. Maintenance data are not complete	Table 5.4.2.4 Table 10.2.1
ΔItchNRS≥4	≥4 points improvement in Itch NRS from baseline	%	Mono +TCS	6.0 20.2	13.6 38.1	23.0 47.7		
Unfavourable Effects								
Adverse events		%	Mono and combi	51.5	56.9	57.7	Safety follow-up was not complete for the 52 week period, notably not for the combination therapy study.	Table 5.5.6
Serious adverse events		%		2.9	1.6	1.8		
Infections		%		28.6	34.3	34.0		Table 5.5.7 Table 5.5.11 AESI section
Serious infections		%		0.7	0.4	0.3		
Thrombocytosis	>400 x 10^9 cells/L	%		3.5	9.3	12.8		
ALT raised	ALT >3xULN	%		0.9	0.5	0.3		
High/borderline cholesterol	LDL-C ≥5.17 mmol/L	%		9.6	21.0	20.8		

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The in/exclusion criteria and disease characteristics of the included patients are in alignement with a population with moderate to severe atopic dermatitis who are candidates for systemic treatment, which is in line with the indication that is aimed for.

Baricitinib 4 mg is the most effective dose to induce a response in patients with moderate to severe AD, with or without concomitant TCS. In both monotherapy studies and in the combination therapy study, baricitinib 4 mg was statistically significantly more effective than placebo regarding IGA 0 or 1 at week 16 (primary outcome). Baricitinib 2 mg was statistically significantly more effective than placebo in reaching IGA 0 or 1 in the monotherapy studies, but not in the combination therapy study. Baricitinib 1 mg was not more effective than placebo. The onset of effect in IGA 0 or 1 appears between 2 – 4 weeks, for baricitinib 2 mg and 4 mg and with or without concomitant TCS, which is considered quite early.

In all three studies, the results for IGA 0 or 1 are supported by all other main secondary outcomes including EASI75, Itch, and also sleep disturbance (ADSS), patient assessed skin manifestations (SCORAD, POEM), Skin pain, health related quality of life (DLQI), anxiety and depression (HADS). It is therefore considered that the treatment effects found for baricitinib are robust over primary and main secondary outcomes, that the treatment effects are largest for the baricitinib 4 mg dose and if used with TCS, that clinical relevance of the treatment effect is supported by the effects on itch, sleep disturbance, skin pain, health-related quality of life and anxiety and depression.

Results of maintenance of effects are complete for the patients who became (partial) responders on monotherapy and are supported by the results of the patients who became (partial) responders on combination therapy. Because similar maintenance of effect is shown of 4 mg and 2 mg, this means that there is an opportunity to lower the dose to 2 mg if a desirable target level of AD is reached, which is included in the SmPC. More information will be available upon completion of the down-titration/stop sub study in period 2 of study JAHN (ongoing – the CHMP recommends to submit the final study results).

For the baricitinib 4 mg dose, the responses in IGA 0 or 1 were 14% and 17% in the monotherapy studies and 31% in the combination therapy study. These responses (and the differences with placebo) may be appreciated as relatively low, seen numerically. This treatment effect also falls below the a priori expectations as derived from dose-finding study JAHG. Notably, in both combination therapy studies, JAHG and JAIY, the treatment effect was higher than in the monotherapy studies. Nevertheless, it is considered that the size of the treatment effects in IGA 0 or 1 and the overall trade-off are of clinical relevance. Patients with IGA 0 or 1 are 'clear' or 'almost clear' and the results are supported by other outcomes that are considered relevant for patients such as partial response, EASI75, Itch-response, skin pain, POEM, DLQI. The treatment effect can be if needed, enhanced if baricitinib is used in combination with TCS, which is included in the SmPC.

Based on the prognostic analysis, substantiated advice is given in the SmPC to stop treatment if insufficient response is achieved at week 8 (instead of week 12). This prevents unnecessary exposure to baricitinib. Single predictors or combinations thereof, analysed at weeks 2, 4 and 8, were assessed for their negative predictive value in EASI75 and Itch NRS $\geq$ 4 and IGA 0,1 response at week 16. These analyses consistently demonstrated that the highest sensitivity and negative predictive value were obtained at week 8 of treatment.

The safety dataset did not reveal new safety signals in comparison to previous assessment and already known safety profile from the patients with RA treated with baricitinib.

There were no clear clinically relevant differences in the safety profile of baricitinib either taken as monotherapy or used in combination with TCS, despite differences in SAEs and discontinuations. However, these differences are small and not consistent for the doses.

Currently, the number of patients and duration of exposure were sufficient to assess long-term safety, also in the follow-up data set events could now attributed to dose. The overall results of the 'as randomised' and the 'as treated' extended data sets basically pointed to the same results. The safety results of the 16-week placebo-controlled phase (see Effects Table 54) were unaffected.

The largest differences between baricitinib 4 mg and 2 mg versus placebo can be noted in infections (URTI, Herpes simplex) headache, blood CPK increased, and upper abdominal pain. Over time, the occurrence of serious adverse events like thrombotic events appears to be slightly higher with the 4 mg dose as compared to the 2 mg dose. The CHMP considered that these events are addressed in the SmPC and RMP and can be well managed in the clinic. In addition, the SmPC allows for down titration to 2mg dose if a desirable target level of AD is reached.

Up to now, the nature of adverse events as occurred in the atopic dermatitis studies is generally in line with what is already known, from the treatment with baricitinib in RA. Patients with atopic dermatitis are younger and used considerable less systemic immunosuppressant comedication, as compared to RA patients, which may give rise to a lower occurrence e.g. for infections and herpes zoster. AD tends to be self-limiting if patients age, and life-long treatment may not be necessary which may be protective against adverse events that develop over extended exposure and at higher age.

Three (3) occurrences of VTE appeared in this relatively young population. A warning that baricitinib should be used with caution in patients at risk for VTE is already included in the SmPC. The MAH proposed to add information on the signs and symptoms of a possible PE and DVT in the Patient Alert Card and the Healthcare Professional training materials; this proposal was endorsed by the PRAC / CHMP. A post authorisation study was proposed to further assess the long-term safety profile in AD, including the risk of VTE which was endorsed by the PRAC / CHMP. Cf RMP Section 2.6.

3.6.2. Balance of benefits and risks

The benefit/risk balance of Olumiant (baricitinib) for the treatment of adult patients with moderate to severe atopic dermatitis who are candidates for systemic therapy is positive.

It is considered that baricitinib 4 mg is the most effective dose, and that the effects can be enhanced by concomitant use of TCS. Though the treatment effects of baricitinib 4 mg as monotherapy can be valued as numerically small, they still are considered of being clinically relevant by the CHMP. In clinical practice, concomitant use of TCS can be expected and is reflected in the SmPC. There is an opportunity to lower the dose to 2 mg if a desirable target level of AD is reached, which is also reflected in the SmPC. More information will be available upon completion of the down-titration/stop substudy in period 2 of study JAHN (ongoing). Based on the prognostic analysis, substantiated advice is given in the SmPC to stop treatment if no response is reached at week 8.

The safety data set and attribution of AEs to dose (2 mg and 4 mg) did not reveal new safety signals in comparison to previous assessment and already known safety profile from the patients with RA treated with baricitinib.

There were no clear clinically relevant differences in the safety profile of baricitinib either taken as monotherapy or used in combination with TCS, despite differences in SAEs and discontinuations. These

differences are small and not consistent for the doses. Altogether, the CHMP concluded that the available data provide reassurance that baricitinib can be used in combination with TCS with an acceptable additional risk compared to treatment with monotherapy.

The CHMP was reassured as the pattern of adverse events that occurred in the atopic dermatitis studies is generally in line with what is already known, from the treatment with baricitinib in RA. Over time, the occurrence of adverse events of all kinds appears to be slightly higher with the 4 mg dose as compared to the 2 mg dose. The CHMP considered that these events are addressed in the SmPC and RMP and can be well managed in the clinic. In addition, the SmPC allows for down titration to 2mg dose if a desirable target level of AD is reached.

For patients with moderate to severe AD for whom treatment with TCS and or TCIs and/or systemic therapies is insufficient, treatment options are limited, and therefore there is a need for new treatment options. An advantage for patients with moderate to severe AD may be that Olumiant is taken orally once daily.

3.7. Conclusions

The benefit/risk balance of Olumiant (baricitinib) for the treatment of adult patients with moderate to severe atopic dermatitis who are candidates for systemic therapy is positive.

4. Recommendations

Outcome

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

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

Extension of Indication to include a new indication in the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy for Olumiant; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.

The guide for HCPs and the patient alert card in the Annex II were updated to reflect the risk of deep venous thrombosis (DVT) and pulmonary embolism (PE).

Minor editorial changes were brought to the Labelling. Furthermore, the Annex II is brought in line with the latest QRD template version 10.1.

The RMP version 8.1 has also been submitted and adopted.

In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.

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

Amendments to the marketing authorisation

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

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

Risk management plan (RMP)

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

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

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

Additional risk minimisation measures

The guide for healthcare professionals shall contain the following supplementary key element:

- That events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving Olumiant. Olumiant should be used with caution in patients with risk factors for DVT/PE. Patients should be instructed to seek immediate medical attention if signs or symptoms of DVT/PE appear.

The patient alert card shall contain the following supplementary key message:

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

5. EPAR changes

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

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion "EMEA/H/C/004085/II/0016"