20 July 2023
EMA/365746/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Olumiant

International non-proprietary name: baricitinib

Procedure No. EMEA/H/C/004085/X/0035/G

Note

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

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List of abbreviations

AA	Alopecia Areata
AD	Atopic Dermatitis
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine transferase
ANA	Anti-nuclear antibodies
AST	Aspartate aminotransferase
BCS	Biopharmaceutics Classification System
BMO	Body Mass Index
CHAQ	Childhood Health Assessment Questionnaire
CHMP	Committee of Human Medicinal products
CPK	Creatine phosphokinase
CRP	C Reactive protein
CTCAE	Common Terminology Criteria for Adverse events
DBW	Double Blind withdrawal
DLP	Data lock point
DMARDs	Disease- modifying antirheumatic drugs
DVT	Deep vein thrombosis
EFD	Embryo-fetal Development
ERA	Enthesitis related arthritis
ESR	Erythrocyre sedimentation rate
GCP	Good Clinical Practices
HPLC	High performance liquid chromatography
HRQoL	Health-related quality of life
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
ID	Identification
IL	Interleukin
ILAR	International League of Associations for Rheumatology
IR	Incidence rate
ITT	Intent-to-treat

JAK	Janus Kinase
JIA	Juvenile Idiopathic Arthritis
jPsA	Juvenile Psoriatic Arthritis
Lte	Long-term extension
MACE	Major adverse cardiovascular event
mg	milligram
mL	Milliliter
MTX	Methotrexate
NSAIDs	Nonsteroidal anti-inflammatory drugs
OAT3	Organic Anion Transporter 3
OLLI	Open-label lead-in
PBT	Persistent, bioaccumulative and toxic
PDE	Permitted Daily Exposure
PEC	Predicted environmental concentration
PedACR30	Paediatric 30% improvement in American College of Rheumatology criteria
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PND	Postnatal day
PNEC	predicted no-effect concentration
PPND	pre-and postnatal development
PRAC	Pharmacovigilance Assessment Committee
QC	Quality Control
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
STAT	Signal transducers and activators of transcription
TE	Treatment emergent
TEAE	Treatment emergent adverse event
TNFα	Tumor Necrosis Factor alpha
TYK	Tyrosine Kinase
ULN	Upper limit of normal
vPvB	very Persistent and very Bioaccumulative

VTE	Venous Thromboembolic events

1. Background information on the procedure

1.1. Submission of the dossier

Eli Lilly Nederland B.V. submitted on 9 September 2022 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
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	II

Extension application to introduce a new strength (1 mg film-coated tablet), grouped with a type II variation (C.I.6.a) in order to extend the indication to include treatment, as monotherapy or in combination with conventional synthetic disease modifying antirheumatic drugs (DMARDs), of active juvenile idiopathic arthritis (JIA) in patients 2 years of age and older who have had an inadequate response or intolerance to one or more prior conventional synthetic or biologic DMARDs, based on final results from the pivotal study JAHV (I4V-MC-JAHV); this is a multicentre, double-blind, randomised, placebo-controlled, medication-withdrawal Phase 3 study in children from 2 years to less than 18 years of age with JIA who have had an inadequate response or intolerance to treatment with at least 1 cDMARD or bDMARD. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance.
Version 15.1 of the RMP has also been submitted.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0004/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0004/2022 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. 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.

1.5. Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Johann Lodewijk Hillege

The application was received by the EMA on	9 September 2022
The procedure started on	29 September 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 December 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	22 December 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 January 2023
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	26 January 2023
The MAH submitted the responses to the CHMP consolidated List of Questions on	23 March 2023
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	28 April 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 May 2023
The CHMP Rapporteur circulated the CHMP updated Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	17 May 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	25 May 2023
The MAH submitted the responses to the CHMP List of Outstanding Issues on	13 June 2023
The PRAC Rapporteur circulated the PRAC Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	26 June 2023
The CHMP Rapporteur circulated the CHMP Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	05 July 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	06 July 2023
The CHMP Rapporteur circulated the updated CHMP Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	13 July 2023

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Olumiant on	20 July 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of diseases characterised by arthritis of unknown origin with onset before age of 16 years, persisting for more than 6 weeks. The currently used International League of Associations for Rheumatology (ILAR) classification distinguishes the following JIA categories: systemic arthritis, polyarthritis rheumatoid factor (RF) negative, polyarthritis RF positive, oligoarthritis, psoriatic arthritis, enthesitis-related and undifferentiated arthritis.

According to the Guideline on clinical investigation of medicinal products for the treatment of JIA, Rheumatoid arthritis (RA), axial spondyloarthritis, and PsA are diseases in adults that correspond most closely to individual categories of JIA with similar clinical manifestations and underlying immunologic mechanisms, i.e. polyarticular JIA, Enthesitis related arthritis (ERA) and JIA-PsA, respectively (EMA/CHMP/239770/2014 Rev. 2). The proposed new indication for baricitinib is: 'for the treatment of active juvenile idiopathic arthritis in patients 2 years of age and older who have had an inadequate response or intolerance to one or more prior conventional synthetic or biologic disease-modifying antirheumatic drugs (DMARDs):

- Polyarticular juvenile idiopathic arthritis (polyarticular rheumatoid factor positive [RF+] or negative [RF-], extended oligoarticular),

- Enthesitis related arthritis, and

- Juvenile psoriatic arthritis.

Systemic JIA is discriminated from other forms of JIA, and it is not included in this submission. For systemic JIA a separate study (JAHU) is ongoing, which is included in the paediatric investigation plan (PIP).

2.1.2. Epidemiology

Estimations of the epidemiology of JIA are limited by its low frequency and difficulties in diagnosis and classification. According to a systematic review, incidence rates of JIA varied from 1,6 to 23/100.000 and prevalence varied from 3,8 to 400/100.000 in Europe (Thierry et al. 2014). Oligoarthritis was the most frequent form. Incidence and prevalence are estimated to be higher for girls than for boys (Thierry et al. 2014; Cardoso et al. 2021). In Europe, the number of incident cases with JIA is estimated to be ~60.000 in 2010 and ~64.000 in 2017 (Thierry et al. 2014; Dave et al. 2020).

2.1.3. Aetiology and pathogenesis

The aetiology and pathogenesis of JIA are still poorly understood. As with many auto-immune and inflammatory diseases, it is hypothesised that a genetically susceptible individual could develop an immune response towards a self-antigen on exposure to an unknown environmental trigger, which generates a self-perpetuating loop of activation of both innate and adaptive immunity that causes tissue inflammation and damage (Ravelli 2016).

JIA shares several immunological abnormalities identified in RA (Ravelli and Martini 2007). The inflammatory synovitis in JIA is similar to that observed in RA. The synovium in JIA shows pronounced hyperplasia of the lining layer and infiltration of the sublining layer with mononuclear cells, including T cells, B cells, macrophages, dendritic cells, and plasma cells, as similarly observed in RA. Levels of inflammatory cytokines elevated in adult patients with RA, such as IL-1β, IL-6, and TNFα, are also elevated in the synovial fluid and serum of patients with JIA; these cytokines also correlate with markers of disease activity such as CRP and ESR (Lepore et al. 1994; Mangge et al. 1995; Rooney et al. 1995, 2000; De Benedetti et al. 1997).

2.1.4. Clinical presentation, diagnosis and prognosis

Depending on the number of joints affected, the presence of extra-articular manifestations, systemic symptoms, serology and genetic factors, JIA is divided into oligoarticular, polyarticular, systemic, psoriatic, enthesitis-related and undifferentiated arthritis (Zaripova 2021).

Oligoarticular JIA is characterised by inflammation of up to four joints that usually proceeds as asymmetrical arthritis of the joints of the lower extremities, such as knee and ankle, with a high frequency of positivity to anti-nuclear antibody (ANA) and high risk of chronic uveitis (Zaripova 2012). Oligoarticular juvenile idiopathic arthritis is further divided into persistent oligoarthritis, in which there is no additional joint involvement after the first six months of illness, and extended oligoarthritis, in which there is involvement of additional joints after the first six months (Up-to-date).

Polyarticular JIA affects five or more large/ small joints and is hallmarked by injury to the metacarpophalangeal joints and wrists (Zaripova 2021; Ravelli 2016). RF-negative polyarticular JIA tends to asymmetrical patterns of joint inflammation, while the RF-positive variant tends to symmetric involvement of the large and small joints of hands and feet (Zaripova 2021; Ravelli 2016).

Enthesitis-related arthritis (ERA) resembles oligoarthritis, affecting the joints of the lower limb in association with enthesitis (Zaripova 2012). The involvement of lower limb joints, sacroiliac joints, enthesitis, uveitis and the association with HLAB27, suggest similarities to spondylarthropathies (Ravelli 2016).

Juvenile psoriatic arthritis in itself is heterogeneous, often proceeding as oligoarthritis or RF-negative polyarthritis and involves more commonly the small joints accompanied by dactylitis, psoriatic rash and/ or nail pitting (Zaripova 2012).

JIA is a major cause of disability in children (EMA/CHMP/239770/2014 Rev. 2). Long-term complications resulting from longstanding inflammation and glucocorticoid therapy can include joint erosions, and deformities, growth retardation with reduced final adult height, body composition changes with reduced bone and muscle mass, metabolic complications, and osteoporosis. These physical complications, as well as the ongoing disease itself, can impair educational, social and emotional development, thereby highlighting the need for early effective treatment. In addition, specific types of JIA may be accompanied by chronic anterior iridocyclitis/uveitis. The prognosis in general, depends on the clinical category of JIA, the severity, the rapidity of diagnosis, appropriate referral, initiation of optimal therapy and response to treatment.

2.1.5. Management

The aim of treatment of JIA is rapid suppression of inflammation in order to prevent joint damage, prevent the occurrence of flares, maximise physical function and promote normal growth and

development. The ultimate treatment goal is the induction of clinical remission or the attainment of minimal disease activity or inactive disease.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are considered a first–line treatment option in most cases of newly diagnosed JIA, followed by intra-articular glucocorticosteroids and conventional disease modifying antirheumatic drugs (DMARDs) including methotrexate and sulfasalazine. However, a substantial proportion of patients do not achieve an adequate response to these therapies (Ringold et al. 2013; Hinze et al. 2015; Ravelli 2016). Biologic agents approved for RA in the last decades have been added to the treatments available to children with JIA (Lovell et al. 2000; Ruperto et al. 2010b; Brunner et al. 2015). Although these biological treatments have led to clinical improvements, many patients do not respond and do not achieve long-lasting remission (Hinze et al. 2015; Onel et al. 2022). These treatments include TNF-inhibitors (adalimumab, etanercept, infliximab), tocilizumab, secukinumab, and abatacept. The only Janus kinase (JAK)-inhibitor approved for JIA up to now is tofacitinib.

Etanercept and adalimumab are TNF-blocking agents that have similar mechanisms of action. Adalimumab is approved for the treatment of active polyarticular juvenile idiopathic arthritis in patients ≥2 years of age and for ERA in patients ≥6 years of age (Humira SmPC). Etanercept is approved for the treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children ≥2 years and for the treatment of psoriatic arthritis and of ERA in adolescents ≥12 years (Enbrel SmPC). Abatacept inhibits T cell production and is approved for the treatment of polyarticular JIA in patients of ≥6 years of age (Orencia SmPC). Tocilizumab is an anti-IL-6 receptor monoclonal antibody that is approved for children ≥2 years of age with polyarticular JIA (rheumatoid factor positive or negative) or extended oligoarthritis (Roactemra SmPC). Secukinumab is approved for children ≥6 years with ERA or with jPsA (Cosentyx SmPC). Tofacitinib (a JAK inhibitor) was approved in the EU in 2021 for the treatment of polyarthritis (rheumatoid factor positive or negative), extended oligoarthritis, and the treatment of psoriatic arthritis, in children ≥2 years (Xeljanz SmPC).

2.2. About the product

Baricitinib belongs to the pharmacological class of JAK inhibitors. JAKs are a family of 4 protein tyrosine kinases (JAK1, JAK2, JAK3, and TYK2) that play an important role in cytokine signal transduction. JAKs are enzymes that transduce intracellular signals from cell surface receptors for a number of cytokines and growth factors involved in haematopoiesis, inflammation, and immune function (O'Shea et al. 2015). Baricitinib is a JAK1/JAK2 inhibitor demonstrating selectivity for and inhibition of JAK1 and JAK2 with lower potency towards inhibition of JAK3 or TYK2 (Fridman et al. 2010). Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants, ATC code: L04AA37

Inflammatory cytokines, such as IL-6, which transduces cell signalling through the JAK/STAT pathway (Rawlings et al. 2004), and TNF, whose expression is reduced by inhibition of JAK1 and JAK2, are considered to be associated with the pathology of JIA (Ravelli and Martini 2007). Inhibition of JAK-STAT signalling by baricitinib can target multiple JIA-associated cytokine pathways and may provide novel therapeutic approaches to disease management.

Baricitinib is already approved in the treatment for moderate to severe RA, for moderate to severe atopic dermatitis (AD) and for severe alopecia areata (AA) in adult patients.

The proposed new indication for baricitinib is: 'for the treatment of active juvenile idiopathic arthritis in patients 2 years of age and older who have had an inadequate response or intolerance to one or more prior conventional synthetic or biologic disease-modifying antirheumatic drugs (DMARDs):

- Polyarticular juvenile idiopathic arthritis (polyarticular rheumatoid factor positive [RF+] or negative [RF-], extended oligoarticular),

- Enthesitis related arthritis, and

- Juvenile psoriatic arthritis.

Baricitinib may be used as monotherapy or in combination with conventional synthetic DMARDs.

The subcategories of JIA in the proposed indication follow the ILAR categories, which is in line with the EMA Guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis (EMA/CHMP/239770/2014 Rev. 2). For the treatment of JIA, the proposed dose of baricitinib is 4 mg once daily for patients weighing 30 kg or greater. For patients weighing less than 30 kg, the recommended dose is 2 mg once daily. The dose is reduced by half for patients using strong Organic Anion Transporter 3 (OAT3) inhibitors or with a creatinine clearance between 30 and 60 mL/min.

2.3. Type of Application and aspects on development

The baricitinib clinical development programme for JIA includes one pivotal Phase 3 study (IV-MC-JAHV) and 1 supportive long-term extension study (IV MC JAHX); the long-term extension study is still ongoing. Dosing for JIA was based on PK/PD modelling of data in RA; the intended doses of 4 mg and 2 mg that were based on body weight, were tested in the PK phase of the pivotal study JAHV. As half doses may be needed for patients with decreased renal function or using strong OAT3 inhibitors, the Applicant has submitted a new 1 mg tablet as a line extension in this application.

Systemic JIA is not included in this dossier; a separate study (JAHU) is included in the PIP. The agreed PIP requires the applicant to develop an age-appropriate liquid oral formulation. The applicant developed and investigated an oral suspension formulation during the study JAHV. However, the oral suspension is not included in this dossier. The applicant provided comparison of *in vitro* dissolution profiles and PK data that supports the bioequivalence between the 2 mg/mL oral suspension formulation and the 4 mg commercial tablet.

The Applicant has not applied for CHMP Scientific Advice. The pivotal study has been performed in basic agreement with the EMA Guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis (EMA/CHMP/239770/2014 Rev. 2). This includes the inclusion of different subclasses of JIA (polyarticular JIA, extended oligoarticular JIA, ERA, juvenile PsA), with a lower age range of 2 years and having moderate to severe active disease, a staggered PK study over age ranges, the use of time-to-flare as the primary outcome in the randomised withdrawal phase, response criteria and low disease states as secondary outcomes, a long term study to confirm effectiveness and safety. The submitted article 46 paediatric study I4V-MC-JAHV (EMEA/C/004085/46/013) is combined with this extension application.

2.4. Quality aspects

2.4.1. Introduction

This line extension concerns the addition of this new strength to the previously approved strengths of 2 mg & 4 mg film-coated tablets. The extension is also linked to the addition of a new indication for paediatric patients applicable to all strengths.

The finished product is presented as film-coated tablets containing 1 mg of baricitinib as active substance.

Other ingredients are:

Tablet core: mannitol, microcrystalline cellulose, croscarmellose sodium, magnesium stearate.

Film-coating mixture: poly (vinyl alcohol), titanium dioxide (E171), macrogol, talc, lecithin (soya) (E322) and iron oxide red (E172).

The product is available in polyvinylchloride/polyethylene/polychlorotrifluoroethylene - aluminium blisters and polyvinylchloride/aluminium/oriented polyamide - aluminium perforated unit dose blisters as described in section 6.5 of the SmPC.

2.4.2. Active Substance

The active substance documentation is identical to that previously approved for the authorised strengths and is acceptable. No new information has been provided.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The proposed 1 mg strength is a very light pink 6.75 mm round film-coated immediate-release tablet debossed with “Lilly” on one side and “1” on the other. It is distinguished from the currently authorized strengths of 2 mg and 4 mg by means of different shape, dimension, inscriptions and colour. 1

The development of the 1 mg strength was based on the work conducted for the approved 2 mg and 4 mg strengths. The 1 mg strength is based on a common blend approach with the 2 mg strength and a slightly different quantitative composition of the coating to achieve a different colour. The same manufacturing process is used as for the already authorised strengths. On this basis, no additional formulation development work has been done for the new proposed strength.

All excipients are well known pharmaceutical ingredients and their quality is compliant with relevant standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The application also included a new indication for use in paediatric patient populations, and the applicant suitably discussed and justified the excipients in the intended paediatric population. In the clinical studies in children the swallowability of the tablets has been evaluated and the results are presented. Most children from 6 years of age had no problem swallowing the tablets. It is also proposed that the tablets could be dispersed for patients who have difficulty swallowing the tablet formulation. The palatability of the dispersed tablets has been adequately discussed and is accepted. Information surrounding the dispersion of the tablets has been included in the product information.

The applicant has also developed an oral suspension formulation, in line with the PIP requirements, although this suspension formulation has not yet been submitted for authorisation. The oral suspension formulation was used in paediatric clinical trials. In order to justify the applicability of the clinical results obtained with the suspension to the tablets, a bioequivalence study has been performed demonstrating bioequivalence of the suspension with the 4 mg tablets. Please refer to the clinical section for detailed information.

The equivalence of kinetics between the 4 mg and 2 mg tablets was already demonstrated *in vivo* in the original dossier. The 2 mg and 1 mg tablets are based on a common blend approach, and in order to bridge the results to the 1 mg strength, comparative dissolution profiles were generated between the 2 mg and 1 mg strengths. However the dissolution profile comparisons originally presented were not in line the Guideline on Investigation of Bioequivalence, as a pH of 5 was used for comparison rather than pH 4.5 for one of the dissolution profile comparisons. As no adequate justification was provided for deviation from the guideline requirements a joint Quality/Pharmacokinetic major objection was raised during the procedure. To resolve this, the applicant presented as requested further comparisons at pH 4.5 and the biowaiver was considered acceptable. The administration proposal for the tablets also included the preparation of dispersions for patients unable or unwilling to swallow whole tablets. A major objection was raised on the need to justify and outline the impact of the tablet dispersion on patient exposure to the active substance. The applicant provided sufficient justification regarding the BCS class III nature of the active substance and *in vitro* dissolution comparisons. On this basis it was accepted that equivalence between whole or dispersed tablets was sufficiently demonstrated.

No discussion was provided about developing the QC method for dissolution and establishing the regular QC limit for this parameter, as the same method and limits will be used for the currently approved strengths this is acceptable.

The primary packaging is polyvinylchloride/polyethylene/polychlorotrifluoroethylene - aluminium blisters and polyvinylchloride/aluminium/oriented polyamide - aluminium perforated unit dose blisters. The packaging materials proposed for the 1 mg tablets are common for this pharmaceutical form and are the same as in use for the currently approved strengths. No new information about microbiological attributes and compatibility has been provided, which is acceptable. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The manufacturing process consists of seven main steps: pre-blending step 1, pre-blending step 2, roller compaction and dry sizing, final blending, tablet compression, film-coating and packaging. The process is considered to be a non-standard manufacturing process due to the low active substance content in the finished product. The manufacturing process for the 1 mg strength is in line with the process for the 2 mg and 4 mg strengths and is conducted at the same site of manufacture.

1Major steps of the manufacturing process have been validated by a number of studies. Information has been provided on the validation of three commercial scale batches of the 1 mg strength. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.4.3.3. Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form; identity (IR), assay (HPLC), degradation products (HPLC), description (visual), uniformity of dosage units (HPLC), dissolution (HPLC), dye identity (chemical reaction).

2The specifications for the 1 mg strength have been set in line with the approved 2 mg and 4 mg strengths. The specifications have been adequately justified, and appropriate limits for degradation products have been set in line with ICH Q3B. As no degradation impurities were detected above the ID threshold no impurities are specified in the specifications.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on batches of the blend common to the 1 mg and 2 mg strengths tested using a ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on this it can be concluded that it is not necessary to include any elemental impurity controls.

No risk evaluation on nitrosamines specific for the new proposed strength has been provided, only a summary of the risk evaluation performed for the other strengths. As the new proposed strength has the same components, manufacturing process and packaging material as the already approved strengths, no question is raised as it is considered that the 1 mg strength is covered by the risk evaluation already performed for the approved higher strengths.

The analytical methods used have been adequately described and appropriately validated in accordance with ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurity testing has been presented.

Batch analysis results are provided for 12 batches, including 3 at the proposed commercial batch size which confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from 3 commercial scale batches of finished product in each of the proposed commercial container closure systems and stored for up to 36 months under long term conditions (30 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for identity, assay, degradation products, description, and dissolution. Water activity and microbiological quality were also tested during the stability studies using validated in-house methods. A bracketing approach was applied to some of the testing time-points and parameters. This was applied at time points 3, 6, 9 and 12 months at long term conditions and at time points 1 and 3 months at accelerated conditions. Complete testing of all parameters was applied at initial, 18, 24 and 36 months at long term conditions and at 6 months at accelerated conditions.

The analytical procedures used are stability indicating. The results of the stability studies remained within the defined specifications with the exception of one result for assay. A single low value out of specification result was observed at one six month time-point during long term testing, this result was seen to be atypical and potentially attributable to analytical variability, subsequent testing of the same batch at later time points showed the assay value returned back within specification. No downward or decreasing trend is seen in the long-term assay results, a slight downward trend is seen at the accelerated conditions.

In addition, 1 batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product is not sensitive to light.

Based on available stability data, the proposed shelf-life of 36 months without special storage conditions as stated in the SmPC (section 6.3) are acceptable.

2.4.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

There are no changes to the active substance. Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The CHMP originally raised two multi-disciplinary major objections impacting Quality, the first regarding the in-vitro dissolution testing needed to bridge the pharmacokinetic data relevant for the 2 mg strength to the proposed 1 mg strength, as originally the dissolution profile comparisons used to support the requested biowaiver of strengths were not conducted in line with the guideline on the investigation of bioequivalence. This was resolved by the provision of the requested data comparisons at pH 4.5 in line with the requirements of the guideline.

The second multi-disciplinary major objection concerned the need to bridge or justify that the exposure to the dispersed tablets would be similar to those of the studied whole tablets. The applicant provided suitable justification to resolve the objection, this was based on the highly soluble BCS class III nature of the active substance and the in-vitro dissolution profile comparisons.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendation(s) for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

No new non-clinical studies have been conducted to support the extension of indication or the line extension of Olumiant (baricitinib) for a new strength of 1 mg tablets. The non-clinical overview summarises the relevant non-clinical data to support the administration of baricitinib to paediatric juvenile idiopathic arthritis patients aged 2 and above and was based on a juvenile animal study in rats. The juvenile rat study was performed to support a paediatric indication for atopic dermatitis. The data from this study has been briefly outlined in this report.

2.5.2. Pharmacology

Baricitinib is a small molecule, selective inhibitor of the Janus kinase (JAK) family of protein tyrosine kinases with potency and selectivity for JAK2 and JAK1, and less potency for JAK3, or Tyrosine kinase

2 (TYK2) (Fridman et al. 2010). Members of the JAK family of protein tyrosine kinases (JAK1, JAK2, JAK3, and TYK2) play an important role in signal transduction following cytokine and growth factor binding to their receptors. Aberrant production of cytokines and growth factors has been associated with a number of chronic inflammatory conditions, including JIA.

2.5.3. Pharmacokinetics

No pharmacokinetic studies were conducted for this line extension.

2.5.4. Toxicology

A juvenile rat study (9000909) was completed in 2017 to support the dosing of baricitinib to patients 1 to <12 years old (assessed in EMEA/H/C/004085/II/0016 and EMEA/H/C/004085/R/0025). Administration of baricitinib to rats by once daily oral gavage at 0, 1, 5, or 25 mg/kg/day from postnatal day (PND) 10 to 90, resulted in changes most notable concerning overall growth, the immune system, and bone. Reductions in overall growth were evidenced by lower body weight and lower body weight gain relative to concurrent controls. With regard to the immune system, decreases in peripheral and tissue lymphocyte counts reduced lymphoid organ weights and decreased lymphoid cellularity in the thymus, spleen, and lymph node were associated with a decrease in the T-cell-dependent antibody response. The immune effects were expected based on the pharmacology of baricitinib. Similar effects on growth (body weight) and the immune system were also observed in the 6-month repeat-dose rat toxicology study in older animals (Study T08-04-05). Bone effects observed in the juvenile rat study included:

- degeneration/atrophy of the femoral head and neck (increased incidence over background)
- a single animal with osteomyelitis and secondary fracture
- slight decrease in bone length and mass, and
- accelerated maturation of secondary ossification centres with normal growth plates

No visible baricitinib-related skeletal effects were observed in previous repeat-dose toxicology studies in rats or dogs, which included near-lifetime exposure in the longest-duration studies. There was no evidence of bone fractures or changes in bone structure based on the lack of clinical signs and affirmed by bone histology. Rats and dogs used in these studies were approximately 8 weeks old and 5 to 6 months old, respectively, at the initiation of dosing. These ages cover the development of major organ systems, including skeletal, during the adolescent period in humans. However, the majority of the findings identified in the juvenile study were from anatomic regions or endpoints that were not included in the repeat-dose rat and dog studies; thus, direct comparisons to the effects observed in the juvenile study are not possible. Effects on the skeleton were also observed in the rat and rabbit embryo-fetal development (EFD) studies and rat pre-and postnatal development (PPND) study. Bent long bones and ribs observed in the EFD and PPND studies reflect developmental delays or variations and were shown to be transient and reversible. Such developmental delays or variations are not considered permanent changes resulting in clinically significant effects. All of the bone effects observed in the PPND and juvenile studies were considered to be manageable and/or not clinically relevant. The effects were either considered non-adverse, reversible or occurred at large exposure multiple to clinical exposures. However, clinical effects in the long term cannot be fully excluded because the duration of treatment in the pre-clinical studies is limited.

Additional safety measures were implemented in all of the ongoing and planned paediatric studies with baricitinib to monitor this potential risk of growth and bone effects in the long term based on the rat juvenile study.

2.5.5. Ecotoxicity/environmental risk assessment

An updated environmental risk assessment has been provided that considers environmental exposure due to both the already registered (RA, AD and AA) and proposed (JIA) indications. The environmental data previously submitted with the initial dossier serves as the basis for the updated environmental risk assessment.

Physical-chemical properties and fate characteristics indicate that baricitinib will not persist in the aqueous environmental compartment since it undergoes some removal by binding to sludge biosolids during sewage treatment and by partitioning to sediment once in the water column. The concentration of baricitinib in sediment 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 there is some potential for persistence of low concentrations in aquatic sediment. Using assumptions of no metabolism, no removal during sewage treatment, and 1% of the European population taking the maximum dose for each indication, the maximum predicted environmental concentration of total baricitinib residue in surface water is 0.08 µg/L and in sediment is 304 µg/kg (dry weight).

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

The initial estimate of the PEC surface water is based on the maximum recommended daily dose of the active ingredient, a default market penetration of 1% of the total population, 200 L of wastewater discharge per capita, and an average dilution factor of 10 for discharge into surface water. For drug substances used for multiple indications, the PECs for each indication are summed. PEC surface water calculated for each indication of baricitinib is 0.02 µg/L and the total PEC surface water. Thus, with this indication, the PEC surface water increases from 0.06µg/L to 0.08 µg/L for the four indications.

2.5.6. Discussion on non-clinical aspects

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

The juvenile rat study completed in 2017 supports an assessment of safety in children aged 1 and up (assessed in EMEA/H/C/004085/II/0016 and EMEA/H/C/004085/R/0025). While data from studies in adult animals did not identify bone as a target organ, the bone findings from the juvenile toxicity study in rats and reproductive toxicity studies in rabbits and rats suggest that skeletal concerns were only noted at exposures that are not clinically relevant. However, clinical effects in the long term cannot be fully excluded because the duration of treatment in the pre-clinical studies is limited. Therefore, the inclusion of “Long-term safety in pediatric patients including growth and bone development, maturation and pubertal development” as missing information in the list of safety concerns of the RMP

is agreed. The protocol of Study I4V-MC-JAHX was updated to include the assessment of maturation and pubertal development.

Physical-chemical properties and fate characteristics indicate that baricitinib could be present in surface water and sediment at low concentrations and be subject to slow removal by biodegradation and irreversible binding to sediments. Based on the slow removal rate, baricitinib has the potential to persist in the aquatic sediment, but the concentrations would be very low.

The predicted no-effect concentrations (PNECs) of baricitinib for organisms associated with surface water, ground water, and for microorganisms are 60, 210, and 100000 µg/L, respectively. The PNEC of baricitinib for sediment-dwelling organisms is 27150 µg/kg. The aqueous predicted environmental concentrations of total baricitinib residues are more than two orders of magnitude lower than these PNEC values. Therefore, excretion by humans of baricitinib and its metabolites is not expected to result in a significant environmental risk. Additionally, baricitinib is not expected to bioaccumulate in aquatic organisms based on a log Kow less than 4.5. Therefore, baricitinib is not classified as a PBT or a vPvB molecule and is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

The non-clinical aspects of baricitinib were thoroughly evaluated during the initial marketing authorisation procedure. No new non-clinical studies were submitted in support of the present application which was considered acceptable to the CHMP.

Section 5.3 “Preclinical safety data” of the SmPC is considered up to date.

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

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

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

Panel 1 Tabular overview of clinical studies

	Pivotal Phase 3 Study JAHV	Supportive Study JAHX
N	220	199
Population	JIA as defined by ILAR criteria: • Polyarticular JIA (N = 143) • Extended oligoarticular JIA (N = 16) • ERA (N = 50) • JPsA (N =10)	Patients from Study JAHV who have rolled over to the long-term extension study*
Ages enrolled	• ≥2 to <6 years (N = 6) • ≥6 to <9 years (N = 9) • ≥9 to <12 years (N = 30) • ≥12 to <18 years (N = 175)	• ≥1 to <6 years (N = 3)* • ≥6 to <9 years (N = 12) • ≥9 to <12 years (N = 14) • ≥12 to <18 years (N = 160) • ≥18 (N = 10)

	Pivotal Phase 3 Study JAHV	Supportive Study JAHX
Primary endpoint(s)	Time to disease flare (flare defined as worsening of ≥30% in at least 3 of the 6 PedACR core criteria for JIA and an improvement of ≥30% in no more than 1 of the criteria) from the beginning of the DBW period to the end of the DBW period	• Treatment-emergent adverse events, adverse events of special interest, and serious adverse events • Temporary investigational product interruptions and permanent investigational product discontinuations • Vital signs, growth and development, and laboratory evaluations (including chemistry and haematology)
Secondary endpoints	• Proportion of patients with disease flare from time of randomisation in DBW through the end of the DBW period • Response rates of PedACR30/50/70/90/100 according to the ACR paediatric response criteria at the end of the OLLI period and at the end of the DBW period • Changes from original baseline (at the beginning of the OLLI period) to the end of the DBW period (due to disease flare or completion) in each of the 6 individual components of the PedACR Core Set variables • Safety assessments	• Proportion of patients who achieve PedACR30/50/70/90/100 response rates using baseline of originator study • Changes from baseline in each of the 6 individual components of the PedACR Core Set variables of the originator study as follows: o Number of active joints o Number of joints with limited range of motion o Physician's Global Assessment of Disease Activity o Parent's Global Assessment of Well-Being o Physical function as measured by the Childhood Health Assessment Questionnaire o Acute-phase reactant (high-sensitivity C-reactive protein) and erythrocyte sedimentation rate
Study design		
Study periods	• Screening (1–42 days) • Safety/PK (2 weeks) • OLLI (12 weeks) • DBW (32 weeks) • Post-Treatment Follow-Up (28 days)	• Open-Label (Up to 264 weeks) • Post-Treatment Follow-Up (28 days)
Participating countries	Argentina, Australia, Austria, Belgium, Brazil, China, Czech Republic, Denmark, France, Germany, India, Israel, Italy, Japan, Mexico, Poland, Russia, Spain, Turkey, UK	Argentina, Australia, Austria, Belgium, Brazil, China, Czech Republic, Denmark, France, Germany, India, Israel, Italy, Japan, Mexico, Poland, Russia, Spain, Turkey, UK

Abbreviations: DBW = double-blind withdrawal; ERA = enthesitis-related juvenile idiopathic arthritis; ILAR = International League of Associations for Rheumatology; JIA = juvenile idiopathic arthritis; JPsA = juvenile psoriatic arthritis; OLLI = open-label lead-in; N = number of participants; PedACR = Paediatric American College of Rheumatology; PedACR30/50/70/90/100 = paediatric 30%/50%/70%/90%/100% improvement in American College of Rheumatology criteria; PK = pharmacokinetics.

* Study JAHX is an ongoing long-term extension study with patients from 1 to less than 18 years old in Study JAHU and patients from 2 to less than 18 years old in Study JAHV. Data cutoff date for Study JAHX was 21 April 2022. For purposes of this submission, only patient data from Study JAHV were included as of this data cutoff date.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Bioequivalence

The Applicant is requesting a line extension for a 1 mg tablet strength and submitted information on the bioequivalence of an oral suspension formulation (2 mg/mL) (oral suspension was used to dose some of the paediatric patients in study JAHV) versus the tablet to support paediatric dosing (study JAGU). A 1 mg tablet strength was developed using a common blend with the approved 2 mg tablet. The 1 mg strengths is thus qualitatively and quantitatively similar to the 2 mg tablet. In addition, the dissolution profiles for the 1 mg tablet are comparable to the 2 mg tablet profiles across the pH range. The *in vitro* dissolution of baricitinib was determined at 3 pHs (pH 1.2, 4.5 and 6.8) in 900 mL fluid at 37°C and at 50 rpm in a paddle apparatus according to the Guideline on Investigation of Bioequivalence.

A clinical study was performed to investigate if the developed commercial 2 mg/mL oral suspension formulation was bioequivalent to the 4 mg commercial tablet (study JAGU Part A).

Study JAGU Part A is a 3-period, randomized, crossover design in 24 subjects per group to evaluate the bioequivalence of 4 mg baricitinib administered as a single dose of suspension formulation, with and without water, and 4 mg baricitinib administered as a 4 mg tablet with water. Subjects had a mean age of 39.9 ± 8.5 years (23-59 years), a mean body weight of 68.8 ± 9.3 kg (48.0-86.7 kg), and a mean BMI of 24.2 ± 2.6 kg/m^2 (20.1-29.9 kg/m^2). Plasma were collected at the following times: pre-dose, and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 9, 12, 24, 36, and 48 hours post-dose. Non-compartmental analysis was used to calculate the PK parameters. Furthermore, log-transformed C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ estimates were evaluated in a linear mixed effects model with fixed effects for formulation, period, sequence, and a random effect for subject (sequence). Bioequivalence between the suspension formulation administered either with or without water and the commercial tablet was concluded if the 95% CI for C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ were all completely contained within the interval (0.80, 1.25). The PK parameters are summarised in Panel 2.

Panel 2 PK parameters of baricitinib oral suspension (test) and tablet (reference)

Treatment	$AUC_{0\text{-last}}$ (ng × h/mL)	$AUC_{0\text{-}\infty}$ (ng × h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test without water (2 mL of the 2 mg/mL oral suspension)	314 (CV%=19)	319 (CV%=19)	49.8 (CV%=21)	1.50 (0.50-4.0)
Reference (4 mg tablet)	316 (CV%=18)	319 (CV%=17)	47.8 (CV%=25)	0.88 (0.50-3.0)
*Ratio (95% CI)	99.6 (96.3-103)	99.9 (96.6-103)	104 (94.6-115)	-
Test with water (2 mL of the 2 mg/mL oral suspension)	315 (CV%=17)	319 (CV%=17)	49.6 (CV%=24)	0.75 0.50-2.0)
Reference (4 mg tablet)	316 (CV%=18)	319 (CV%=17)	47.8 (CV%=25)	0.88 (0.50-3.0)
*Ratio (95% CI)	99.8 (96.5-103)	99.9 (96.6-103)	104 (94.4-114)	-

A clinical study was performed to investigate the food effect on the oral suspension formulation (study JAGU Part B). Study JAGU Part B is a 2-period, randomized, crossover design to determine the effect of a high-fat, high-calorie meal on the PK of 4 mg baricitinib administered as a single dose of the suspension formulation without water. Subjects were dosed according to their treatment sequence on Day 1 following an overnight fast of 10 hours; with the exception of 1 period for subjects in Part B, where a high-fat, high-calorie meal was started 30 minutes pre-dose, with the intention that the meal be ingested in its entirety over an approximate 25 minute period. A high-fat meal decreased the C_{max} of the oral suspension by 33% in healthy volunteers and no effect on the AUC was observed. Therefore, the decrease in C_{max} is clinically not relevant, since it is not expected that the efficacy will be influenced and decreased exposure does not lead to additional safety issues.

Pharmacokinetics in target population

Study JAHV is a randomized, double-blind, placebo-controlled, withdrawal, safety and efficacy study of oral baricitinib in patients from 2 years to less than 18 years old with juvenile idiopathic arthritis. This study was conducted at 75 centres that screened and randomised patients in 20 countries (Argentina, Australia, Austria, Belgium, Brazil, China, Czech Republic, Germany, Denmark, Spain, France, United Kingdom, Israel, India, Italy, Japan, Mexico, Poland, Russia, and Turkey). Subjects were enrolled in 4 age groups with 5 to 8 patients in each of the following groups:

- 12 to <18 years
- 9 to <12 years
- 6 to <9 years, and
- 2 to <6 years.

Subjects aged 9 to <18 years received a dose of 4 mg once daily and subjects aged 2 to <9 years received a dose of 2 mg once daily for approximately 2 weeks. All patients <6 years of age received oral suspension. Patients aged 6 years or older and <12 years, had the option of receiving either the oral suspension or tablet. Patients aged 12 years and older received tablets. At Day 1, patients will take baricitinib and PK samples will be collected 15 minutes and 1 hour post-dose. At Day 4, patients will take their investigational product at home. The first blood sampling collected during this visit is collected 2 hours after the dose is taken. The second blood sample is collected 4 hours after the dose is taken. At Day 14, a PK sample will be collected before baricitinib is taken. Immediately after the PK sample is collected, the patient will take baricitinib. A PK sample will also be collected at each of the

following times after the dose is given: 30 minutes and 6 hours. In addition, PK samples were obtained during OLLI assessment and blood samples were collected at Week 2 (2 to 4 hours post-dose), Week 4 (4 to 6 hours post-dose), Week 8 (pre-dose) and Week 12 (pre-dose). All samples were analysed within 347 days of collection. PopPK modelling was used to obtain PK parameters from the measured concentrations. Subjects had a mean age of 13.0 ± 3.4 years (2-17 years), a mean body weight of 48.5 ± 16.7 kg (11.0-90.1 kg), and a mean BMI of 19.9 ± 4.2 kg/m^2 (11.8-30.3 kg/m^2). The PK parameters are summarised in Panel 3. Population PK analysis showed that CL/F and apparent volume of distribution decrease with decrease in body weight and age.

Panel 3 PopPK parameter estimates in juvenile idiopathic arthritis patients based on study JAHV per age category

age (years)	dose (mg)	$C_{max,ss}$ (ng/ml)	$C_{max,ss}$ (nM)	$AUC_{T,ss}$ (ng × h/mL)	$AUC_{T,ss}$ (nM × h)	V/F (L)	$t_{½}$ (h)	CL/F (L/h)
2 - <6	2 mg (n=6)	87.4 (CV%=38)	235 (CV%=38)	410 (CV%=57)	1104 (CV%=57)	27.5 (CV%=43)	6.39 (CV%=61)	4.87 (CV%=57)
6 - <9	2 mg (n=10)	66.5 (CV%=42)	179 (CV%=42)	254 (CV%=27)	684 (CV%=27)	39.9 (CV%=28)	7.40 (CV%=58)	7.84 (CV%=27)
9 - <12	4 mg (n=29)	78.5 (CV%=38)	211 (CV%=38)	500 (CV%=57)	1346 (CV%=57)	62.0 (CV%=24)	8.53 (CV%=48)	7.98 (CV%=57)
12 - <18	4 mg (n=172)	57.7 (CV%=28)	155 (CV%=28)	386 (CV%=45)	1039 (CV%=45)	88.3 (CV%=30)	8.73 (CV%=45)	10.3 (CV%=45)

Since weight is a more physiologically relevant patient factor, the effect of weight on the C_{max} and AUC was further evaluated to identify an optimal weight cut off value for dosing. PopPK was used to predict the PK with dosing based on body weight. The results are shown in Panel 4.

Panel 4 PopPK parameter estimates in juvenile idiopathic arthritis patients based on study JAHV per body weight category

body weight (kg)	dose (mg)	$C_{max,ss}$ (ng/ml)	$C_{max,ss}$ (nM)	$AUC_{T,ss}$ (ng × h/mL)	$AUC_{T,ss}$ (nM × h)	V/F (L)	$t_{½}$ (h)	CL/F (L/h)
<30	2 mg (n=29)	85.7 (CV%=40)	231 (CV%=40)	464 (CV%=76)	1249 (CV%=76)	41.9 (CV%=40)	7.60 (CV%=64)	6.30 (CV%=61)
≥30	4 mg (n=188)	58.1 (CV%=28)	156 (CV%=28)	388 (CV%=45)	1045 (CV%=45)	86.8 (CV%=29)	8.75 (CV%=44)	10.2 (CV%=45)

The exposure in paediatric patients with juvenile idiopathic arthritis with the current posology is higher than observed in healthy volunteers. In addition, the C_{max} is higher in paediatric patients with juvenile idiopathic arthritis weighing <30 kg with the current posology compared to adult patients with rheumatoid arthritis, atopic dermatitis and alopecia areata. The C_{max} in paediatric patients with juvenile idiopathic arthritis weighing ≥30 kg and the AUC in paediatric patients with juvenile idiopathic arthritis weighing <30 kg and ≥30 kg appears comparable to adult patients with rheumatoid arthritis, atopic dermatitis and alopecia areata.

2.6.2.2. Pharmacodynamics

Mechanism of action

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

JAKs are enzymes that transduce intracellular signals from cell surface receptors for a number of

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

Primary and Secondary pharmacology

In vitro assays indicate that baricitinib is a selective inhibitor of JAKs with potency and selectivity for JAK1 and JAK2 and less potency for JAK3 or TYK2 (Fridman et al. 2010). Inflammatory cytokines, like IL-6 and TNF, are considered associated with the immunopathology of JIA. Baricitinib inhibits the cell signalling through the JAK-signal transducer and activator of transcription (STAT) pathway and JAK1 and JAK 2, which in response decreases expression of IL-6 and TNF, respectively.

2.6.3. Discussion on clinical pharmacology

Following the Guideline on the Investigation of Bioequivalence, dissolution comparison of the 1 mg and 2 m strengths were provided at pH 1.2, 4.5 and 6.8 in 900 mL fluid at 37°C and at 50 rpm using a paddle apparatus. Similar dissolution was shown between the 1 mg and 2 mg strength and therefore the biowaiver of strength was granted.

The Applicant provided a bioequivalence study of the 2 mg/mL oral suspension (with and without concomitant water intake) versus the 4 mg commercial tablet. The oral suspension requested by PDCO as part of the agreed PIP, is currently not part of the line extension and dispersion of the tablet is proposed for paediatric patients not able to swallow the tablet. The Applicant provided *in vitro* data that the tablet is dispersable as described in the SmPC section 4.2 and 6.6 and dispersion can be used for patients not able to swallow the tablet.

The same validated analytical method was used to determine the plasma concentrations in studies JAGU and JAHV as in the Marketing Authorisation application. No effect of age is expected in children aged 2 years and older, therefore the approach of the Applicant to use the already developed PopPK model to determine the PK in juvenile idiopathic arthritis patients aged 2 to <18 years is acceptable.

The 2 mg/mL oral suspension is bioequivalent to the 4 mg tablet (95% CI for the C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ were between 80 and 125). The pharmacokinetics of baricitinib are dose-proportional over the clinical dose range of 1 to 4 mg baricitinib; therefore, the exposure results obtained with the oral suspension in study JAHV can be used to predict the exposure following intake of a tablet. The oral suspension and tablets are switchable as indicated. For the treatment of JIA, the proposed dose of baricitinib is 4 mg once daily for patients weighing 30 kg or greater. For patients weighing less than 30 kg, the recommended dose is 2 mg once daily. Section 5.2 of the SmPC was updated accordingly. The dose is reduced by half for patients using strong Organic Anion Transporter 3 (OAT3) inhibitors or with a creatinine clearance between 30 and 60 mL/min.

The peak and total exposure in paediatric patients with juvenile idiopathic arthritis with the current posology is higher than observed in healthy volunteers. In addition, the C_{max} is higher in paediatric patients with juvenile idiopathic arthritis weighing <30 kg with the current posology compared to adult patients with rheumatoid arthritis, atopic dermatitis and alopecia areata. The AUC in paediatric patients with juvenile idiopathic arthritis weighing ≥30 kg and the AUC in paediatric patients with juvenile idiopathic arthritis weighing <30 kg and ≥30 kg appears comparable compared to adult patients with rheumatoid arthritis, atopic dermatitis and alopecia areata. The number of patients weighing 10 to <20 kg and 20 to <30 kg at baseline of study JAHV was small which hampers the safety evaluation in light of the higher exposure observed, especially in subjects weighing 10 to <20 kg.

Due to the higher exposure in paediatric patients with juvenile idiopathic arthritis weighing <30 kg, the probability of developing adverse events could increase. However, reducing the dose to 1 mg once daily would lead to too low exposure and could compromise efficacy. Therefore, based on the available data the posology paediatric patients with juvenile idiopathic arthritis weighing <30 kg is acceptable, as reflected in the section 4.2 of the SmPC.

To address the probability of increased adverse reaction in the paediatric subpopulation, the CHMP requested the Applicant to follow up the safety in this subgroup post-authorisation. The Applicant agreed to add Study JAHX as a Category 3 PASS of the RMP to evaluate the long-term safety paediatric patients weighing <30 kg. The Applicant also agreed to routinely monitor events reported from post-marketing sources and that any significant findings will be reported in Periodic Safety Update Reports (PSURs).

The effect of food intake on the PK of the oral suspension was investigated. A high-fat meal decreased the C_{max} of the oral suspension by 33% in healthy volunteers, and no effect on the AUC was observed. Therefore, the decrease in C_{max} is not considered clinically relevant. The oral suspension can, similar to the tablet, be given independently of food.

2.6.4. Conclusions on clinical pharmacology

The pharmacokinetics of baricitinib in paediatric patients with JIA have been sufficiently characterised. The following posology in JIA patients 2 years and older is endorsed by the CHMP: 4 mg once daily for patients weighing 30 kg or greater, 2 mg once daily for patients weighing less than 30 kg and the dose is reduced by half for patients using strong Organic Anion Transporter 3 (OAT3) inhibitors or with a creatinine clearance between 30 and 60 mL/min.

Similar dissolution was shown between the 1 mg and 2 mg strength and therefore the biowaiver of strength can be granted. The Applicant performed a bioequivalence study of the 2 mg/mL oral suspension (with and without concomitant water intake) versus the 4 mg commercial tablet. The 2 mg/mL oral suspension is bioequivalent to the 4 mg tablet (95% CI for the C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ were between 80 and 125 according to the acceptance region for bioequivalence). Further safety data in paediatric patients weighing <30 kg will be provided as a Category 3 PASS of the RMP.

The Applicant provided *in vitro* data that the tablet is dispersible and dispersion in water can be used for patients who are not able to swallow the tablet, which is endorsed by CHMP.

2.6.5. Clinical efficacy

The baricitinib clinical development programme for JIA includes one pivotal Phase 3 study (IV-MC-JAHV) and 1 supportive long-term extension study (IV MC JAHX); the long-term extension study is still ongoing. Dosing for JIA was based on PK/PD modelling of data in RA; the intended doses of 4 mg and 2 mg that were based on age range, were tested in the PK phase of the pivotal study JAHV.

2.6.5.1. Dose response studies

A dose response study has not been performed. Instead, the dose selection for the pivotal JAHV trial (open-label and randomised withdrawal phases) was based on modelling using PK data of adults with RA, and verified in age cohorts in the initial PK/safety phase of the pivotal study. The age cohorts were 12 to less than 18 years, 6 to less than 12 years, and 2 to less than 6 years, with 5-8 participants per cohort. The dose that was derived from the PK modelling in RA adults was: 4 mg for children aged 9

years and above and adolescents up to 18 years, and 2 mg for children less than 9 years of age. The dose proposed in the SmPC however is weight based: 4 mg QD for patients ≥30 kg and 2 mg QD for patients <30 kg, for patients aged 2-18 years.

2.6.5.2. Main study

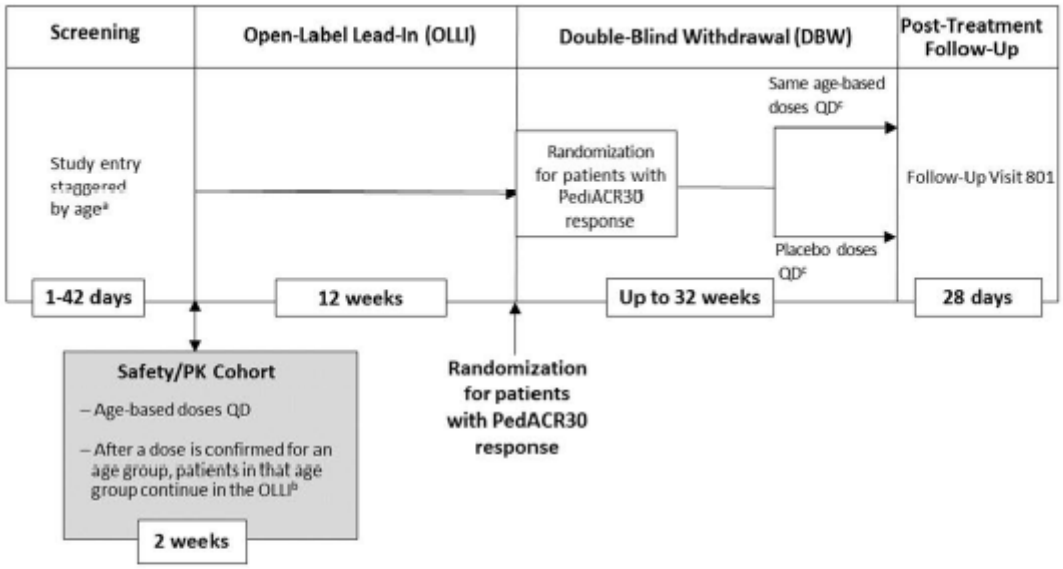
A Randomised, Double-Blind, Placebo-Controlled, Withdrawal, Safety and Efficacy Study of Oral Baricitinib in Patients from 2 Years to Less Than 18 Years Old with Juvenile Idiopathic Arthritis (I4V-MC-JAHV).

Methods

Study JAHV was a multicentre, double-blind, randomised, placebo-controlled, medication-withdrawal Phase 3 study, in patients aged 2-18 with JIA. The study had 3 periods (Figure 1):

- A PK/safety period of 2 weeks treatment with staggered enrolment of 4 age groups with 5 to 8 patients each: (12 to <18, 9 to <12, 6 to <9 and 2 to <6).
- A 12-week open-label lead in (OLLI) period.
- An up to 32 weeks double-blind withdrawal (DBW) period, in responders (PedACR30) at end of the open-label period.

Patients having had a flare, or completing the trial, could continue with baricitinib treatment in the open-label follow-up trial (JAHX).



Abbreviations: DBW = double-blind withdrawal; OLE = open-label extension; OLLI = open-label lead-in; PedACR30 = Pediatric American College of Rheumatology 30 criteria; PK = pharmacokinetics; QD = once daily; RA = rheumatoid arthritis.

[a] Staggered approach to enrolment by age group (4 age groups with 5 to 8 patients in each group, including 12 to less than 18 years, 9 to less than 12 years, 6 to less than 9 years, 2 to less than 6 years) was implemented, with older groups completing the PK/Safety assessment period before younger groups were enrolled.

[b] Once the PK and safety profiles for an age group were confirmed, subsequent patients in that age group could enrol directly into the OLLI period. If the comparability assessment in the PK/Safety period for an age group was inconsistent with baricitinib 4-mg exposures in adults with RA, such that baricitinib dosage for the age group needed to be adjusted, the patients on the inconsistent dosage discontinued the study and could enter the separate OLE study (JAHX).

[c] Patients who experienced a disease flare during the DBW period discontinued the study and proceeded directly to the separate OLE study (JAHX).

Figure 1 Design of study JAHV

- Study Participants

The study population were children with non-systemic active JIA, from 2 to less than 18 years old with an inadequate response or intolerance to treatment with at least 1 cDMARD or bDMARD. Patients with systemic JIA or with persistent oligoarticular arthritis were not included.

Main inclusion criteria

- Being at least 2 years and less than 18 years of age.
- Have a diagnosis with onset before the age of 16 years of any of the following forms of JIA as defined by ILAR criteria, and having active disease:
    - Polyarticular JIA (positive or negative for RF), with at least 5 active joints at screening and baseline
    - Extended oligoarticular JIA, with at least 5 active joints at screening and baseline
    - Juvenile PsA, with at least 3 active joints at screening and baseline
    - Enthesitis-related arthritis, with at least 3 active joints at screening and baseline, or

involvement of at least 1 sacroiliac joint and a physician global assessment of at least 3 (on the 21-circle NRS).

- Have had an inadequate response or intolerance to treatment with ⩾1 conventional or biological DMARD. Patients must have been treated for at least 12 weeks before inadequate response may be determined.

Main exclusion criteria

- Have systemic JIA, as defined by ILAR criteria, with or without active systemic features, or have persistent oligoarticular arthritis as defined by ILAR criteria.
- Have a history or presence of any autoimmune inflammatory condition other than JIA, such as Crohn's disease or ulcerative colitis.
- Have active anterior uveitis or are receiving concurrent treatment for anterior uveitis (patients with a history of uveitis should not be excluded).
- Have received prior or concomitant therapy not in line with the protocol, received any JAK inhibitors (including, but not limited to, tofacitinib or baricitinib) previously.
- Have a current or recent (<4 weeks prior to baseline) clinically serious viral, bacterial, fungal, or parasitic infection or any other active or recent infection that, would pose an unacceptable risk. Bone, joint infections within 6 months prior to screening.
- Have symptomatic herpes simplex at baseline. Have had symptomatic herpes zoster infection within 12 weeks prior to baseline. Have a history of multidermatomal herpes zoster, complicated herpes zoster (e.g. ocular or motor nerve involvement or disseminated herpes zoster such as systemic infection).
- Have a positive test for hepatitis B or C virus at screening. Have evidence of human immunodeficiency virus (HIV) infection and/or positive HIV antibodies.
- Have evidence of active tuberculosis (TB) or latent TB; or have had household contact with a person with active tuberculosis (TB) and did not receive appropriate and documented prophylaxis for TB.

- History of a VTE or are considered at high risk of VTE. History of lymphoproliferative disease; or have signs or symptoms suggestive of possible lymphoproliferative disease, or have primary or recurrent malignant disease.
- Received a live vaccine within 28 days prior to baseline or intend to receive a live vaccine (except booster immunization with attenuated vaccine for measles, mumps, and rubella [MMR] or varicella-zoster virus [VZV]) during the course of the study.
- Have any of the following specific abnormalities on screening laboratory tests:
    - AST or ALT ⩾2 x upper limit of normal (ULN)
    - Total bilirubin level (TBL) ⩾1.5 x ULN
    - Alkaline phosphatase (ALP) ⩾2 x ULN
    - Haemoglobin <10.0 g/dL (100.0 g/L)
    - Total white blood cell count <3000 cells/µL (<3.00 x 10^3/µL or <3.00 billion/L)
    - Neutropenia (absolute neutrophil count [ANC] <1500 cells/µL) (<1.50 x 10^3/µL or <1.50 billion/L)
    - Lymphopenia (lymphocyte count <1000 cells/µL) (<1.00 x 10^3/µL or <1.00 billion/L)
    - Thrombocytopenia (platelets <100,000/µL) (<100 x 103/µL or <100 billion/L)
    - eGFR <40 mL/min/1.73 m^2; but eGFR <60 mL/min/1.73 m^2 for the Safety/PK period of the study
- Major surgery within 8 weeks prior to screening or requiring major surgery during the study. History or presence of cardiovascular, respiratory, hepatic, gastrointestinal, endocrine, haematological, neurological, or neuropsychiatric disorders or any other serious and/or unstable illness that, in the opinion of the investigator, could constitute an unacceptable risk when taking investigational product or interfere with the interpretation of data.

- Treatments

Experimental treatment

The intended doses of baricitinib of 2 mg and 4 mg were based on PK modelling of data of adults with RA (see PK section) and could be adjusted during and after the safety/PK period of the pivotal trial.

The dose of baricitinib was stratified by age: 4-mg for children ⩾9 years of age and adolescents 12 to <18 years of age and 2-mg for children <9 years of age. Baricitinib was provided as 4 mg or 2 mg tablets, or as ready-to-use suspension in a bottle containing 2-mg/mL of baricitinib; and matching placebo formulations in the double-blind withdrawal phase. All patients <6 years of age received oral suspension; patients ⩾6 to <12 years old had the option of receiving the oral suspension or the tablets; patients >12 years old received tablets.

Treatment compliance

Patient compliance with study medication was assessed at each visit up to week 44. Patients were considered noncompliant if they missed ⩾20% of the prescribed doses, or if they intentionally or repeatedly took more than the prescribed amount of study medication. Patients found to be non-compliant were provided with counselling intended to improve compliance.

Concomitant treatment

Additional drugs were to be avoided unless required to treat adverse events (AEs) or for the treatment of an ongoing medical condition. Treatment with concomitant JIA therapies during the study was permitted within dose limits and while on stable dose, use of more than 1 concomitant DMARD was not allowed (Panel 5). The dosages of concomitant treatment could be adjusted only for safety reasons. Not permitted were: biological DMARDs; parenteral corticosteroids; live vaccines within 28 days prior to baseline (except booster immunization with attenuated vaccine for MMR or VZV).

Panel 5 Overview of concomitant JIA therapies

Drug Class	As Needed	Chronic Use	Conditions for Use
MTX[a]	No	Yes	If on MTX, must be on a stable average dose of ≤20 mg/m^2/week for the 8 weeks preceding screening and must continue at that dose throughout the study
cDMARDs other than MTX[a]	No	Yes	If receiving cDMARDs (other than MTX), must be on a stable dose for at least 4 weeks prior to the screening and must continue at that dose throughout the study.
Oral corticosteroids	No	Yes	If receiving oral corticosteroids, daily doses of ≤10 mg/day or 0.2 mg/kg/day prednisone equivalent, whichever is less. Must be on stable dose for at least 2 weeks prior to screening and 6 weeks prior to baseline; the dose must be continued throughout the study.
NSAIDs[b] • including cyclooxygenase-2 inhibitors, e.g., celecoxib	No	Yes	• Must be on stable dose at least 1 week prior to baseline. • Changes in dose, discontinuation and/or introduction of new NSAIDs are only allowed for treatment of an AE.
Analgesics • including local anaesthetics, e.g., lidocaine, and • topical anaesthetics, e.g., EMLA cream.	No	Yes	• Must be on stable dose at least 1 week prior to baseline. • Changes in dose, discontinuation and/or introduction of new analgesics are only allowed for treatment of an AE.

Abbreviations: cDMARD = conventional disease-modifying antirheumatic drug; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug.

[a] Concomitant use of >2 of any cDMARDs (including MTX) is not allowed.

[b] For use as an anti-inflammatory agent.

Treatment interruption

Treatment could be temporary interrupted as a result of AEs or abnormal laboratory values. Specific guidance was provided for temporarily interrupting and restarting treatment (Panel 6).

Panel 6 Criteria for temporary interruption of experimental treatment.

Hold Investigational Product if the Following Laboratory Test Results or Clinical Events Occur:	Investigational Product May be Resumed When:
WBC count <2000 cells/μL (<2.00 x 10^3/μL or <2.00 billion/L)	WBC count ≥3000 cells/μL (≥3.00 x 10^3/μL or ≥3.00 billion/L)
ANC <1000 cells/μL (<1.00 x 10^3/μL or <1.00 billion/L)	ANC ≥1500 cells/μL (≥1.50 x 10^3/μL or ≥1.50 billion/L)
Lymphocyte count <500 cells/μL (<0.50 x 10^3/μL or <0.50 billion/L)	Lymphocyte count ≥1000 cells/μL (≥1.00x10^3/μL or ≥1.00 billion/L)
Platelet count <75,000/μL (<75 x 10^3/μL or <75 billion/L)	Platelet count ≥100,000/μL (≥100 x 10^3/μL or ≥100 billion/L)
eGFR <40 mL/min/1.73 m^2 (from serum creatinine) for patients with screening eGFR ≥60 mL/min/1.73 m^2	eGFR ≥50 mL/min/1.73 m^2
eGFR <30 mL/min/1.73 m^2 (from serum creatinine) for patients with screening eGFR ≥40 to <60 mL/min/1.73 m^2	eGFR ≥40 mL/min/1.73 m^2
ALT or AST >5 x ULN	ALT and AST return to <2 x ULN, and IP is not considered to be the cause of enzyme elevation
Hemoglobin <8 g/dL (<80.0 g/L)	Hemoglobin ≥10 g/dL (≥100.0 g/L)
Symptomatic herpes zoster	All skin lesions have crusted and are resolving
Infection that, in the opinion of the investigator, merits the IP being interrupted.	Resolution of infection that, in the opinion of the investigator, merits the IP being restarted.

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

Treatment was to be permanently discontinued on patient or designee wish. Treatment also was to be discontinued in case of in case of pregnancy, malignancy, HBV infection, or VTE, and in case of specific laboratory abnormalities: in ALT, AST, ALP, with or without clinical manifestations, pointing to liver failure; a low white blood cell count (WBC) <1000 cells/μL (1.00 x 10^3/μL or 1.00 billion/L); an absolute neutrophil count (ANC) <500 cells/μL (0.50 x 10^3/μL or 0.50 billion/L); a lymphocyte count (ALC) <200 cells/μL (0.20 x 10^3/μL or 0.20 billion/L); a low hemoglobin level <6.5 g/dL (<65.0 g/L).

- Objectives

The primary objective of study JAHV was to evaluate the efficacy of baricitinib versus placebo; secondary objectives included evaluations of efficacy, PK, PD, safety, acceptability, and palatability of baricitinib, in children from 2 years to less than 18 years of age with non-systemic JIA, who have had an inadequate response or intolerance to treatment with at least 1 conventional or biological DMARD.

- Outcomes/endpoints

Primary outcome

The primary outcome is time-to-flare from time of randomisation at week 12, to the end of the double-blind withdrawal period. Flare was defined as a worsening of ⩾30% in at least 3 of the 6 PedACR core criteria for JIA and an improvement of ⩾30% in no more than 1 of the criteria.

Secondary Outcomes

The secondary outcomes were assessed during the both the open-label lead-in period and during the double-blind withdrawal period, unless denoted otherwise. Main secondary outcomes were:

- Proportion of patients with disease flare, during the double-blind withdrawal period.

- Changes from baseline in each of the 6 individual components of the PedACR core set variables.
- PedACR30/50/70/90/100 response rates.
- Change from baseline in JADAS-27.
- Changes from baseline in arthritis-related pain severity with the CHAQ pain severity VAS.
- Changes from baseline in Physical function as assessed by the CHAQ.
- Proportion of patients with inactive disease (Wallace et al. 2011), and proportion of patients in remission/inactive disease for 24 weeks (Wallace et al. 2012) during the double-blind withdrawal period.
- Change from baseline in PASI score (in patients with JPsA)
- Change from baseline in SPARCC enthesitis index and in JSpADA (in patients with jPsA or ERA)
- Changes from baseline in the Physical Summary Score (PhS) and Psychosocial Summary Score (PsS) of the Child Health Questionnaire-Parent Form 50 (CHQ-PF50).
- Assessment of tablet or oral suspension product acceptability and palatability at baseline and week 12.

Assessment instruments

The PedACR30/50/70/90/100 consist of 6 core criteria. The definition of improvement in PedACR30 is at least 30% improvement from baseline in 3 of any 6 variables in the core set, with no more than 1 of the remaining variables worsening by >30%.

- Number of active joints (defined as a joint that is swollen or in the absence of swelling has loss of passive motion accompanied by either pain on motion or joint tenderness) in 73 joints.
- Number of joints with limited range of motion in 69 joints.
- Physician's Global Assessment of Disease Activity. The instrument uses a 21-circle VAS ranging from 0 to 10 (using 0.5 increments) where 0 = "no activity" and 10 = "maximum activity" (Filocamo et al. 2010).
- Parent's Global Assessment of Well-Being. The instrument is a 0 to 100 mm VAS assessing the current level of well-being where 0 = 'Very well' and 100 = 'Very poor'.
- Physical function as assessed by the Childhood Health Assessment Questionnaire (CHAQ).
- Acute-phase reactant (hsCRP and ESR)

ACR50, ACR70, ACR90, and ACR100 responses are calculated as improvements of at least 50%, 70%, 90% and 100%, respectively, in the PedACR Core Set values listed above.

The JADAS-27 score is a validated composite disease activity measure for JIA (Consolaro et al. 2012) using the 27-joint count (Bazso et al. 2009) and hsCRP or ESR (Nordal et al. 2012). The JADAS-27 score was determined based on 4 components: Physician's Global Assessment of Disease Activity; Parent's Global Assessment of Well-Being; Number of joints with active disease (27-joint count); ESR.

Remission is defined as inactive disease for at least 24 consecutive weeks (Wallace et al. 2012). Inactive disease is indicated by the presence of all of the following (Wallace et al. 2011):

- No joints with active arthritis based on JADAS-27.
- No fever, rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to JIA as assessed by the investigator.
- No active uveitis as assessed by the investigator.

- Normal erythrocyte (ESR) or hsCRP (i.e., within normal limits in the local laboratory or, if elevated, not attributable to JIA).
- Physician's Global Assessment of Disease Activity indicating no active disease (best possible score on scale =0).
- Duration of morning stiffness ⩽15 minutes.

The PASI (Psoriasis Area and Severity Index) combines assessments of the extent of body-surface involvement in 4 anatomical regions (head, trunk, arms, and legs). It also assesses the severity of erythema (redness), plaque induration/infiltration (thickness), and desquamation (scaling) in each region, yielding an overall score of 0 to 72 (Fredriksson and Pettersson 1978; Mease 2011). The body scores are multiplied by the disease severity score and the weighting for each body area, yielding a score between 0 and 72, with higher scores indicating more manifestations of psoriasis.

The SPARCC enthesitis index (Spondyloarthritis Research Consortium of Canada Enthesitis Index) was used to measure the severity of enthesitis, using absence (0) or presence (1) of enthesitis at 16 sites, and ranges from 0 to 16 (Maksymowych et al. 2009).

The JSpADA (Juvenile Spondyloarthritis Disease Activity Index) was used to evaluate the disease activity of juvenile spondyloarthritis (Weiss et al. 2014). The range of possible scores is 0 to 8, where higher scores indicate more disease activity. The JSpADA has 8 graded components:

- Active joint count: 0 joints = 0, 1 to 2 joints = 0.5, >2 joints = 1
- Active enthesitis count: 0 entheses = 0, 1 to 2 entheses = 0.5, >2 entheses = 1
- Pain over the past week as assessed using a 0-10 NRS (0 = no pain; 10 = pain as bad as your child can imagine: 0 = 0, 1 to 4 = 0.5, 5 to 10 = 1
- CRP level related to juvenile spondyloarthritis activity: normal = 0, 1 to 2 times normal = 0.5, >2 times normal = 1
- Morning stiffness >15 minutes: Absent = 0, Present = 1
- Clinical sacroiliitis (defined as the presence of ⩾2 of the following: tenderness on examination, positive Patrick's test or flexion, abduction and external rotation (FABER) test, and inflammatory back pain): Absent = 0, Present = 1
- Uveitis (any uveitis including acute/symptomatic and chronic/asymptomatic disease): Absent = 0, Present =1
- Back mobility (abnormal back mobility defined as modified Schober's test <20 cm): Normal = 0, Abnormal = 1

The CHAQ (Childhood Health Assessment Questionnaire) assesses health status and physical function in children with juvenile arthritis over the past week, which the parent or legal guardian completes, regardless of the age of the patient. The CHAQ Disability Index contains 30 items grouped into the following 8 domains (not including assistive devices/aids questions): dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities. The domains are averaged to calculate the Disability Index (physical function) which ranges from 0 to 3 with higher scores indicating more disability (Singh et al. 1994). Pain assessment due to illness, which is a 0 to 100 mm VAS that assesses the current level of pain severity over the past week, where 0 = 'No pain' and 100 = 'Very severe pain'.

The CHQ-PF50 (Childhood Health Questionnaire-Parent Form 50) is a generic observer-reported instrument designed to capture the health-related quality of life of children and adolescents (from 5- to 18-years of age), as well as the impact of the child's disease on the caregivers (HealthActCHQ 2013). The CHQ-PF50 is completed by the caregivers and has been validated for use in patients with JIA

(Ruperto et al. 2001). The CHQ-PF50 consists of 50 questions covering 14 health concepts: Global Health; Physical Functioning; Role/Social Limitations-Physical; Role/Social Limitations-Emotional/Behavioral; Bodily Pain/Discomfort; General Behavior; Mental Health; Self-Esteem; General Health Perceptions; Change in Health; Parental Impact-Emotion; Parental Impact-Time; Family-Activities; and Family-Cohesion. From these subscales, 2 summary scores are calculated, the Physical Summary Score (PhS) and Psychosocial Summary Score (PsS).

- Sample size

The sample size was determined to provide 80% power for detecting an absolute reduction of 25% in the proportion of patients experiencing flare in the double-blind withdrawal (DBW) period using a two-sided significance level of 5%. The proportion of patients experiencing flare was assumed to be 60% under placebo and 35% under baricitinib. The calculated required number of patients to be randomised in the DBW period was 128 (64 per treatment arm), assuming a drop-out rate of less than 10%. To reach this number, 197 patients needed to be included in the open-label lead-in (OLLI) period, assuming that 65% meet the criterion of PediACR30 response required for inclusion in the DBW period. A futility analysis was planned after the first 100 patients completed the OLLI period. The study would stop for futility if less than 50% of these patients had a PediACR30 response.

- Randomisation and Blinding (masking)

Patients included in the DBW part of the study were randomised 1:1 to age-based doses of baricitinib or placebo. Randomisation was stratified by history of prior bDMARD use, JIA category and in polyarticular patients by pre-dose exposure erythrocyte sedimentation rate (ESR). Assignment was determined by a computer-generated random sequence and using an interactive web-response system. The experimental treatment was matched with placebo tablets or suspension, as appropriate. All study assessments were performed by study personnel who were blinded to the patient's treatment group. To prevent potential unblinding due to observed efficacy or laboratory changes, two different assessors were used for assessing efficacy and safety outcomes.

- Statistical methods

Analysis populations are defined in Panel 7. Efficacy analyses for the DBW study were conducted following the ITT principle including all the patients that were randomized. Safety analyses were restricted to patients that received at least one 1 dose of baricitinib or placebo (for the DBW safety population) or at least 1 dose of baricitinib (for the general safety population).

Panel 7 Overview of efficacy and safety analysis populations for OLLI and DBW

	Population	Description
	Entered population	All participants who sign informed consent.
Efficacy Analysis population	Safety/PK population	All patients who received at least 1 dose of investigational product in the Safety/PK assessment period.
	OLLI population	All participants who take at least 1 age-based final dose, as confirmed by PK assessments of investigational product, in the OLLI period, other than the Safety/PK population.
	OLLI population 2	All patients who received at least 1 dose of investigational product in the OLLI period.
	Safety/PK and OLLI population	All enrolled patients who were initially assigned to the open-label investigational product in Safety/PK assessment period and OLLI period, following intent-to-treat (ITT) principles.
	DBW population	All randomized patients in the DBW period following intent-to-treat (ITT) principles.

	Population	Description
Safety Analysis population	DBW safety population	All randomized patients in the DBW period who receive at least 1 dose of investigational product.
	General safety population	All patients who received at least 1 dose of investigational product, which is baricitinib.

All statistical tests will be performed at a two-sided significance level of 5%. The primary endpoint of time-to-flare will be analysed using Kaplan-Meier analysis and compared between treatment arms using a stratified log-rank test. In addition, Cox proportional hazard regression analyses adjusted for stratification factors may be performed for which hazard ratio and its 95% confidence interval will be reported as effect size. Patients that do no experience flare during the DBW period or discontinue earlier without flare will be censored. Similarity of treatment effect on time-to-flare will be compared across JIA categories using Cox regression analysis adjusted for stratification factors. The SAP further states that redundant variables will be removed from the models.

Categorical secondary endpoints for the DBW phase will be compared between the treatment arms using logistic regression adjusting for stratification factors. Continuous secondary endpoints for the DBW phase will be compared between arms using ANCOVA adjusted for stratification factors. A mixed model for repeated measurements (MMRM) will be considered as a supplementary analysis for the continuous endpoints. For secondary endpoints defined for the OLLI phase will be summarised without inferential statistics. Categorial safety endpoints for the DBW phase will be compared between arms using the chi-squared test. ANCOVA will be used for continuous safety variables in the DBW safety population. Secondary endpoints are not included in a prespecified hierarchical testing strategy.

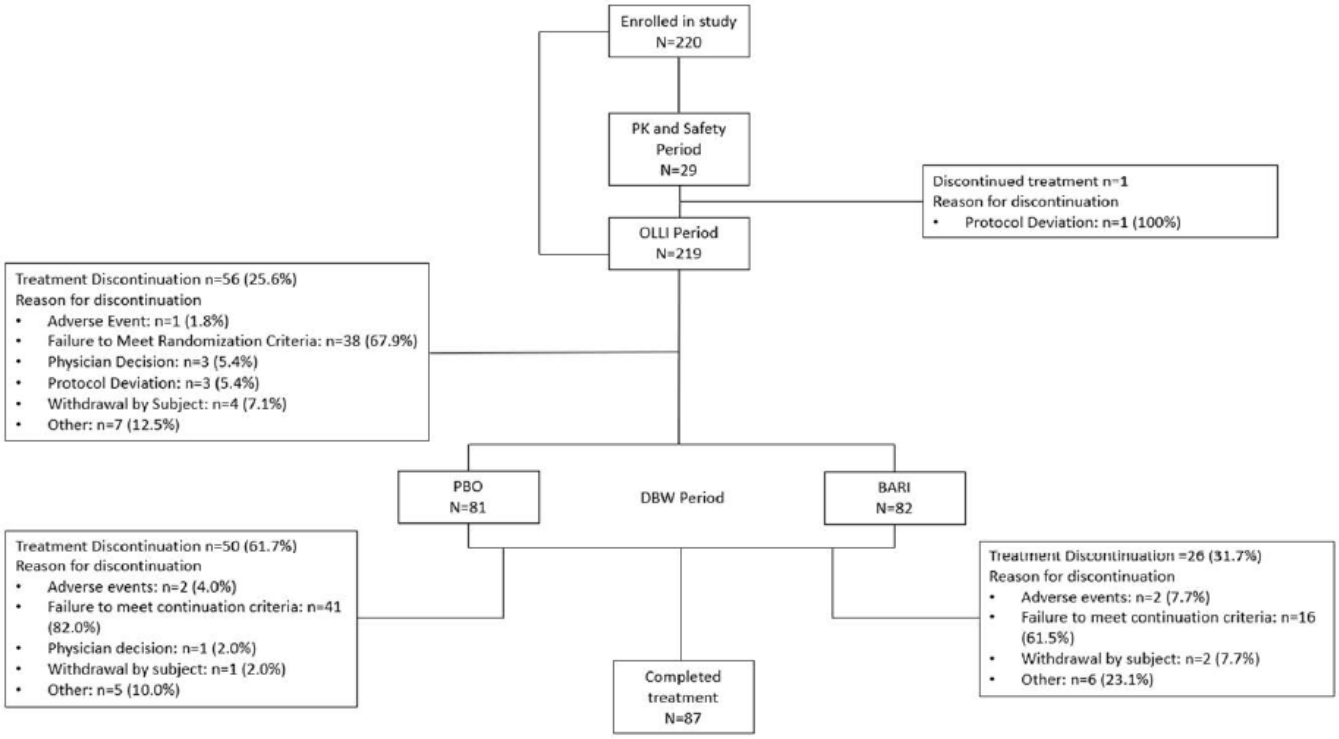
The SAP specifies a general censoring rule that states that all efficacy outcomes collected after permanent study drug continuation will be excluded from analyses. LOCF will be used for the continuous endpoints after flare (a while-on-treatment estimand strategy). Non-responder imputation will be used for those failing to remain on study treatment (a composite estimand strategy).

The following subgrouping variables may be considered for efficacy analyses: gender, age group, geographic region, baseline use of MTX, history or prior use of bDMARD, baseline ESR category, JIA subtype, and baseline corticosteroid use.

Results

- Participant flow

A total of N=220 patients had enrolled the study (Figure 2). There were n=29 patients included in the PK/Safety part of the study, while n=191 patients were directly enrolled into the open-label lead-in period. Of the n=163 (74%) patients who completed the open-label lead-in period, n=82 were randomised to baricitinib and n=81 were randomised to placebo. The most common reasons for discontinuation were: failure to meet randomisation criteria in n=38 patients (17% of total) at the end of the open-label lead-in period; failure to meet continuation criteria in the randomised withdrawal period for n=41 patients (51%) of the placebo group and for n=16 patients (20%) of the baricitinib group. The withdrawals for other reasons (adverse events, physician decision, withdrawal by subject, other reasons) occurred with similar frequency in both groups, with 9 withdrawals in the placebo group and 10 withdrawals in the baricitinib group.



Abbreviations: BARI = baricitinib; DBW = double-blind withdrawal period N = number of patients in the analysis population; n = number of patients in the specified category; OLLI = open-label lead-in; PBO = placebo; PK = pharmacokinetics.

Figure 2 Patient flow in study JAHV

Protocol deviations

In the PK/Safety and open-label lead-in periods, there were n=51 patients (23%) with important protocol deviations. In the randomised withdrawal period, n=17 patients (21%) in the placebo group and n=14 patients (17%) in the baricitinib group had important protocol deviations. Compliance issues included patients who did not return the investigational product to the visit, meaning that the degree of compliance could not be calculated. The use of unallowed co-medication included starting an NSAID or analgesic, or a case of quitting MTX in the baricitinib group; new DMARDs were not started. Issues with source documents most often were data recorded on paper or remote, instead of the e-CRF. Issues with Informed Consent usually were untimely signing/agreement of the IC form after an update.

- Recruitment

The first patient's first visit was performed on 17 December 2018, and the last patient's last visit was performed on 26 January 2022. The analyses presented in the CSR of study JAHV are based on a database lock date of 16 March 2022.

The study was conducted at 75 centres that screened and randomised patients in 20 countries (Argentina, Australia, Austria, Belgium, Brazil, China, Czech Republic, Germany, Denmark, Spain, France, United Kingdom, Israel, India, Italy, Japan, Mexico, Poland, Russia, and Turkey). Of the 220 patients enrolled, 150 patients (68%) were enrolled though centres in European countries.

- Conduct of the study

The initial protocol of study JADV was approved by the MAH at 05 July 2018. The protocol has been amended four times: amended protocol a) on 14 March 2019, b) on 15 April 2019, c) on 15 August 2020, d) on 07 November 2020.

With amendment c): Baseline assessment of sexual maturity (Tanner Staging) in patients >8 years old was included based on feedback from regulatory agencies. Height measurements were added for all study visits to allow for additional growth monitoring. X-ray imaging was added based on feedback from regulatory agencies for additional monitoring of bone growth and assessment of symptomatic areas of bones/joints. Semi-annual wrist, hand, finger, and AP knee radiographs were included to monitor bone age and long bone growth. For patients already enrolled in JAHV at the time of this amendment, the X-ray procedures were optional.

Audits had been performed in 6 centres.

- Baseline data

At baseline of the PK/safety and open-label lead-in periods (N=220), the mean (SD) age of the patients was 13 (3) years. Included were n=6 (2.7%) patients of ⩾2 to 6 years, n=9 (4.1%) patients of ⩾6 to 9 years, n=30 (14%) of ⩾9 to 12 years, and n=175 (80%) of ⩾12 to 18 years of age. Most (70%) patients were female, and the vast majority (71%) was Caucasian. The mean (SD) weight of the patients was 50 (17) kg, with a mean (SD) length of 155 (18) cm and a mean (SD) BMI of 20 (4.5). After randomisation, these figures were basically similar in the placebo (n=81) and baricitinib (n=82) groups. The exception is that for the youngest age group of ⩾2 to 6 years, only 1 patient was randomised to placebo and 5 were randomised to baricitinib.

Panel 8 Baseline disease characteristics by JIA subtype in study JAHV.

Baseline Parameter	All Patients N=220	Polyarticular N=144	Extended Oligoarticular N=16	Enthesitis-Related JIA N=50	Juvenile Psoriatic Arthritis N=10
Time since JIA diagnosis (years), mean (SD)	4.0 (3.7)	3.8 (3.5)	7.9 (4.5)	3.1 (2.9)	4.3 (4.2)
Age at JIA diagnosis (years), mean (SD)	9.3 (4.4)	9.2 (4.6)	4.9 (4.1)	10.8 (2.7)	8.9 (3.4)
Number of active joints, mean (SD)	12.8 (11.0)	15.1 (10.9)	10.4 (8.4)	8.0 (11.3)	7.7 (4.8)
Number of joints with limited range of motion, mean (SD)	8.8 (9.6)	10.4 (10.8)	10.6 (8.1)	4.7 (4.2)	4.0 (2.1)
Physician's global assessment, mean (SD)	6.5 (1.9)	6.9 (1.7)	6.6 (2.1)	5.5 (1.8)	5.9 (1.8)
Parent's global assessment, mean (SD)	53.6 (25.0)	56.4 (25.4)	50.1 (20.6)	47.3 (23.2)	49.2 (31.3)
JADAS-27 (score)	21.8 (8.8)	24.6 (8.4)	19.9 (6.9)	15.2 (6.4)	16.5 (6.2)
CHAQ (score)	1.1 (0.7)	1.3 (0.7)	0.9 (0.5)	0.9 (0.6)	0.9 (0.6)
ESR (mm/hr)	27.9 (26.3)	30.7 (26.9)	29.1 (21.2)	21.0 (26.1)	21.4 (20.1)
Prior biologic JIA therapy					
Never used, n (%)	104 (47.3)	68 (47.2)	4 (25.0)	28 (56.0)	4 (40.0)
Ever use, n (%)	116 (52.7)	76 (52.8)	12 (75.0)	22 (44.0)	6 (60.0)
Prior biologics used					
0, n (%)	104 (47.3)	68 (47.2)	4 (25.0)	28 (56.0)	4 (40.0)
1, n (%)	51 (23.2)	29 (20.1)	6 (37.5)	15 (30.0)	1 (10.0)
2, n (%)	36 (16.4)	25 (17.4)	4 (25.0)	4 (8.0)	3 (30.0)
>2, n (%)	29 (13.2)	22 (15.3)	2 (12.5)	3 (6.0)	2 (20.0)
Baseline use of methotrexate					
No, n (%)	93 (42.3)	52 (36.1)	9 (56.3)	26 (52.0)	6 (60.0)
Yes, n (%)	127 (57.7)	92 (63.9)	7 (43.8)	24 (48.0)	4 (40.0)

Baseline use of corticosteroid					
No	148 (67.3)	88 (61.1)	14 (87.5)	43 (86.0)	3 (30.0)
Yes	72 (32.7)	56 (38.9)	2 (12.5)	7 (14.0)	7 (70.0)
Prior use of corticosteroid					
No	103 (46.8)	63 (43.8)	7 (43.8)	28 (56.0)	5 (50.0)
Yes	117 (53.2)	81 (56.3)	9 (56.3)	22 (44.0)	5 (50.0)

Abbreviations: CHAQ = Childhood Health Assessment Questionnaire; ESR = erythrocyte sedimentation rate; JADAS = Juvenile Arthritis Disease Activity Score; JIA = juvenile idiopathic arthritis; N = number of patients in the analysis population; n = number of patients in the specified category; SD = standard deviation.

Previous medications used for JIA treatment used by patients included: MTX (60.5%), sulfasalazine (11.4%), etanercept (35.5%), adalimumab (32.3%), tocilizumab (22.3%), prednisone (24.1%), triamcinolone (16.4%), methylprednisolone (12.3%), prednisolone (10.5%), naproxen (22.3%), ibuprofen (15.0%), and diclofenac (10.0%).

- Numbers analysed

Efficacy analyses for the placebo-controlled randomised withdrawal period was conducted following ITT principles, including all n=163 patients who were randomised (1:1) to baricitinib or placebo (Panel 9).

Panel 9 Number of patients for analysis in study JAHV

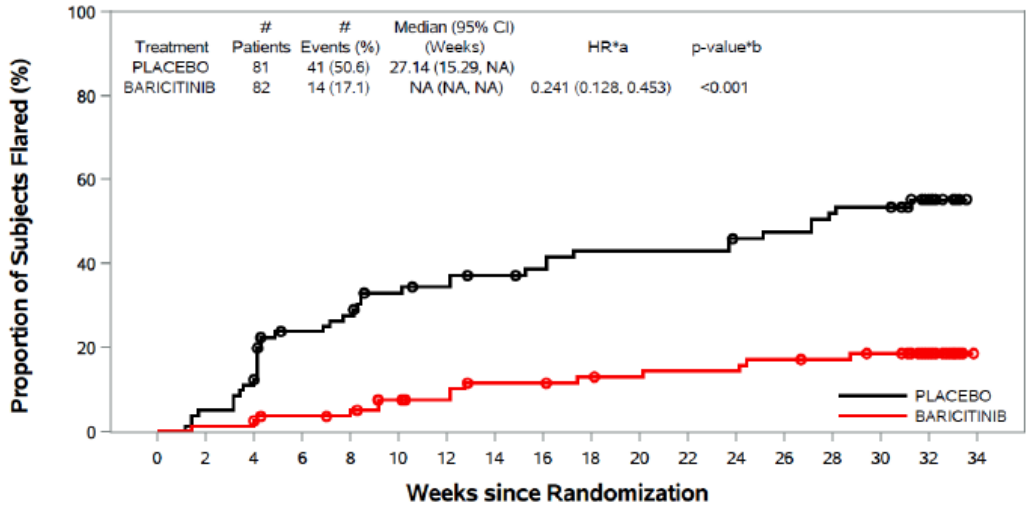
	Population	Description	Total No. of Patients in the Population	No. of Patients in the PBO Population
	Entered	All patients who sign informed consent	263	81
Efficacy Analysis Population	PK/Safety	All patients who received at least 1 dose of investigational product in the PK/Safety assessment period	29	NA
	OLLI	All patients who take at least 1 age-based final dose, as confirmed by PK assessments of investigational product, in the OLLI period, other than the PK/safety population	191	NA
	OLLI2	All patients who received at least 1 dose of investigational product and entered OLLI period	219	NA
	PK/Safety and OLLI population	All enrolled patients who were initially assigned to the open-label investigational product in PK/Safety assessment period and OLLI period, following intent-to-treat (ITT) principles	219	NA
	DBW population	All randomised patients in the DBW period following intent-to-treat (ITT) principles	163	81
Safety Analysis Population	DBW safety	All randomised patients in the DBW period who receive at least 1 dose of investigational product	163	81
	General safety	All patients who received at least 1 dose of investigational product, which is baricitinib	220	81

Abbreviations: DBW = double-blind withdrawal; NA = not applicable; No. = number; OLLI = open-label lead-in; OLLI2 = open-label lead-in population 2; PBO = placebo; PK = pharmacokinetics.

- Outcomes and estimation

Primary outcome

The baseline of the analysis of time-to-flare was week 12, which was the start of the randomised withdrawal period of up to 32 weeks. By study week 44, 14 (17%) patients receiving baricitinib had a disease flare as compared with 41 (51%) patients receiving placebo (Figure 3). Patients receiving baricitinib were significantly less likely to experience disease flare when compared with those receiving placebo (hazard ratio = 0.241, p-value: <.001).



No. of Subjects at Risk

Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
PLACEBO	81 (4)	77 (6)	70 (9)	58 (3)	55 (4)	49 (1)	47 (2)	44 (1)	42 (3)	39 (0)	39 (0)	39 (2)	36 (1)	35 (3)	32 (1)	31 (1)	18 (0)	0
BARICITINIB	82 (1)	81 (1)	79 (1)	77 (1)	75 (2)	71 (0)	69 (3)	65 (0)	65 (1)	63 (0)	62 (1)	61 (0)	61 (2)	59 (0)	58 (1)	56 (0)	38 (0)	2 (0)

Abbreviations: BARI = baricitinib; CI = confidence interval; ERA = enthesitis-related juvenile idiopathic arthritis; HR = hazard ratio; JIA = juvenile idiopathic arthritis; JPsA = juvenile psoriatic arthritis; NA = not applicable; PBO = placebo.

Note: Circle indicate patients who discontinue during the DBW period or complete the DBW period without experiencing a flare will have their data censored at the time of their discontinuation date or completion date.

[a] HR - stratified by JIA categories (polyarticular and extended oligoarticular versus ERA and JPsA).

[b] p-value is from log-rank test stratified by JIA categories (polyarticular and extended oligoarticular versus ERA and JPsA).

Figure 3 Time-to-flare comparison between baricitinib and placebo in the randomised withdrawal period of study JAHV

In the combined subgroup of patients with polyarticular and extended oligoarticular JIA (Figure 4), the proportions of patients with a flare were 53% in the placebo group and 18% in the baricitinib group, with a hazard ratio of 0.23 (p<0.001). In the combined subgroup of patients with ERA and juvenile PsA (Error! Reference source not found.), the proportions of patients with a flare were 44% in the placebo group and 15% in the baricitinib group, with a hazard ratio of 0.33 (p=0.072).

In the subgroup of patients with polyarticular JIA, the proportion of patients with a flare was 51% (26/51) for placebo and 18% (10/57) for baricitinib (p<0.001). In the subgroup of patients with extended oligoarticular JIA, the proportion of patients with a flare was 71% (5/7) for placebo and 20% (1/5) for baricitinib (p=0.24). In the subgroup of patients with ERA, the proportion of patients with a flare was 50% (10/20) for placebo and 19% (3/16) for baricitinib (p=0.083). In the subgroup of patients with juvenile PsA, no patients flared in the placebo group (n=3) nor in the baricitinib group (n=4).

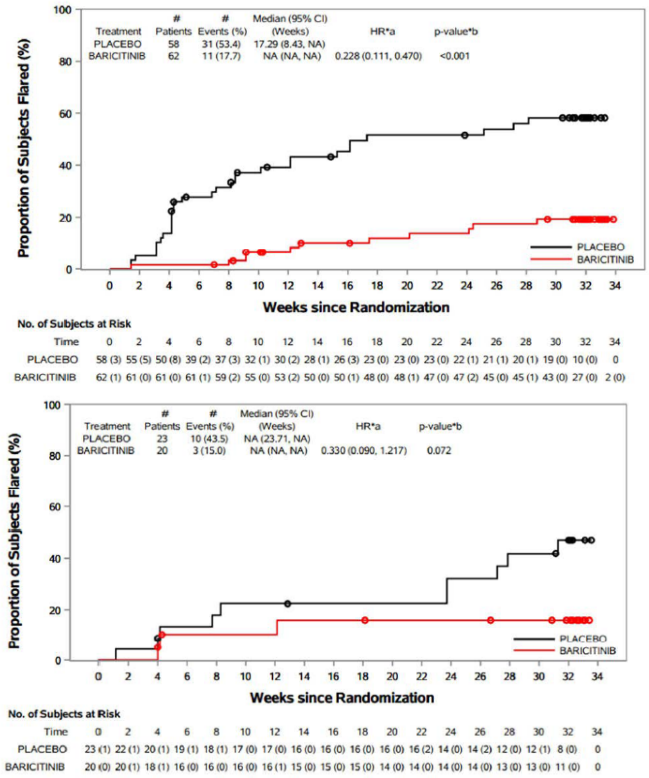


Figure 4 Time-to-flare comparison between baricitinib and placebo in the randomised withdrawal period of study JAHV, for patients with polyarthritis/oligoarthrits (left) and patients with ERA and jPsA (right)

Secondary outcomes in the open-label phase

The open-label period started at first age-based dose and ended at week 12 or with early discontinuation. A total of 167 (76%) patients reached a PedACR30 response at Week 12 of the combined PK/Safety and open-label lead-in period. The proportion of patients with a PedACR50 response was 64%, with PedACR70 was 46%, with PedACR90 response was 20%, and a PedACR100 response was reached in 10% (Panel 10). PedACR30 and PedACR50 responses varied between 79% - 60% and 69% - 60% over JIA subtypes. The 6 PedACR components all showed numerical improvements from baseline over weeks 2, 4, 8 and 12 (Panel 11).

Panel 10 PedACR responses overall and by JIA subtype in the OLLI period of study JAHV

JIA Sub-diagnosis	N	PedACR Response Rate, n (%)				
		30, n (%)	50, n (%)	70, n (%)	90, n (%)	100, n (%)
Polyarticular JIA	143	113 (79.0)	89 (62.2)	63 (44.1)	26 (18.2)	12 (8.4)
Extended oligoarticular JIA	16	11 (68.8)	11 (68.8)	9 (56.3)	4 (25.0)	1 (6.3)
ERA	50	37 (74.0)	33 (66.0)	27 (54.0)	13 (26.0)	9 (18.0)
JPsA	10	6 (60.0)	6 (60.0)	2 (20.0)	1 (10.0)	1 (10.0)

Abbreviations: ERA = enthesitis-related juvenile idiopathic arthritis; JIA = juvenile idiopathic arthritis; JPsA = juvenile psoriatic arthritis; N = number of patients; n = number of patients showing a response at the relevant response rate; PedACR = Pediatric American College of Rheumatology.

Panel 11 Changes in the items of the PedACR in the open-label period of study JAHV

PedACR Core Set Variable	Baseline		Week 2		Week 4		Week 8		Week 12	
	n	Mean (SD)	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)
Number of active joints	219	12.79 (11.1)	216	-4.62 (0.4)	216	-6.30 (0.4)	217	-7.29 (0.5)	217	-8.02 (0.4)
Number of joints with limited range of motion	219	8.82 (9.6)	216	-2.81 (0.3)	216	-3.91 (0.4)	217	-4.31 (0.4)	217	-4.36 (0.4)
Physician's Global Assessment of Disease Activity	219	6.51 (1.9)	216	-2.00 (0.1)	216	-2.78 (0.1)	217	-3.27 (0.2)	217	-3.72 (0.2)
Parent's Global Assessment of Well-being (CHAQ)	217	53.60 (25.1)	213	-13.93 (1.5)	213	-17.23 (1.6)	215	-20.25 (1.6)	215	-24.42 (1.6)
Physical function (CHAQ)	217	1.15 (0.7)	214	-0.22 (0.03)	214	-0.32 (0.03)	215	-0.41 (0.04)	215	-0.46 (0.04)
Acute-phase reactant (ERA)	216	27.27 (24.6)	212	-5.99 (0.8)	213	-6.30 (1.0)	214	-7.50 (1.2)	214	-8.39 (1.1)

Abbreviations: CHAQ = Childhood Health Assessment Questionnaire; ERA = enthesitis-related juvenile idiopathic arthritis; LSM = least squares mean; n = number of patients showing a response at the relevant response rate; PedACR = Pediatric American College of Rheumatology; SD = standard deviation; SE = standard error.

In total, 16 (7.3%) patients reached a status of inactive disease during or at week 12. The mean (SD) JADAS-27 score at baseline was 21.7 (8.8) and was decreased with mean (SE) of -12.4 (0.5) at week 12. The mean (SD) CHAQ Pain score at baseline was 55 (25) and was decreased with a mean (SE) of -25 (1.6) at week 12.

The mean PASI score for patients with JPsA (n=10) improved from baseline to week 12. The mean (SD) PASI score at baseline was 0.98 (1.8) and decreased with a mean (SE) of -0.65 (0.3) at week 12. In patients with enthesitis (ERA, jPsA), the mean (SD) SPARCC Enthesitis Index at baseline (n=59) was 3.2 (4.5) and decreased with a mean (SE) of -1.0 (0.3) at week 12. The mean (SD) JSpADA score at baseline (n=54) was 3.8 (1.3) and decreased with a mean (SE) of -1.2 (0.2) at week 12.

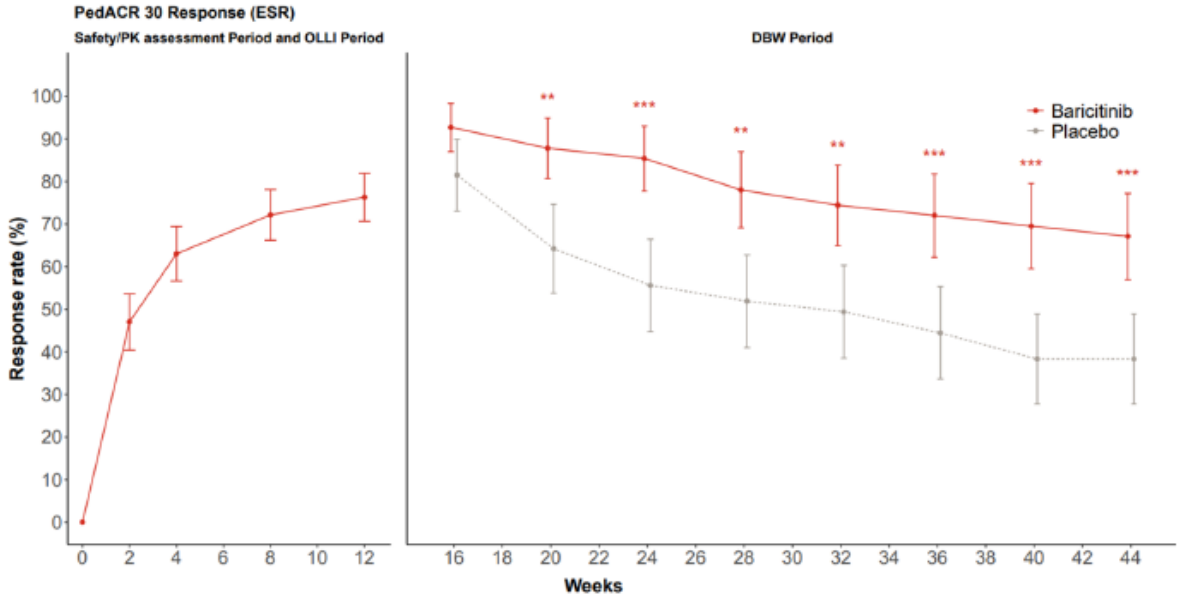
In CHQ-PF50 Phs, there was a mean (SE) improvement in Physical summary score of 13.1 (0.86) at week 12, while the mean (SD) score at baseline was 24.9 (14.8). In CHQ-PF50 PsS, there was a mean (SE) improvement in Psychosocial summary score of 5.4 (0.55) at week 12, while the mean (SD) score at baseline was 42.8 (10.9).

Secondary outcomes in the randomised withdrawal phase

The randomised withdrawal period started at the time of randomisation and ended when patients had a flare (time-to-flare was the primary outcome), at study week 44, or at earlier discontinuation.

Regarding PedACR responses, a total of 67% of patients receiving baricitinib, and 38% of patients receiving placebo reached a PedACR30 response (p<.001), Figure 5). A total of 63% of patients receiving baricitinib, and 37% of patients receiving placebo reached a PedACR50 response (p=0.002).

Also for PedACR70, 90, but not 100, between-group differences were (borderline) statistically significant at week 44 (Panel 12). During the randomised withdrawal period, the values of the 6 components of the PedACR decreased from week 12 (baseline) up to week 44 in both treatment groups, while the changes in the 6 components were all numerically larger in the baricitinib group, as compared to the placebo group (Figure 6 for joint counts).



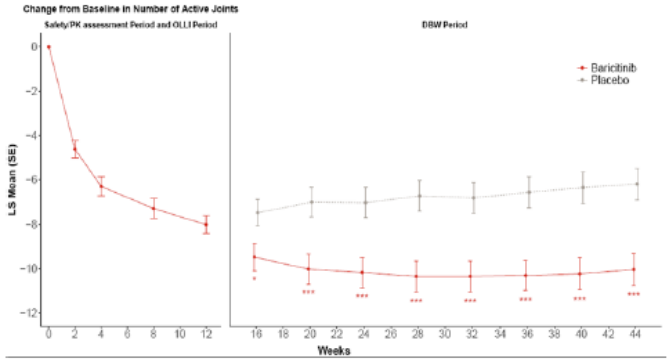
Abbreviation: ESR = erythrocyte sedimentation rate; PedACR30 = paediatric 30% improvement in American College of Rheumatology criteria.

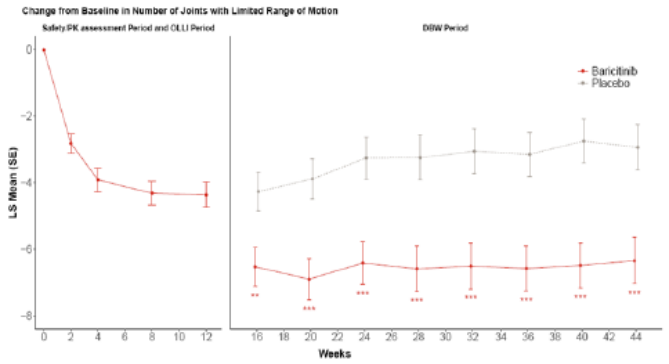
Figure 5 PedACR30 responses over time, in the randomised withdrawal part of study JAHV

Panel 12 PedACR responses over time by treatment group, in the randomised withdrawal period of study JAHV

Response	Week 16 n (%)		Week 20 n (%)		Week 24 n (%)		Week 28 n (%)		Week 32 n (%)		Week 36 n (%)		Week 40 n (%)		Week 44 n (%)	
	PBO N = 81	BARI N = 82	PBO N = 81	BARI N = 82	PBO N = 81	BARI N = 82	PBO N = 81	BARI N = 82	PBO N = 81	BARI N = 82	PBO N = 81	BARI N = 82	PBO N = 81	BARI N = 82	PBO N = 81	BARI N = 82
NRI																
30	66 (81.5)	76 (92.7)	52 (64.2)	72 (87.8)	45 (55.6)	70 (85.4)	42 (51.9)	64 (78.0)	40 (49.4)	61 (74.4)	36 (44.4)	59 (72.0)	31 (38.3)	57 (69.5)	31 (38.3)	55 (67.1)
50	61 (75.3)	65 (79.3)	47 (58.0)	67 (81.7)	40 (49.4)	67 (81.7)	41 (50.6)	62 (75.6)	38 (46.9)	59 (72.0)	35 (43.2)	56 (68.3)	31 (38.3)	56 (68.3)	30 (37.0)	52 (63.4)
70	44 (54.3)	45 (54.9)	37 (45.7)	56 (68.3)	30 (37.0)	49 (59.8)	32 (39.5)	55 (67.1)	29 (35.8)	47 (57.3)	29 (35.8)	50 (61.0)	25 (39.0)	47 (57.3)	29 (35.8)	44 (53.7)
90	19 (23.5)	24 (29.3)	20 (24.7)	35 (42.7)	17 (21.0)	31 (37.8)	21 (25.9)	35 (42.7)	22 (27.2)	36 (43.9)	22 (27.2)	32 (39.0)	19 (23.5)	33 (40.2)	19 (23.5)	35 (42.7)
100	14 (17.3)	12 (14.6)	16 (19.8)	20 (24.4)	13 (16.0)	15 (18.3)	16 (19.8)	22 (26.8)	17 (21.0)	23 (28.0)	17 (21.0)	24 (29.3)	14 (17.3)	24 (29.3)	13 (16.0)	24 (29.3)

Abbreviations: BARI = baricitinib; DBW = double-blind withdrawal; N = number of patients in the analysis population; n = number of patients who showed a response in that category; NRI = non-responder imputation; PBO = placebo; PedACR = Pediatric American College of Rheumatology; PedACR30/50/70/90/100 = paediatric 30%/50%/70%/90%/100% improvement in American College of Rheumatology criteria.





Abbreviations: DBW = double-blind withdrawal; OLLI = open-label lead-in; PK = pharmacokinetic.
p-Value vs placebo: ***p<0.001; **p<0.01; *p<0.05.

Figure 6 Course over time of two of the PedACR core set variables in study JAHV

In the proportion of patients with inactive disease, there were no significant differences between treatment groups at any week, including week 44. At week 44, there were 11 (14%) patients with inactive disease in the placebo group and 19 (23%) in the baricitinib group (p=0.11).

The mean change in JADAS-27 score showed statistically significant differences between treatment groups at weeks 20, 24, 28, 32, 36, 40, and 44 (Panel 13). At week 44, the mean (SE) change in JADAS-27 was -9.9 (1.0) in the placebo group and -14.2 (1.0) in the baricitinib group (p=0.001).

Panel 13 Change in JADAS-27 score over time in the randomised withdrawal part of study JAHV

Visit (Week Number)	PBO (N=81)		BARI (N=82)		p-value
	Obs n, mean (SD)	NRI n, LSM (SE)	Obs n, mean (SD)	NRI n, LSM (SE)	
16	78, -11.75 (8.6)	78, -12.35 (0.8)	79, -15.35 (8.3)	79, -14.16 (0.8)	.094
20	61, -12.36 (8.8)	78, -11.31 (0.9)	72, -16.93 (8.1)	80, -14.72 (0.9)	.004
24	49, -13.99 (8.0)	78, -11.15 (0.9)	69, -16.95 (8.1)	80, -14.64 (0.9)	.004
28	47, -13.98 (7.7)	78, -10.84 (0.9)	63, -17.66 (7.7)	80, -14.86 (0.9)	.001
32	41, -14.75 (7.9)	78, -10.76 (0.9)	60, -17.80 (7.6)	80, -14.70 (0.9)	.002
36	39, -14.65 (8.5)	78, -10.79 (1.0)	59, -17.64 (8.0)	80, -14.44 (1.0)	.005
40	36, -14.20 (9.7)	78, -9.99 (1.0)	57, -18.13 (8.0)	80, -14.54 (1.0)	<.001
44	33, -15.09 (9.9)	78, -9.91 (1.0)	54, -17.83 (8.3)	80, -14.24 (1.0)	.001

Abbreviations: BARI = baricitinib; JADAS-27 = Juvenile Arthritis Disease Activity Score-27; LSM = least squares mean; N = number of patients; n = number of patients that showed a response in that category; NRI = non-responder imputation; Obs = observed; PBO = placebo; SD = standard deviation; SE = standard error.

In CHAQ pain severity, a statistically significant difference between treatment groups was observed at weeks 20, 24, 28, 32, 36, 40, and 44. At week 44, the mean (SE) change in CHAQ pain severity was -16.7 (3.2) in the placebo group and -29.7 (3.3) in the baricitinib group (p=0.003).

In patients with juvenile PsA, at week 44 the mean (SE) change from baseline in PASI score was -0.8 (0.4) in the patients (n=3) on placebo and -1.2 (0.3) in patients (n=4) on baricitinib (p=0.57). Within each treatment group, the within-group changes were numerically similar over time, from week 20 up to and including week 44 .

In patients with juvenile PsA or with ERA, at week 44 the mean (SE) change in SPARCC enthesitis index was -1.9 (0.2) in the placebo (n=23) group and -1.5 (0.3) in the baricitinib (n=20) group (p=0.21). Within each treatment group, the within-group changes were numerically similar over time.

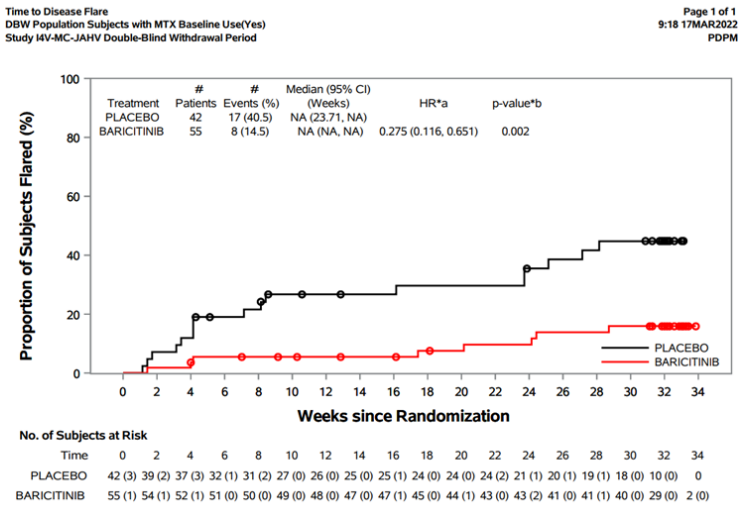
In patients with juvenile PsA or with ERA, at week 44 the mean (SE) change in JSpADA index was -1.5 (0.3) in the placebo (n=23) group and -2.6 (0.3) in the baricitinib (n=20) group (p=0.019).

In CHQ-PF50 Phs, at week 44 the mean (SE) change from baseline was 10.5 (1.7) in the placebo group and 16.5 (1.7) in the baricitinib group (p=0.009). Statistically significant differences between the treatment groups in favour of the baricitinib group were observed at weeks 24, 28, 32, 36, 40 and 44. In CHQ-PF50 PsS, at week 44 the mean (SE) change from baseline was 4.7 (1.1) in the placebo group and 6.1 (1.1) in the baricitinib group (p=0.36). A statistically significant difference between the treatment groups, in favour of the baricitinib group (p=0.043), was observed at week 20.

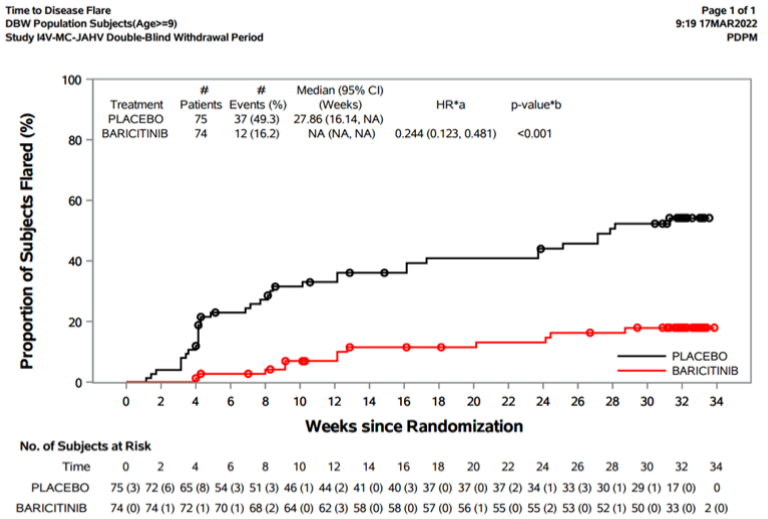
- Ancillary analyses

Results of subgroup analysis for time-to-flare (primary outcome) in the randomised withdrawal period showed that the treatment effect (hazard ratio) was consistent in size over subgroups of: prior biological DMARD use (yes/no), MTX use at baseline (yes/no), baseline ESR elevated (yes/no), JIA subtype (polyarticular and extended oligoarticular/juvenile PsA and ERA), female/male, age (⩾9 / <9), region EU, corticosteroid use at baseline (yes/no), weight class (⩾30 kg/<30 kg). The majority of hazard ratios lay in the range between 0,22 – 0,30 with p-values <0.001, while the overall treatment effect in time-to-flare had a hazard ratio of 0.24. Exceptions were the treatment effect in the juvenile PsA and ERA group with a non-significant p-value (HR=0.33, p=0.072), while smaller effects were found in the subgroups of age<9 years (HR=0.15, p=0.11) and with corticosteroid use at baseline (HR=0.14, p<0.011).

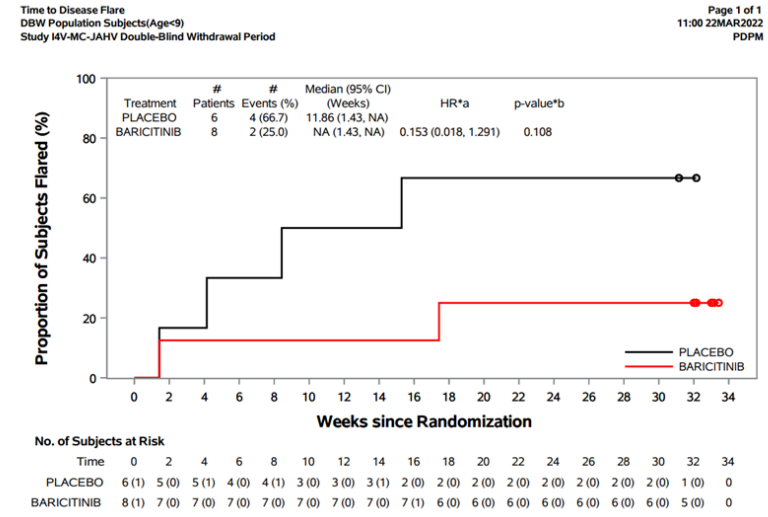
The treatment effects of baricitinib versus placebo on time-to-flare are also shown in the survival curves of subgroups of: methotrexate at baseline (yes) and age groups of 9 and older and younger than 9 (Figure 7). Survival curves for JIA subtypes have been presented above, in connection to the primary outcome.



A Methotrexate use



B age ⩾9 years



C age <9 years

Figure 7 Time-to-flare comparing baricitinib versus placebo for subgroups with methotrexate at baseline (A), age ≥9 years (B), age <9 years (C)

- Summary of main efficacy results

The following panels 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).

Panel 14 Summary of efficacy for trial JAHV

<table>
<tr><td colspan="4">Title: A Randomized, Double-Blind, Placebo-Controlled, Withdrawal, Safety and Efficacy Study of Oral Baricitinib in Patients from 2 Years to Less Than 18 Years Old with Juvenile Idiopathic Arthritis (JIA)</td></tr>
<tr><td>Study identifier</td><td colspan="3">JAHV (I4V-MC-JAHV)</td></tr>
<tr><td rowspan="2">Design</td><td colspan="3">Multicentre, double-blind, randomised, placebo-controlled, withdrawal trial, with an open-label lead-in period.</td></tr>
<tr><td colspan="2">Duration of open-label phase:
Duration of withdrawal phase:</td><td>12 weeks
32 weeks</td></tr>
<tr><td>Hypothesis</td><td colspan="3">Superiority</td></tr>
<tr><td rowspan="2">Treatment groups</td><td colspan="2">Baricitinib</td><td>2 mg QD or 4 mg QD, weight based; n = 81</td></tr>
<tr><td colspan="2">Placebo</td><td>Matching placebo; n = 82</td></tr>
<tr><td rowspan="2">Endpoints and definitions</td><td>Primary endpoint</td><td>In the withdrawal period.</td><td>Time to disease flare (flare defined as worsening of ≥30% in at least 3 of the 6 PedACR core criteria for JIA and an improvement of ≥30% in no more than 1 of the criteria) from the beginning of the double-blind withdrawal (DBW) period to the end of the DBW period</td></tr>
<tr><td>Secondary endpoints</td><td>In the Open label period: change from baseline up to week 12.*

In the withdrawal period: between-group difference up to week 44.</td><td>• PedACR30/50/70/90/100 responses
• Changes from baseline in the 6 PedACR core set variables:
- number of active joints
- number of joints with limited range of motion
- Physician’s Global Assessment of Disease Activity
- Parent’s Global Assessment of Well-being
- CHAQ disability index
- hsCRP and ESR
• Proportion of patients with inactive disease (Wallace et al. 2011)
• Change from baseline in JADAS-27</td></tr>
</table>

			• Change from baseline in CHAQ pain severity VAS item • Change in Psoriasis Area and Severity Index (PASI) score (jPsA) • Change from baseline in SPARCC enthesitis index (jPsA/ERA) • Change from baseline in JSpADA (jPsA/ERA) • Change from baseline in the Physical Summary Score (PhS) and Psychosocial Summary Score (PsS) of the Child Health Questionnaire-Parent Form 50

Database lock	16 March 2022		
Results and analysis			
Analysis description	Primary analysis		
Analysis population, time point and statistical model	Full Analysis Set Week 12 up to week 44 Log-Rank Test		
Descriptive statistics and estimate variability	Treatment group	PBO	BARI
	Number of patients	81	82
	Number of Events (%)	41 (50.6)	14 (17.1)
Effect estimate per comparison	Time to flare	Comparison groups	Placebo *versus* baricitinib
		Hazard Ratio	0.241
		95% CI	(0.128 - 0.453)
		p-value LR test	<0.001

Results and analysis				
Analysis description	Secondary analysis			
Analysis population, time point	Full Analysis Set Baseline up to week 12 (OLLI) Week 12 up to week 44 (PBO versus BARI)			
Descriptive statistics and estimate variability	Treatment group	OLLI	PBO	BARI
	Number of patients	219	81	82
	PedACR30, n (%)	145 (76)	31 (38)	55 (67)
	PedACR50, n (%)	119 (62)	30 (37)	52 (63)
	PedACR70, n (%)	88 (46)	29 (36)	44 (54)
	PedACR90, n (%)	38 (20)	19 (24)	35 (43)
	PedACR100, n (%)	20 (11)	13 (16)	24 (29)
	Number of active joints, LSM (SE)	-8.0 (0.4)	-6.2 (0.7)	-10.0 (0.7)
	Joints with limited ROM, LSM (SE)	-4.4 (0.4)	-2.9 (0.7)	-6.3 (0.7)
	PhysGA, LSM (SE)	-3.7 (0.2)	-2.9 (0.3)	-4.3 (0.3)
	ParentGA, LSM (SE)	-24 (1.6)	-19 (3.2)	-29 (3.3)
	CHAQ-di, LSM (SE)	-0.46 (0.04)	-0.38 (0.1)	-0.66 (0.1)
	ESR, LSM (SE)	-8.3 (1.1)	-6.6 (2.1)	-9.0 (2.2)
	Inactive disease, n (%)	--	11 (14)	19 (23)
	JADAS-27, LSM (SE)	-12.4 (0.5)	-9.9 (1.0)	-14.2 (1.0)
	CHAQ Pain, LSM (SE)	-25.2 (1.6)	-16.7 (3.2)	-29.7 (3.3)
	CHQ-PF50 PhSC, LSM (SE)	42.8 (10.9)	10.5 (1.7)	16.5 (1.7)
Effect estimate per comparison		Comparison groups	Placebo *versus* baricitinib	
	PedACR30*	Difference†	--	
		p-value	<0.001	
	PedACR50	Difference	--	
		p-value	0.002	
	PedACR70	Difference	--	

		p-value	0.052
	PedACR90	Difference	--
		p-value	0.019
	PedACR100	Difference	--
		p-value	0.043
	Inactive disease	Difference	--
		p-value	0.11
	JADAS-27	Difference	--
		p-value	0.001
	CHAQ Pain	Difference	--
		p-value	0.003
	CHQ-PF50 PhSC	Difference	--
		p-value	0.009
Notes: *Changes from baseline in the 6 PedACR core set variables were not subject to statistical testing of between-group changes; † size of between-group difference was not universally supplied.			

Abbreviations: BARI = baricitinib; CHAQ = Childhood Health Assessment Questionnaire; CHQ-PF50 = Child Health Questionnaire-Parent Form 50; ERA = enthesitis-related juvenile idiopathic arthritis; ESR = erythrocyte sedimentation rate; JADAS-27 = Juvenile Arthritis Disease Activity Score-27; OLLI = open-label lead-in; PBO = placebo; PedACR = Pediatric American College of Rheumatology; VAS = visual analogue scale;

2.6.5.3. Supportive study

Title: A Phase 3 Multicentre Study to Evaluate the Long-Term Safety and Efficacy of Baricitinib in Patients from 1 Year to <18 Years of Age with Juvenile Idiopathic Arthritis (I4V-MC-JAHX)

Objectives

The objectives are to evaluate the long-term safety and tolerability and the long-term efficacy of baricitinib in patients with JIA or systemic JIA.

Design

Study JAHX is a multicentre, long-term extension study to evaluate the safety and efficacy of baricitinib in patients with JIA. The treatment period lasts up to 264 weeks (5 years). Patients who participated in an originating study (Study JAHV or JAHU) are eligible for enrolment in Study JAHX.

The patients followed the age-based dosing strategy of the original trial (2 mg QD for patients <9 years of age and 4 mg QD for patients ≥9 years of age, which includes oral suspension for patients <6 years, tablets for patients ≥12, and a choice option for patients aged in between. The age-based dose and formulation was adjusted if the patient entered the next age cohort during the study. Patients were allowed to continue to receive concomitant treatments for JIA used during the study in which they were previously enrolled. MTX or other cDMARDs could be initiated or the dose increased, but all bDMARD and other JAK inhibitor therapies were prohibited. A change in analgesics/NSAIDs dosing or

the addition of analgesics/NSAIDs was permitted. Initiating oral corticosteroids and increasing/ decreasing oral corticosteroid dose was allowed. Intra-articular joint and bursal corticosteroid injections could be given.

Efficacy outcomes included, amongst others: the proportion of patients who achieve PedACR30/50/70/90/100 response rates using a baseline of the originator study, the proportion of patients who maintain PedACR30/50/70/90/100 response rates from baseline of the current study; the proportion of patients with a durable PedACR30/50/70/90/100 response from the time of randomisation in the originator study; the proportion of patients who have disease flare; time to disease flare. The scheduled visits in JAHX are approximately 12 weeks apart, while these were approximately 4 weeks apart in JAHV.

Results

Conduct of the study

A total of 199 patients entered Study JAHX from Study JAHV and were included in the JAHX ITT population for interim analysis at data cut-off date of 21 April 2022.

Patient disposition

A total of 199 patients entered Study JAHX from JAHV and were included in the JAHX ITT population. At the time of data cut-off, 174 patients were ongoing in the study. The most common reasons for discontinuation were: lack of efficacy (n = 9, 4.5%), withdrawal by subject (n = 9, 4.5%), and adverse event (n = 5, 2.5%). It was determined that 97 (49%) patients had at least 1 important protocol deviation; the most common reasons for important protocol deviation were related to: informed consent (57, 29%), data quality/source documents (29, 15%), and study procedures (25, 13%).

Exposure

The mean (SD) time of exposure was 59 (29) weeks, with 226 patient-years. In total, 196 patients were analysed for the determination of compliance with treatment. 186 patients were deemed compliant as they did not miss 20% or more of the prescribed doses during the study.

Baseline

The mean (SD) age of patients was 14 (3.1) years and most (69%) patients were female. The mean (SD) BMI was 20 (4). The majority of patients were Caucasian (70%) followed by Asian (23%).

Efficacy

The proportion of patients who achieve PedACR30/50/70/90/100 response using their baseline values in study JAHV shows that after 48 weeks (n=126), 89% have at least PedACR30, while 81% have PedACR50 and 66% PedACR70, PedACR90 is reached by 49%. The proportions of patients with responses tended to increase over time, seen from baseline of study JAHX (Panel 15).

Panel 15 Proportion of patients with PedACR responses in study JAHX

PedACR response rates (N = 199)	Week 0 (Nx = 184)	Week 4 (Nx = 190)	Week 12 (Nx = 188)	Week 24 (Nx = 178)	Week 36 (Nx = 150)	Week 48 (Nx = 126)	Week 60 (Nx = 96)	Week 72 (Nx = 64)	Week 84 (Nx = 47)	Week 96 (Nx = 32)	Week 108 (Nx = 7)	Week 120 (Nx = 1)
30, n (%)	111 (60.3)	149 (78.4)	164 (87.2)	156 (87.6)	134 (89.3)	112 (88.9)	87 (90.6)	60 (93.8)	42 (89.4)	27 (84.4)	5 (71.4)	0
50, n (%)	98 (53.3)	131 (68.9)	142 (75.5)	144 (80.9)	121 (80.7)	102 (81.0)	82 (85.4)	58 (90.6)	38 (80.9)	26 (81.3)	4 (57.1)	0
70, n (%)	83 (45.1)	103(54.2)	119 (63.3)	124 (69.7)	106 (70.7)	83 (65.9)	74 (77.1)	45 (70.3)	29 (61.7)	20 (62.5)	4 (57.1	0
90, n (%)	54 (29.3)	67 (35.3)	78 (41.5)	81 (45.5)	72 (48.0)	62 (49.2)	53 (55.2)	33 (51.6)	21 (44.7)	12 (37.5)	3 (42.9)	0
100, n (%)	39 (21.2)	46 (24.2)	59 (31.4)	71 (39.9)	61 (40.7)	47 (37.3)	41 (42.7)	24 (37.5)	17 (36.2)	7 (21.9)	3 (42.9)	0

Abbreviations: N = number of patients; Nx = number of patients with non-missing values; n = number of patients showing a response at the relevant response rate; PedACR = Pediatric American College of Rheumatology

The proportion of patients who maintain their PedACR30/50/70/90/100 response from baseline of the current study. Shows that at week 148, the majority of patients (81% - 96%) could maintain the response they had at baseline of study JAHX (Panel 16).

Panel 16 Proportion of patients maintaining PedACR responses in study JAHX

PedACR response rates	Week 0	Week 4	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 108	Week 120
30, n/Nx (%)	111/111 (100.0)	106/111 (95.5)	108/111 (97.3)	100/103 (97.1)	78/79 (98.7)	59/62 (95.2)	46/48 (95.8)	28/28 (100.0)	13/15 (86.7)	4/5 (80.0)	0/1 (0.0)	0/1 (0.0)
50, n/Nx (%)	98/98 (100.0)	94/98 (95.9)	94/98 (95.9)	88/90 (97.8)	65/68 (95.6)	52/54 (96.3)	40/43 (93.0)	22/23 (95.7)	10/12 (83.3)	2/3 (66.7)	0/1 (0.0)	0/1 (0.0)
70, n/Nx (%)	83/83 (100.0)	76/83 (91.6)	80/83 (96.4)	74/77 (96.1)	54/57 (94.7)	43/47 (91.5)	37/39 (94.9)	20/21 (95.2)	10/10 (100.0)	2/2 (100.0)	0/0 (NA)	0/0 (NA)
90, n/Nx (%)	54/54 (100.0)	49/54 (90.7)	48/54 (88.9)	44/50 (88.0)	31/35 (88.6)	24/28 (85.7)	24/26 (92.3)	11/12 (91.7)	8/8 (100.0)	1/1 (100.0)	0/0 (NA)	0/0 (NA)
100, n/Nx (%)	39/39 (100.0)	31/39 (79.5)	34/39 (87.2)	31/36 (86.1)	23/26 (88.5)	17/21 (81.0)	16/20 (80.0)	8/10 (80.0)	7/7 (100.0)	1/1 (100.0)	0/0 (NA)	0/0 (NA)

Abbreviations: NA = not applicable; Nx = number of patients with non-missing values; n = number of patients showing a response at the relevant response rate; PedACR = Pediatric American College of Rheumatology

When resuming or continuing baricitinib when entering study JAHX, few patients had a flare of disease activity (Panel 17).

Panel 17 Proportion of patients with a disease flare in study JAHX, stratified by allocated group in JAHV

Study Week		Week 0	Week 4	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 108	Week 120
DBW PBO (N = 78)	n (%)	40 (51.3)	41 (52.6)	42 (53.8)	42 (53.8)	42 (53.8)	42 (53.8)	42 (53.8)	43 (55.1)	43 (55.1)	43 (55.1)	43 (55.1)	43 (55.1)
DBW BARI (N = 77)	n (%)	13 (16.9)	13 (16.9)	13 (16.9)	13 (16.9)	16 (20.8)	17 (22.1)	17 (22.1)	17 (22.1)	17 (22.1)	17 (22.1)	17 (22.1)	17 (22.1)
p-value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Abbreviations: BARI = baricitinib; DBW = double-blind withdrawal period; N = number of patients; n = number of patients in that category; PBO = placebo

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Design

The overall study design, with an open-label lead-in period of 12 weeks, followed by a randomised double-blind withdrawal phase for patients with at least some response (PedACR30) and time-to-flare as primary outcome, in patients at least 2 years of age with JIA according to ILAR categories, is in line with the expectations, as expressed in the Guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis (EMA/CHMP/239770/2014 Rev. 2). Use of placebo as a comparator is acceptable in light of the randomised withdrawal design.

Patient population

The selected JIA study population of 2-18 years of age is in line with the guideline and in line with the proposed indication. The diagnoses according to ILAR subtypes are endorsed, and the definitions of 'active' disease and of failure to previous treatment with a conventional or biologic DMARD are agreed. The exclusion criteria are considered reasonable and not overly restrictive. Patients with active uveitis at baseline were not included and uveitis has not been followed as an efficacy outcome, but it has been covered as TEAE (see Safety section).

The baseline demographic variables appear representative for the target population. Although the vast majority (80%) of patients was adolescent and most (65%) of patients had polyarticular disease, it appears that sufficient data are available for all JIA subtypes and age classes to extrapolate efficacy. Because of the low prevalence of JIA and its subtypes over age classes, it is expected to rely on extrapolation to some extent, as explained in the EMA Guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis (EMA/CHMP/239770/2014 Rev. 2).

A majority (68%) of patients was included through centres in European countries, which supports the translation of study results to children with JIA living in the EU.

Based on the average (SD) values of disease activity assessments and the inclusion criteria, the included patients will have active disease at baseline, as expected. Overall it seems that at baseline of the randomised-withdrawal phase the patients in the baricitinib group where somewhat more ill than the patients in the placebo group, regarding level of active joints and because at baseline more patients used concomitant methotrexate and corticosteroid use. This not necessarily has led to unconservative bias for efficacy comparisons. In time to flare (primary outcome), the treatment effect (HR) comparing baricitinib with placebo was basically similar over these subgroups.

All patients entering study JAHV had taken prior DMARDs, 97% had used csDMARDs and 53% had used biologics. The included population therefore is in line with the target population of JIA patients

'*who have had an inadequate response or intolerance to one or more prior conventional synthetic or biologic disease-modifying antirheumatic drugs (DMARDs)*'.

Treatment and dose

A dose-response study has not been performed. Instead, dose selection for the pivotal JAHV trial (open-label and randomised withdrawal phases) was based on modelling using PK data of adults with RA, and verified in age cohorts in the initial PK/safety phase of the pivotal study. The dose that was derived from the PK modelling in RA adults was: 4 mg for children aged 9 years and above and adolescents up to 18 years, and 2 mg for children less than 9 years of age, and this dose regimen was carried forward in pivotal trial JAHV and open-label extension trial JAHX. However, the dose proposed in the SmPC is weight-based: 4 mg QD for patients ⩾30 kg and 2 mg QD for patients <30 kg, for patients aged 2-18 years. This posology is considered acceptable as discussed in the clinical pharmacology section.

The experimental treatment, provided as tablets or suspension, appears to be adequately matched by placebo in the blinded withdrawal phase. The 1 mg tablet was not used for the study because the posology derived from the PK modelling in RA adults was: 4 mg for subjects aged 9 years up to 18 years, and 2 mg for subjects less than 9 years of age. The 1 mg tablet will be needed in practice as it is needed for halving the dose of patients using 2 mg dose when needed for patients using a strong OAT3 inhibitor or having reduced renal function. The suspension used in the study is not yet approved. For this reason, the Applicant proposed to dissolve tablets in water for those patients who are not able to swallow tablets as reflected in sections 4.2 and 6.6 of the SmPC. The Applicant provided data supporting the bioequivalence of the 2 mg/ml solution and the 4 mg tablet, which the CHMP considered acceptable.

Concomitant treatment with a stable dose of oral corticosteroids of ⩽10 mg/day or 0.2 mg/kg/day prednisone equivalent, stable use of MTX or another DMARD (not >2 DMARDs), stable use of NSAIDs and analgesics, was permitted. This is reasonable, given the requirement of patients having the active disease but also an insufficient response to a previous DMARD. Biological DMARDs were not allowed, and neither was any previous use of a JAK inhibitor, which is agreed. The discontinuation criteria are understood and are in line with what is already included in the SmPC.

The initially proposed indication included use with concomitant DMARDs. However, most patients used methotrexate concomitantly and few patients used other DMARDs. Methotrexate was no effect modifier (see subgroups below). Therefore, at the CHMP's request, the MAH accepted to remove the concomitant use of Olumiant with DMARDs from the indication and the indication only includes concomitant use with methotrexate.

Outcomes and endpoints

The primary outcome, time-to-flare in the withdrawal portion of the trial, and secondary outcomes, including proportion of patients with a flare, PedACR responses, JADAS, pain, concepts of remission/low disease activity, PASI, enthesitis, are in line with the expectations, as outlined in the Guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis (EMA/CHMP/239770/2014 Rev. 2). The use of outcomes assessing functional ability and 'quality of life' is recommended. These domains are covered by the CHQ-PF50, an internationally recognised standarised measurement tool, which is considered reasonably valid for use in patients with JIA (Ruperto et al. 2001; Hullmann 2011). No information regarding the validity of CHAQ in JIA was found in the dossier, but it also appears to be sufficiently valid (Pouchot et al 2014).

Sample size

The planned sample size of 128 patients in the DBW part yields 80% power to demonstrate a difference in proportions of patients experiencing a flare in case 60% of patients on placebo experienced flare and 35% of patients on baricitinib.

Randomisation and blinding

Randomisation was stratified by i) history of prior bDMARD use, yes versus no; JIA category, polyarticular and extended oligoarticular (combined) versus ERA and JPsA (combined); and in the polyarticular patients: Predose exposure erythrocyte sedimentation rate (ESR), elevated (>20 mm/hour) versus not elevated. The experimental treatment was matched with placebo tablets or suspension, as appropriate. All study assessments were performed by study personnel who were blinded to the patient's treatment group. To prevent potential unblinding due to observed efficacy or laboratory changes, two different assessors were used for assessing efficacy and safety outcomes.

Statistical methods

The primary analysis for comparison of time to flare between placebo and baricitinib in the double-blind washout study was performed using Kaplan-Meier analysis with the hazard ratio from Cox regression reported as effect size. Primary analysis was performed on an ITT basis and censored patients that discontinued treatment before experiencing flare or end of treatment assuming censoring at random. Secondary endpoints were not included in the confirmatory testing strategy and can therefore only be considered supportive. No interim analyses are performed as part of the DBW study.

Study conduct

Although the protocol has been amended 4 times after the study started, the amendments did not appear to have complicated the study or the interpretation of results.

Patient disposition

Of the 219 patients entering open-label treatment in the 12-week lead-in period, 56 (26%) dropped out, which in most cases (n=38) was a failure to meet randomisation criteria (PedACR30 response) at week 12. The drop-out in the open-label phase due to any other reason was ~10% of the total, which is acceptable. After randomisation, more patients in the placebo group as compared to the baricitinib group dropped out, which can be attributed to failure to meet continuation criteria (a flare defined as a worsening of ⩾30% in at least 3 of the 6 PedACR core criteria). The important protocol violations do not appear to have distorted the assessment of efficacy or safety, not by their nature and not because they were grossly equally divided over the two treatment groups.

Efficacy data and additional analyses

Primary outcome

The primary outcome of the pivotal study JAHV was met: patients on baricitinib were less likely to get a flare than patients on a placebo. By the end of the randomised withdrawal part of the study, 17% (14/81) of patients receiving baricitinib had a disease flare as compared with 51% (41/82) of patients receiving placebo, with a hazard ratio of 0.24 (p<0.001). In the placebo group, more than half of the number of flares (26/41) occurred within the first 8 weeks, but this also occurred in the baricitinib group (9/14). Nevertheless, the survival curves of time-to-flare clearly separate the placebo group from the baricitinib group.

It is supportive for the proposed indication that the treatment effect in time-to-flare was present in three of the JIA subtypes but not in the small juvenile PsA group where no flares occurred. In the subgroup of patients with polyarticular JIA, the proportion of patients with a flare was 51% (26/51) for placebo and 18% (10/57) for baricitinib (p<0.001). In the subgroup of patients with extended

oligoarticular JIA, the proportion of patients with a flare was 71% (5/7) for placebo and 20% (1/5) for baricitinib (p=0.24). In the subgroup of patients with ERA, the proportion of patients with a flare was 50% (10/20) for placebo and 19% (3/16) for baricitinib (p=0.083). In the subgroup of patients with juvenile PsA, no patients flared in the placebo group (n=3) nor in the baricitinib group (n=4). Due to the small group size, the absence of flares in the jPsA group may be a chance finding. Juvenile PsA is known to come with flares, and flares in this subgroup did occur in a similar trial with an IL-17 inhibitor or placebo (Cosentyx SmPC), for example. Within-group changes in the jPsA subgroup in the open-label period were supportive for efficacy, also in psoriasis area severity score (PASI) (see further below).

Secondary outcomes

The result for the primary outcome was supported by the main secondary outcomes in the randomised withdrawal phase, notably by between-group differences in PedACR30 and higher cut-offs such as PedACR50, 70 and 90, the 6 individual PedACR components (number of active joints, number of joints with limited ROM, PhGA, Parent GA, CHAQ disability index, ESR), change in JADAS-27, change in CHAQ Pain; and to some extent the changes in SPARCC enthesitis index and the JSpADA score in patients with juvenile PsA or ERA. In the randomised withdrawal period, the proportion of patients with a PedACR30 response steadily decreased from 100% at week 12 to 67% at week 44 in the baricitinib group. However, the loss of response on a group level was clearly more pronounced in the placebo group in which only 38% of patients still had a PedACR30 response at week 44. The results in PedACR30 are supported by the similar trends over time in its 6 individual components, that all show numerical improvements over time (statistical analysis was not planned). NRI was used in the calculation of PedACR responders, meaning that patients who drop-out due to a flare are counted as non-responders, which is agreed. The results in PedACR50 and 70 showed similar trends as the PedACR30, while in the baricitinib group the proportions of patients with a PedACR90 or 100 slowly increased over time. By the end of the randomised withdrawal phase at week 44, there were numerically somewhat more patients with inactive disease in the baricitinib group (23%) as compared to the placebo group (14%), which, however, was not statistically significant (p=0.11). The frequency of remission (inactive disease for 24 weeks) was declared as a secondary outcome, but results were not found in the dossier (not pursued). Based on the low occurrence of patients reaching PedACR100/inactive disease (and minimal disease activity, not shown), these ultimate treatment goals appear to be difficult with baricitinib in JIA.

As pointed out above, the subgroup of patients with juvenile PsA was small, and the baseline PASI scores low, preventing meaningful comparison between baricitinib and placebo, though the numerical results in the withdrawal phase do not suggest an absence of effect on PASI. The results on SPARCC enthesitis index and JSpADA index in patients with juvenile PsA/ERA were also supportive; improvements were numerically and/or statistically significant in favour of baricitinib.

Effects in the open-label period

The treatment effect is also supported by the changes in outcomes during the 12-week open-label lead-in period. A total of 167 (76%) patients had a PedACR30 response at Week 12 of the open-label period, which means that not all patients reached at least a moderate response (PedACR30) after 12 weeks of treatment. However, there still were considerable proportions of patients who had a PedACR50 response (64%), a PedACR70 response (46%) or a PedACR90 response (20%). Remission, or near-remission, was infrequently reached, according to the low (<10%) proportions of patients with PedACR100 or inactive disease. Decreases in the 6 components of the PedACR (number of active joints, number of joints with limited ROM, PhGA, Parent GA, CHAQ disability index, ESR), JADAS-27 score, CHAQ Pain, and CHQ-PF50 Physical Summary Score were all supportive, showing numerical improvements over the course of 12 weeks. The improvement in CHQ-PF50 Psychosocial Summary

Score was relatively small. Despite the small group and relatively low PASI score at baseline, the mean PASI score for patients with juvenile PsA (n=10) numerically improved from baseline to week 12. In patients with ERA or jPsA, the SPARCC enthesitis index and the JSpADA also showed numerical improvements.

Clinical relevance

The difference between baricitinib and placebo in occurrence of flare is considered clinically relevant, which is notably supported by clinically relevant proportions of patients with a PedACR30, (50, 70 or 90), large reductions in the joint counts of -7 (active) to -4 (limited ROM) that remain when staying on baricitinib in the withdrawal phase, a mean change of -12 in JADAS-27 that exceeds the estimated MID of -5.5 (Bulatovic 2013), a change of ~0.5 in CHAQ disability index (range 0-3) which is supported by the change in CHQ-PF50 Phs, average changes >20 mm on Parent's global assessment of well-being and CHAQ assessment of pain. It is acknowledged that the study design, with an open-label phase and a randomised placebo-controlled withdrawal phase, makes it more difficult to evaluate the clinical relevance of the treatment effect of baricitinib, as compared to placebo. However, overall the treatment effect in the randomised withdrawal period, supported by changes in the open-label lead-in period, is considered to be clinically relevant, and the treatment effect on the primary outcome, time-to-flare (hazard ratio=0.24; p<0.001) seems – acknowledging all limitations of comparisons from 2 different studies – to be in line with the effect found for treatment with anti-IL17 (hazard ratio=0.28; p<0.001) although the population was ERA and juvenile PsA (Cosentyx SmPC). While reasonable numbers of JIA patients reached an overall good response with baricitinib, it appeared still to be difficult to reach the ultimate treatment goals of remission/low disease activity within the 1-year duration of the pivotal study. After a treatment duration of 1-2 years, the number of patients with low disease activity seems to increase (study JAHX, see further below).

Subgroup analysis

According to the results of the subgroup analysis in predefined subgroups, the results on time-to-flare in the randomised withdrawal phase appear to be stable across predefined subgroups, including JIA subtype, age, weight, concomitant methotrexate use, and within the EU region. The age class is also relevant because the dose was stratified by age class (2 mg if <6 years of age and 4 mg if ≥6 years). The treatment effect in time-to-flare (proportion with a flare) and PedACR30 is reversed for the youngest subgroup of children aged 2 to <6 and for the jPsA subgroup. Both subgroups are limited in size: n=6 for the youngest children 2 to <6, and n=7 for the jPsA subgroup, which means that these reversed treatment effects may be a chance effect. It is considered that the favourable effects in the older children, in other JIA subtypes and adults with PsA, can be generalised to these two subgroups. The results in the youngest children are supported by the size of the PedACR30 response in the open-label phase. The results in the jPsA subgroup are supported by improvements in the open-label phase and numerical treatment effects in the randomised-withdrawal phase (PedACR response, PASI, SPARCC, JSpADA). Consequently, despite reversed treatment effects in time-to-flare (primary outcome) in patients 2 to <6 and in patients with jPsA, it is considered that the efficacy has been demonstrated in these subgroups of the target population.

Maintenance of efficacy

In the long-term follow-up study JAHX, 199 patients of the original 219 patients in study JAHV were included and 126 patients were followed up to 1 year. The available long-term efficacy data suggest that up to approximately one year, the effects of baricitinib on disease activity are generally maintained, and few patients got a flare. Follow-up is still limited, but few patients dropped out, which is reassuring.

Upon CHMP request, the MAH included in the Section 4.2 of the SmPC a stopping rule for patients with JIA, in case of non-response at 12 weeks. This is in line with the design of pivotal study JAHV, which had an open-label treatment phase of 12 weeks, after which patients with non-response did not proceed to the randomised-withdrawal phase. At the end of the 12-week open-label period, non-response (according to PedACR30) occurred in 38/220 (17%) of patients.

2.6.7. Conclusions on the clinical efficacy

The primary outcome of the pivotal study JADV was met: patients on baricitinib were less likely to get a flare than patients on placebo. By the end of the randomised withdrawal part of the study, 17% of patients receiving baricitinib had a disease flare compared to 51% of patients receiving placebo. The difference between baricitinib and placebo is clinically relevant and supported by the results of secondary outcomes including PedACR responses, the 6 individual components of the PedACR, changes in pain and in JADAS-27 score in functioning.

Most patients used methotrexate, which was not an effect modifier for the primary outcome. At the CHMP's request, the MAH accepted to remove the concomitant use of Olumiant with DMARDs from the indication and the indication only includes concomitant use with methotrexate.

There were trends supportive for improvement for patients with psoriasis, enthesis and axial spondyloarthritis, although these subgroups were smaller and between-group differences not always statistically significant.

The results on time-to-flare in the randomised withdrawal phase appear to be stable across predefined subgroups, including JIA subtypes. In the subgroup of patients with polyarticular JIA, the proportion of patients with a flare was 51% (26/51) for placebo and 18% (10/57) for baricitinib ($p<0.001$). In the subgroup of patients with extended oligoarticular JIA, the proportion of patients with a flare was 71% (5/7) for placebo and 20% (1/5) for baricitinib ($p=0.24$). In the subgroup of patients with ERA, the proportion of patients with a flare was 50% (10/20) for placebo and 19% (3/16) for baricitinib ($p=0.083$). In the subgroup of patients with juvenile PsA, no patients flared in the placebo group ($n=3$) nor in the baricitinib group ($n=4$). Because of the low prevalence of JIA and its subtypes over age classes, it is expected to rely on extrapolation to some extent, as explained in the EMA Guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis (EMA/CHMP/239770/2014 Rev. 2). The CHMP considers that sufficient data are available for all JIA subtypes and age classes to extrapolate efficacy.

Over 1 – 2 years of treatment, it appears that in most patients, responses can be maintained without the occurrence of flares.

In conclusion, the CHMP considers that the efficacy of baricitinib is supported by the data submitted in the claimed indication: "Juvenile Idiopathic Arthritis: Olumiant is indicated for the treatment of Juvenile idiopathic arthritis in patients 2 years of age and older who have had an inadequate response or intolerance to one or more prior conventional synthetic or biologic disease-modifying antirheumatic drugs (DMARDs): Polyarticular juvenile idiopathic arthritis (polyarticular rheumatoid factor positive [RF+] or negative [RF-], extended oligoarticular), Enthesitis related arthritis, and Juvenile psoriatic arthritis. Baricitinib may be used as monotherapy or in combination with methotrexate"

2.6.8. Clinical safety

Safety data for the applied indication come from two studies on baricitinib-treated patients aged 2 to less than 18 years with non-systemic JIA:

- Study JAHV; a multicentre, randomised, double-blind, placebo-control, withdrawal phase 3 study, with final database lock 16 March 2022, and
- Study JAHX; a multicentre, open label, long-term extension study, with interim database cut-off date 21 April 2022.

The two main analysis sets for evaluating the safety of baricitinib in JIA were: 1) The placebo controlled double-blind withdrawal (PC DBW) period of study JAHV, and 2) the All Bari JIA safety analysis set composed of the data from studies JAHV and JAHX.

2.6.8.1. Patient exposure

A total of 220 patients was exposed to any dose of baricitinib in the JIA clinical trial program (Panel 18). In the PK/Safety and OLLI period, the exposure was mean (SD) 12.4 (1.6) weeks of exposure and 52.2 PY of exposure. In the PC DBW period 82 patients were exposed to baricitinib and 81 to placebo, with a mean (SD) exposure of 26.3 (sd 10.0) versus 18.9 (sd 12.3) weeks, and 41.4 PY versus 29.4 PY of exposure. In the placebo-controlled DBW period, the total exposure was approximately 40% higher in the baricitinib group than that in the placebo group due to more number of patients in the placebo group who flared and discontinued treatment (see Efficacy section).

Overall exposure in the All JIA safety analysis set was 325.7 PY; 171 patients were exposed to baricitinib for at least 52 weeks.

Panel 18 Summary of exposure in the randomised withdrawal period and the JIA safety analysis set.

	PC DBW Period		All JIA Safety Analysis Set (n)
	PBO (n)	BARI (n)	
N	81	82	220
Days of exposure (Mean)	NR	NR	540.7
Days of exposure (Median)	NR	NR	546.0
Weeks of exposure (Mean)	18.91	26.34	NR
Weeks of exposure (Median)	17.14	31.86	NR
Weeks of Exposure, n (%)			
≥4	NR	NR	218
≥8	58 (71.6)	76 (92.7)	216
≥12	NR	NR	212
≥16	43 (53.1)	65 (79.3)	204
≥24	NR	NR	197
≥32	18 (22.2)	40 (48.8)	185
≥52[a]	NR	NR	171
≥76	NR	NR	115
≥104	NR	NR	62
Total PYE	29.35	41.39	325.7

Abbreviations: BARI = baricitinib; JIA = juvenile idiopathic arthritis; N = number of patients in the safety analysis set; n = number of patients in the specified category; NR = not reported; PBO = placebo; PYE = patient years of exposure.

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

Notes: Time spent within any temporary study drug interruption is included within exposure time. Time after permanent study drug discontinuation is not included within exposure time. Total patient years is calculated as sum of duration of exposure in days for all patients in dosing regimen/365.25.

2.6.8.2. Adverse events

Summary of adverse events

In the open-label periods, 57% of patients had at least one treatment emergent adverse event (TEAE), which in 4 cases (1.8%) was a severe adverse event (AE) and in 6 cases (2/7%) was a serious adverse event (SAE); two (0.9%) patients discontinued due to an AE (Panel 19).

In the placebo-controlled period, 47% (38/81) of patients in the placebo group had at least 1 TEAE, which was 66% (54/82) in the baricitinib group. Exposure to study treatment was larger in the baricitinib group (41 PY) as compared to the placebo group (29 PY). Most TEAEs were mild or

moderate in severity. In the placebo group, 2 patients (2.5%) had at least one severe AE and also 2 patients in the baricitinib group. No deaths occurred; there were 3 patients (3.7%) in the placebo group and 4 patients (4.9%) in the baricitinib group with at least one SAE. Discontinuations due to AEs were infrequent in the placebo (n=2) and baricitinib (n=1) groups.

Panel 19 Overview of Adverse events in the study JAHV

Treatment Period	**PK/Safety & OLLI**	**DBW**	
Treatment	**BARI**	**PBO**	**BARI**
N	220	81	82
	n (%)	**n (%) [EAIR]**	**n (%) [EAIR]**
Patients with ≥1 TEAE[a]	126 (57.3)	38 (46.9) [214.6]	54 (65.9) [254.7]
TEAEs by severity			
Mild	83 (37.7)	24 (29.6) [107.1]	31 (37.8) [98.2]
Moderate	39 (17.7)	12 (14.8) [45.4]	21 (25.6) [60.8]
Severe	4 (1.8)	2 (2.5) [6.8]	2 (2.4) [4.8]
Death	0	0	0
SAEs	6 (2.7)	3 (3.7) [10.2]	4 (4.9) [9.7]
AEs leading to discontinuation of study intervention (including death) [b]	2 (0.9)	2 (2.5) [6.8]	1 (1.2) [2.4]

Abbreviations: AE = adverse event; BARI = baricitinib; DBW = double-blind withdrawal; N = number of patients; n = number of patients in specified category; OLLI = open-label lead-in; PBO = placebo; PK = pharmacokinetic; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

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

[b] One patient (I4V-MC-1101-12005) discontinued the study drug during the DBW period due to consistent mild headache that later led to hospitalisation. Although the discontinuation happened in the DBW period, the site reported the discontinuation in the PK/OLLI study period when the AE of headache was first reported.

Common adverse events

In the open-label periods (N=220), most TEAEs occurred in the SOCs of infections and infestations (25%), gastro-intestinal disorders (15%), investigations (12%), musculoskeletal and connective tissue disorders (11%), nervous system disorders (8.2%), respiratory disorders (6.8%), skin and subcutaneous disorders (6.4%), blood and lymphatic system disorders (5.9%). In the open-label baricitinib treatment period, the most frequently occurring TEAEs were:

- nasopharyngitis n: 19 (8.6%)
- headache n: 14 (6.4%)
- arthralgia n: 12 (5.5%)
- nausea n: 11 (5%)
- upper respiratory tract infection n: 11 (5%)
- (upper) abdominal pain, n=11 (5%)
- vomiting n: 10 (4.5%)

In the placebo-controlled period, the occurrence of TEAEs in the placebo versus baricitinib groups differed for the SOCs of infections and infestations (19% *versus* 38%), investigations (2.5% *versus* 17%), respiratory disorders (14% *versus* 17%), musculoskeletal and connective tissue disorders (9.9% *versus* 16%), gastro-intestinal disorders (6.2% *versus* 15%), nervous system disorders (4.9% versus 12%), skin and subcutaneous disorders (3.7% *versus* 8.5%). For the SOC blood and lymphatic system disorders the comparison of placebo versus baricitinib was (3.7% versus 4.9%). The most common TEAE's by PT in baricitinib treated patients were:

- upper respiratory tract infection (n = 9; 11%, IR 22.9),
- headache (n = 9; 11%, IR 23.3),
- nasopharyngitis (n = 6, 7.3%, IR 15.3),

- arthralgia (n = 6; 7.3%, IR 15), and
- oropharyngeal pain (n = 5, 6.1%, IR 12.5).

TEAE's were mostly mild to moderate in severity; 2 severe events were reported in the baricitinib group (COVID-19 and PE), and 3 in the placebo group (bronchospasm, overdose, suicide attempt). Numerical differences of TEAEs between the baricitinib and placebo groups were detected for upper respiratory tract infection, oropharyngeal pain, and headache (Panel 20).

Panel 20 Treatment emergent Adverse Events with a numerical imbalance, in the placebo controlled period of study JAHV

Treatment Period	DBW		IRR
	PBO	BARI	
	n (%) [EAIR]	n (%) [EAIR]	
Infections and Infestations			
Upper respiratory tract infection	1 (1.2) [3.4]	9 (11) [22.9]	6.8
Respiratory, Thoracic, and Mediastinal Disorders			
Oropharyngeal pain	1 (1.2) [3.4]	5 (6.1) [12.5]	3.7
Nervous System Disorders			
Headache	3 (3.7) [10.4]	9 (11.0) [23.3]	2.2

Abbreviations: BARI = baricitinib; DBW = double-blind withdrawal; EAIR = exposure-adjusted incidence rate; IRR = incidence rate ratio; n = number of patients in the specified category; PYR = patient years at risk.
Note: EAIRs are calculated based on PYR.

As clustered group of events, upper respiratory tract infections/oropharyngeal pain, abdominal pain, and rash, were more frequent in the baricitinib group (). The occurrence of upper respiratory tract infections/ oropharyngeal pain was 11% in the placebo group and 22% in the baricitinib group; abdominal pain occurred in 6.9% versus 17% in the placebo and baricitinib groups, rash occurred in 3.4% (n=1) and in 10 % (n=4) of the placebo and baricitinib groups.

Panel 21 Clusters of Treatment emergent Adverse Events, in the placebo-controlled period of study JAHV

	PC DBW			
Treatment group	**PBO**		**BARI**	
N	81		82	
PYE	29.4		41.4	
CLUSTER	**n**	**% (IR)**	**N**	**% (IR)**
Upper respiratory tract infections (HLT) and oropharyngeal pain	9	11.1 (33.2)	18	22.0 (52.0)
Abdominal pain (3 categories)	2	2.5 (6.9)	7	8.5 (17.2)
Rash	1	1.2 (3.4)	4	4.9 (9.8)
Fractures*	1	1.2 (3.4)	2	2.4 (4.9)
Acnes (HLT)	0	0	1	1.2 (2.4)
Coronavirus infection (HLT)	0	0	1	1.2 (2.4)
Gastroenteritis	1	1.2 (3.4)	1	1.2 (2.4)
Herpes simplex	2	2.5 (6.8)	1	1.2 (2.4)
Face swelling	1	1.2 (3.4)	0	0

Abbreviations: BARI = baricitinib; CI = confidence interval; DBW = double-blind withdrawal; HLT = high level term; IR = incidence rate; N = number of patients in the analysis population; n = number of patients in the specified category; PC = placebo-controlled; PBO = placebo; PT = preferred term; PYE = patient-year exposure.

* The Fracture cluster included 1 patient with Wrist fracture PT and 1 patient with Joint injury PT in the baricitinib treatment group; and 1 patient with Joint injury PT in the placebo treatment group.

In the All JIA safety analysis set (JAHV + JAHX), most (89%) of patients had at least 1 TEAE, while 7.7% of patients has a severe TEAE and 10% had a SAE. In 9 patients (4.1%) baricitinib was stopped due to an AE. The most common TEAE's by PT were:

- COVID-19 (n = 43; 19.5%),
- nasopharyngitis (n = 39; 17.7%),
- headache (n = 33, 15%),
- upper respiratory tract infection (n = 29, 13.2%), and
- arthralgia (n = 25, 11.4%).

Also, juvenile idiopathic arthritis (PT term), nausea and vomiting, (upper) abdominal pain, were relatively frequent (Panel 22). When analysed in clusters, upper respiratory tract infections/oropharyngeal pain (39%, IR=36.4/1PY), abdominal pain (10%, IR=7.3/1PY), and rash (6.8%, IR=4.9/1PY) were most frequent (Panel 23). Fractures occurred in 4.1% of patients with an IR (95%CI) of 2.8 (1.3-5.3).

Panel 22 The most common (>10%) Treatment emergent AEs in the all JIA safety set (JAHV and JAHX)

	All JIA Safety Analysis Set			
N	220			
PYE	325.7			
System Organ Class **Preferred Term**	**n**	**%**	**IR**	
			Estimate	**95% CI**
Patients with ≥1 AE	195	88.6	241.8	209.1, 278.3
Infections and infestations	138	62.7	75.8	63.7, 89.6
COVID-19	43	19.5	13.8	10.0, 18.6
Nasopharyngitis	39	17.7	13.6	9.7, 18.6
Upper respiratory tract infection	29	13.2	9.6	6.4, 13.8
Musculoskeletal and connective tissue disorders	68	30.9	27.3	21.2, 34.6
Arthralgia	25	11.4	8.4	5.4, 12.4
Juvenile idiopathic arthritis	22	10.0	7.2	4.5, 10.8
Gastrointestinal disorders	61	27.7	24.0	18.4, 30.8
Nausea	23	10.5	7.7	4.9, 11.5
Investigations	54	24.5	20.6	15.5, 26.9
Respiratory, thoracic, and mediastinal disorders	44	20.0	15.8	11.5, 21.3
Nervous system disorders	41	18.6	14.4	10.4, 19.6
Headache	33	15.0	11.3	7.8, 15.8
Skin and subcutaneous tissue disorders	38	17.3	13.4	9.5, 18.4
Injury, poisoning, and procedural complications	37	16.8	12.6	8.8, 17.3
General disorders and administration site conditions	28	12.7	9.1	6.0, 13.1
Blood and lymphatic system disorders	26	11.8	8.6	5.6, 12.6

Abbreviations: AE =adverse event; COVID-19 = coronavirus disease 2019; CI = confidence interval; IR = incidence rate; JIA = juvenile idiopathic arthritis; N = number of patients in the analysis population; n = number of patients in the specified category; PYE = patient-year exposure.

Panel 23 Clusters of Treatment-emergent AEs in the All JIA safety set (JAHV and JAHX)

	All JIA Safety Analysis Set			
Treatment group	**BARI**			
N	220			
PYE	325.7			
CLUSTER	**n**	**%**	**IR**	
			Estimate	**95% CI**
Upper respiratory tract infections (HLT) and oropharyngeal pain	86	39.1	36.4	29.1, 44.9
Abdominal pain (3 categories)	22	10.0	7.3	4.6, 11.0
Rash	15	6.8	4.9	2.7, 8.0
Fractures	9	4.1	2.8	1.3, 5.3
Acnes (HLT)	11	5.0	3.5	1.7, 6.2
Coronavirus infection (HLT)	45	20.5	14.6	10.6, 19.5
Gastroenteritis	5	2.3	1.5	0.5, 3.6
Herpes simplex	4	1.8	1.2	0.3, 3.1
Herpes zoster	4	1.8	1.2	0.3, 3.1
Face swelling	1	0.5	0.3	0.0, 1.7

Abbreviations: BARI = baricitinib; CI = confidence interval; DBW = double-blind withdrawal; HLT = high level term; IR = incidence rate; JIA = juvenile idiopathic arthritis; N = number of patients in the analysis population; n = number of patients in the specified category; PYE = patient-year exposure.

Infections

It is referred to the section below including adverse event of special interest (AESI)'s.

Headache

In the placebo-controlled period, there were 3 (3.7%) cases of headache in the placebo group and 9 (11%), IR: 23.3) in the baricitinib group. In the All JIA safety set, there were 33 (15%, IR: 11.3) patients with headache. One case of headache was a severe AE and one was an SAE, as it lead to hospitalisation. The case was also described in the section for SAEs.

Musculoskeletal

In the placebo-controlled period, in the placebo versus baricitinib groups, there were cases of arthralgia (3 *versus* 6), joint effusion (0 versus 1), joint swelling (2 versus 1), synovitis (0 versus 1), juvenile idiopathic arthritis 'sic' (2 versus 0). In the All JIA safety set, there were 25 (11%) patients with arthralgia, 22 (10%) with juvenile idiopathic arthritis (PT), 5 (2.3%) patients with arthritis, 4 (1.8%) with joint swelling. Lower IRs of Musculoskeletal and connective tissue disorders were reported in the All JIA safety analysis set (n = 22, 10%, IR: 7.2) compared with the IR for baricitinib-treated patients in the PC DBW period (n = 13, 16%, IR: 15/PY).

Gastro-intestinal

Five patients reported TEAEs within the gastroenteritis cluster (IR: 1.5) in the All JIA safety set compared with 1 patient (IR: 2.4) in the baricitinib treatment group of the placebo-controlled period.

Skin and subcutaneous tissue

There were no anaphylactic reactions (narrow) reported in the JIA clinical trial programme, in the All JIA safety analysis set, 2 patients (0.9%, IR: 0.6) had an event within the Angioedema (narrow) SMQ.

A similar proportion of baricitinib (6.1%)- and placebo (4.9%)-treated patients reported TEAEs in the Hypersensitivity (narrow) SMQ in the PC DBW period and 11.4% (IR: 8.3) of patients reported such events in the All JIA safety analysis set.

The IR of rash as a cluster was higher in the baricitinib (IR: 9.8) than in the placebo treatment group (IR: 3.4) in the PC DBW period. IR of rash as a cluster was lower (4.9) in the All JIA safety analysis set compared with the IR in the baricitinib treatment group (9.8) in the placebo controlled period.

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

No deaths were reported in the JIA clinical trial programme through the data cutoff date 21 April 2022.

Serious adverse events

In the placebo-controlled period, 7 patients reported an SAE: 3 (3.7%, IR: 10.2) patients in the placebo treatment group had an SAE (Bronchospasm, Juvenile idiopathic arthritis, Suicide attempt) and 4 (4.9%, IR: 9.7) patients in the baricitinib treatment group had an SAE (COVID-19, Gastroenteritis, Headache, and Pulmonary embolism). No SAEs were reported more than once either in the baricitinib or in the placebo treatment group (Panel 24).

Panel 24 Serious Adverse Events in the placebo-controlled period of study JAHV

Treatment Period	PC DBW	
Treatment	**PBO**	**BARI**
N	81	82
PYE	29.4	41.4
System Organ Class **Preferred Term**	**n (%) [IR]**	**n (%) [IR]**
Patients with ≥1 SAE	3 (3.7) [10.2]	4 (4.9) [9.7]
Infections and infestations	0	2 (2.4) [4.9]
COVID-19	0	1 (1.2) [2.4]
Gastroenteritis	0	1 (1.2) [2.4]
Nervous system disorders	0	1 (1.2) [2.4]
Headache	0	1 (1.2) [2.4]
Respiratory, thoracic, and mediastinal disorders	1 (1.2) [3.4]	1 (1.2) [2.4]
Pulmonary embolism	0	1 (1.2) [2.4]
Bronchospasm	1 (1.2) [3.4]	0
Musculoskeletal and connective tissue disorders	1 (1.2) [3.4]	0
Juvenile idiopathic arthritis	1 (1.2) [3.4]	0
Psychiatric disorders	1 (1.2) [3.4]	0
Suicide attempt	1 (1.2) [3.4]	0

Abbreviations: BARI = baricitinib; COVID-19 = coronavirus disease 2019; DBW = double-blind withdrawal; IR = incidence rate; N = number of patients; n = number of patients in the specified category; PBO = placebo; PC = placebo-controlled; PT = preferred term; PYE = patient-year exposure; SAE = serious adverse event; SOC = system organ class.

In the All JIA safety set, 22 (10.0%) patients had ≥1 SAE (Panel 25). Most SAEs were reported in the Musculoskeletal and connective tissue disorders SOC (n = 9, 4.1%) with PTs of Arthralgia, Joint effusion, and Juvenile idiopathic arthritis accounting for a majority of events. SAEs reported by more than 1 patient were: Arthralgia, n = 2 (0.9%); Joint effusion, n = 2 (0.9%); Juvenile idiopathic arthritis, n = 2 (0.9%), but arthritis and joint destruction were also reported as SAE. The IR of patients presenting with at least 1 SAE in the All JIA safety analysis set was 7.1/100 PY and was 9.7/100PY in the baricitinib treatment group during the placebo-controlled period.

Panel 25 Serious Adverse Events in the All JIA safety data set.

	All JIA Safety Analysis Set			
N	220			
PYE	325.7			
System Organ Class **Preferred Term**	**n**	**%**	**IR**	
			Estimate	**95% CI**
Patients with ≥1 SAE	22	10.0	7.1	4.4, 10.7
Musculoskeletal and connective tissue disorders	9	4.1	2.8	1.3, 5.3
Arthralgia	2	0.9	0.6	0.1, 2.2
Joint effusion	2	0.9	0.6	0.1, 2.2
Juvenile idiopathic arthritis	2	0.9	0.6	0.1, 2.2
Arthritis	1	0.5	0.3	0, 1.7
Back pain	1	0.5	0.3	0, 1.7
Joint destruction	1	0.5	0.3	0, 1.7
Musculoskeletal chest pain	1	0.5	0.3	0, 1.7
Pain in extremity	1	0.5	0.3	0, 1.7
Infections and infestations	5	2.3	1.5	0.5, 3.6
Abscess soft tissue	1	0.5	0.3	0, 1.7
Bartholin's abscess	1	0.7	0.4	0, 2.4
COVID-19	1	0.5	0.3	0, 1.7
Gastroenteritis	1	0.5	0.3	0, 1.7
Gastrointestinal disorders	4	1.8	1.2	0.3, 3.2
Constipation	1	0.5	0.3	0, 1.7
Dental caries	1	0.5	0.3	0, 1.7
Haematochezia	1	0.5	0.3	0, 1.7
Ileus	1	0.5	0.3	0, 1.7
Injury, poisoning, and procedural complications	2	0.9	0.6	0.1, 2.2
Fracture displacement	1	0.5	0.3	0, 1.7
Procedural pain	1	0.5	0.3	0, 1.7
Respiratory, thoracic, and mediastinal disorders	2	0.9	0.6	0.1, 2.2
Bronchospasm	1	0.5	0.3	0, 1.7
Pulmonary embolism	1	0.5	0.3	0, 1.7
Eye disorders	1	0.5	0.3	0, 1.7
Trichiasis	1	0.5	0.3	0, 1.7
Hepatobiliary disorders	1	0.5	0.3	0, 1.7
Hepatic cytolysis	1	0.5	0.3	0, 1.7
Metabolism and nutrition disorders	1	0.5	0.3	0, 1.7
Decreased appetite	1	0.5	0.3	0, 1.7
Nervous system disorders	1	0.5	0.3	0, 1.7
Headache	1	0.5	0.3	0, 1.7
Psychiatric disorders	1	0.5	0.3	0, 1.7
Stress	1	0.5	0.3	0, 1.7
Skin and subcutaneous tissue disorders	1	0.5	0.3	0, 1.7
Parapsoriasis	1	0.5	0.3	0, 1.7

Abbreviations: CI = confidence interval; COVID-19 = coronavirus disease 2019; IR = incidence rate; JIA = juvenile idiopathic arthritis; N = number of patients in the analysis population; n = number of patients in the specified category; PYE = patient-year exposure; SAE = serious adverse event.

Other significant events

Infections

In the placebo-controlled period, infections were more frequent in the baricitinib group as compared to the placebo group (38% versus 19%); (Panel 26). The most commonly reported infections in the baricitinib treatment group were upper respiratory tract infections (n = 9, 11%, IR: 22.9), and nasopharyngitis (n = 6, 7.3%, IR: 15.3). None of the treatment emergent infections led to permanent baricitinib discontinuation. There was no tuberculosis reported in the study.

Serious infections were reported in 2 patients in the baricitinib treatment group and none in the placebo group: One of the baricitinib-treated patients was hospitalised due to an SAE of severe COVID-19 infection, the other SAE was acute gastroenteritis with hospitalisation.

Panel 26 Occurrence of infections in the placebo-controlled period of study JAHV

Treatment Period	PC DBW	
Treatment	PBO	BARI
N	81	82
PYE	29.4	41.4
	n (%) [IR]	n (%) [IR]
Patient with ≥1 TE infection	15 (18.5) [59.0]	31 (37.8) [102.1]
Serious infection	0	2 (2.4) [4.9]
Tuberculosis	0	0
Herpes simplex	2 (2.5) [6.8][a]	1 (1.2) [2.4]
Herpes zoster	0[a]	0
Confirmed opportunistic infections[b]	1 (1.2) [3.4]	1 (1.2) [2.4]
Led to study drug DC	0	0

Abbreviations: BARI = baricitinib; DBW = double-blind withdrawal; DC = discontinuation, IR = incidence rate; N = number of patients; n = number of patients in the specified category; PBO = placebo; PC = placebo-controlled; PYE = patient-year exposure; TE = treatment emergent.

[a] One patient in the placebo treatment group reported a mild herpes infection of left eyelid (I4V-MC-JAHV-1186-13707). After medical review, it was considered as opportunistic herpes zoster infection with ocular involvement and 2 non-contiguous dermatomes.

[b] Based on medical review.

In the All JIA safety set, 138 patients (62.7%) reported ≥1 TE infections with an IR of 75.8, compared to an IR of 102.1 in the baricitinib treatment group in the placebo-controlled period (Panel 27). Five patients (2.3%, IR: 1.5) had a serious infection (COVID-19, gastroenteritis, appendicitis, Bartholin's abscess, and abscess soft tissue).

The IR (1.5) of serious infection in the All JIA safety analysis set was lower compared with the IR (4.9) in the baricitinib treatment group in the PC DBW period. None of the treatment emergent infections led to permanent baricitinib discontinuation, whereas 16% of patients temporarily interrupted study treatment due to the infection. There was no tuberculosis case reported in the JIA clinical trial programme. Forty-five patients (21%) had ≥1 TEAE within the Coronavirus infection (HLT); none of these patients permanently discontinued baricitinib and 16 patients temporarily interrupted baricitinib.

Panel 27 Occurrence of infections in the All JIA safety set (JAHV and JAHX)

Treatment Period	All JIA Safety Analysis Set			
N	220			
PYE	325.7			
Infection AE	n	%	IR	
			Estimate	95% CI
Patients with ≥1 TEAE	138	62.7	75.8	63.7, 89.6
Serious infection	5	2.3	1.5	0.5, 3.6
Tuberculosis	0	0	0	0
Herpes simplex	4	1.8	1.2	0.3, 3.1
Herpes zoster	4[a]	1.8	1.2	0.3, 3.1
Confirmed opportunistic infections	0	0	0	NA, 1.1
Permanent DC from study drug due to AE	0	0	0	NA, 1.1

Abbreviations: AE = adverse event; CI = confidence interval; DC = discontinuation; IR = incidence rate; JIA = juvenile idiopathic arthritis; N = number of patients in the analysis population; n = number of patients in the specified category; PYE = patient-year exposure; TEAE = treatment-emergent adverse event.

[a] In addition to the 4 patients summarised in the table, 1 patient (I4V-MC-JAHV-1262-15222) had mild herpes zoster infection reactivation.

In the All JIA safety period, Herpes zoster was reported in 4 patients (1.8%). All events were mild or moderate in severity, non-SAE, and 2 of them resolved within 2 weeks, all led to temporary baricitinib interruption. Three patients recovered and 1 event was ongoing at the time of data cutoff.

Herpes simplex occurred in 4 patients (1.8%), 2 patients had oral herpes, 1 had genital herpes and 1 herpes virus infection (unspecified). All TEAEs were mild or moderate in severity, and all resolved. None led to permanent baricitinib discontinuation, and 3 events led to temporary interruption.

Opportunistic infections did not occur in the baricitinib treated groups during the placebo-controlled period or in the All JIA safety set. No events of detectable post-baseline Hepatitis B virus DNA were observed in the JIA clinical trial programme.

MACE and VTE

There was no positively adjudicated MACE or arterial thrombotic event reported in the JIA clinical trial programme. One patient had developed pulmonary embolism (PE) while on baricitinib.

- Pulmonary embolism was reported (Study Day 162) in an adolescent patient. PE was positively adjudicated by an external adjudication committee. The patient was hospitalised and discontinued baricitinib due to PE. Two days after hospitalisation, the patient received antibiotics for suspected pneumonia. Platelet counts were elevated at baseline (500 × 10^9/L) and at the time of the event (Study Day 147: 464 ×10^9/L, Study Day 176: 603 × 10^9/L). Approximately 1 month after baricitinib discontinuation, platelet counts returned to normal level (Study Day 195: 342 × 10^9/L). The patient had multiple risk factors for PE. It was reported by the investigator that the patient had stayed in bed for several weeks before the PE event. Positive RF and ACPA, the failure of two prior biological treatments and the high inflammation indices were identified as poor prognostic factors of JIA. The patient recovered from the event.

Platelet counts

Increases in platelet counts did occur. In the placebo-controlled period, 9 patients (30%) in the baricitinib treatment group and 1 patient (8.3%) in the placebo treatment group had platelet shifts to >400 × 10^9/L. Mean increase from baseline to final post-baseline value for platelets was higher in the baricitinib treatment group (12.1 × 10^9/L) compared with the placebo treatment group (-11.5 × 10^9/L). In the All JIA safety analysis set, 53 patients (33.1%) had platelet shifts to >400 × 10^9/L, and 10 patients (4.8%) had platelet shifts to >600 × 10^9/L.

Malignancy and NMSC

There was no malignancy reported in the JIA clinical trial programme.

Hepatic function

In the placebo-controlled period, 1 patient in the baricitinib treatment group had ALT increase to ≥5× ULN, and no patient had AST increase to ≥3× ULN. Baricitinib was not interrupted, ALT decreased to normal level within 4 weeks and stayed within the normal range afterwards. Before hypertransaminasaemia was reported, the patient received measles, mumps, and rubella vaccine (Study Day 173) and influenza vaccine (Study Day 270). Three patients (7.9%) had elevations of ALP ≥1.5× ULN in the baricitinib treatment group, compared with none in the placebo treatment group.

In the All JIA safety analysis set, 9 patients (4.1%) had ALT ≥3× ULN, 6 patients (2.7%) ALT ≥5× ULN, and 1 (0.5%) patient had ALT ≥10× ULN (Panel 28). Three patients (1.4%) were observed with AST ≥3× ULN and 2 (0.9%) with AST ≥5× ULN. All 3 patients observed with AST≥3× ULN recovered without interrupting baricitinib. The patients with larger changes all recovered, with or without interrupting baricitinib. Nine patients (4.1%) had increased ALP to ≥1.5× ULN in the All JIA safety analysis set.

In the All JIA data set, one case of hepatic cytolysis occurred that was not considered related to treatment by the investigator. Also, in the All JIA analysis set, it appeared that a second patient had

Hepatic cytolysis, 3 patients reported Hepatic steatosis, 1 patient reported Liver injury; all patients were reported as recovered. There were no patients meeting Hy's law criteria.

- An adolescent patient was observed with ALT ≥3×ULN and AST increase (ALT: 130 U/L, AST: 50 U/L, CPK: normal) (Study Day 511) without any clinical symptoms and was hospitalised for monitoring and investigation of the causes of liver test abnormalities. Concomitant medication included MTX, prednisolone, and ciclopirox. In the hospital, he was diagnosed with hepatic cytolysis (peak ALT: 297 U/L (11.5× ULN) based on hospital local laboratory result). Hepatic cytolysis TEAE was considered severe (Study Day 511), and due to hospitalisation event, was reported as an SAE. Baricitinib was not interrupted, and the patient recovered. ALT and AST levels returned to normal levels (Study Day 594). Based on PI opinion, MTX association could be suspected. Based on internal medical review - due to AST and ALT levels returned to normal levels, the patient recovered without baricitinib interruption (patient received baricitinib for longer period of time), concomitant medications included MTX - this case was assessed as unlikely related to baricitinib.
- A pre-adolescent patient had ALT elevation of 14× ULN (ALT: 437 U/L, normal range: 5 to 30 U/L) and AST elevation of 6× ULN (AST:220 U/L, normal range: 0 to 36 U/L) (ALP: 357 U/L, normal range: 0 to 186 U/L, TBL level: normal) (Study Day 28) and reported a non-serious TEAE of moderate liver injury (Study Day 28) with right upper quadrant abdominal pain. The patient met permanent discontinuation criteria due to hepatic enzyme increases and discontinued baricitinib (Study Day 31). One week before the hepatic event, mild upper respiratory tract infection was reported. After discontinuation of NSAID, MTX (7.5 mg/week) and baricitinib, hepatic enzymes decreased to normal or near normal levels (ALT: 33 U/L, Study Day 54) (AST and ALP normal [Study Day 54]), and the patient recovered. This case was assessed by the sponsor as possibly related to baricitinib.

Panel 28 Abnormal hepatic tests in the All JIA safety set (JAHV and JAHX)

	All JIA safety analysis Set		
Treatment Period	**BARI**		
N	220		
PYE	325.7		
Abnormal Hepatic Test	**N**	**n**	**%**
ALT ≥3× ULN	219	9	4.1
ALT ≥5× ULN	219	6	2.7
ALT ≥10× ULN	219	1*	0.5
AST ≥3× ULN	218	3	1.4
AST ≥5× ULN	218	2	0.9
AST ≥10× ULN	218	0	0
ALP ≥1.5× ULN	218	9	4.1
TBL ≥2× ULN	219	0	0

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BARI = baricitinib; IR = incidence rate; JIA = juvenile idiopathic arthritis; N = number of patients in the analysis population; n = number of patients in the specified category; PYE = patient-year exposure; PYR = patient years at risk; SAE = serious adverse event; TBL = total bilirubin; ULN = upper limit of normal.

*One additional patient with ALT ≥10× ULN was identified (reported in SAE narrative), but not included in the table, as the table presents cases based on central laboratory values, not local laboratory values.

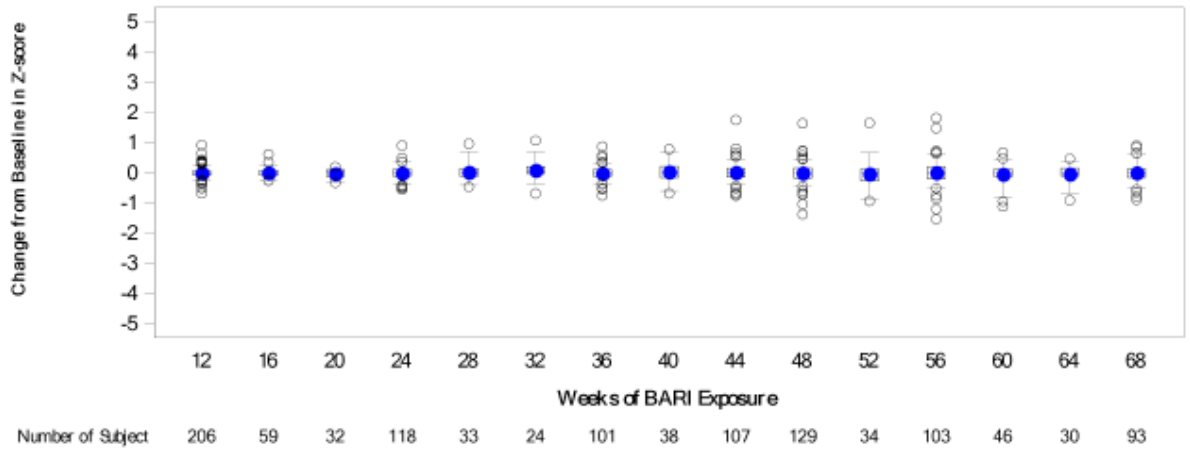
Note: IRs are calculated based on PYR.

Growth

In the All JIA safety set, the population's relative height was consistent over time with a reduced median height when compared with other children of their age (Figure 8). The height percentile of patients relative to healthy children of the same age in the All JIA safety analysis set was similar at Week 52 to that observed at baseline, indicating a growth velocity consistent with their healthy peers.

Time point (Weeks)	n	Height change (cm) from Baseline	
		Mean	SD
Baseline	220	154.63	17.59
8	3	-0.43	0.51
12	206	0.70	1.22
16	59	0.87	1.17
20	32	0.79	0.93
24	118	1.47	1.73
28	33	1.58	1.96
32	24	2.34	2.67
36	101	2.12	2.21
40	38	2.55	2.49
44	107	2.91	2.80
48	129	2.88	2.93
52	34	2.69	3.35
56	103	3.50	3.56
60	46	2.64	2.99
64	30	3.24	3.20
68	93	3.85	3.75

Abbreviations: JIA = juvenile idiopathic arthritis; n = number of patients in the specified category; N/A = not applicable; SD = standard deviation.



Abbreviations: BARI = baricitinib; JIA = juvenile idiopathic arthritis.

Figure 8 Mean change in height over time (Table) and mean change in height z-scores (Figure) in the All JIA safety set

Skeletal development

There were no reported abnormalities in knee x-rays or MRIs. For patients with growth potential (that is, those <18 years of age), patients (n = 18) demonstrated increased tibial length proportional to increases in height across the assessment period. Occipital frontal circumference measurement was a requirement in 2-year-old patients. There were two 2-year-old patients enrolled in the All JIA safety analysis set. However, no occipital circumference measurement raw data were collected.

Fractures

In the All JIA safety set, 9 patients had a TEAE within the “Fracture cluster” (4.1%, IR: 2.8). Of those, 7 patients reported a PT specific to Fracture, and 2 patients reported a PT of Joint injury (1 with left ankle injury and the other with left elbow injury due to fall).

All fractures were upper extremities fractures (n = 4) or lower extremities fractures (n = 3). One fracture was confirmed as a sport injury (skateboarding). There were no patients with recurrent fractures during the study.

Most fractures were considered mild or moderate in severity. One fracture TEAE was severe and also serious due to hospitalisation (Fracture displacement PT). No patient permanently discontinued study drug due to fracture. All patients recovered.

Time to onset of fracture ranged from 86 to 582 days since baricitinib treatment started, and events were spread over time. There was no accumulation of fractures with longer baricitinib exposure. All patients with fractures were 12 to 15 years of age at the time of the event (3 male and 4 female patients). This is in line with literature data that show that nearly 50% of healthy children sustain at least 1 fracture by the age of 18 years and that incidence peaks during early adolescence, shortly after the pubertal growth spurt (Wasserman and Gordan 2017).

Six of the 7 patients (86%) who reported a fracture had corticosteroid use prior to study entry, and out of these 6 patients, 2 had concomitant corticosteroid use at the time of the fracture. In Study JAHV, the mean BMI at baseline for the total population was 20.3 kg/m2, and 38.6% of patients were underweight (⩽18.5 kg/m2). Of the 7 patients with a fracture, 2 were underweight (⩽18.5 kg/m2) at baseline.

2.6.8.4. Laboratory findings

Response to vaccination

The number of patients receiving booster doses of tetanus, diphtheria, and acellular pertussis vaccine and/or pneumococcal conjugate vaccine was minimal (n = 6). The majority of patients who received booster doses had detectible antibody titre levels at 12 weeks.

Blood lipids

The classification of lipid values differs between the adult and the paediatric population. Categorical analyses were performed using Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (2011).

In the placebo-controlled period, among the patients who had an “acceptable” total cholesterol level at baseline, 14 patients (21.9%) in the baricitinib treatment group and 4 patients (6.8%) in the placebo treatment group increased to “borderline high”, and 3 patients (4.7%) in the baricitinib treatment group and 3 patients (5.1%) in the placebo group increased to “high”. Among the patients who had an “acceptable” triglyceride level at baseline, 7 patients (15.2%) in the baricitinib treatment group and 9 patients (17.3%) in the placebo treatment group increased to “borderline high” and 2 patients (4.3%) in the baricitinib and 6 patients in the placebo treatment group (11.5%) increased to “high” in this period. For LDL en HDL, no between-group differences were apparent (Panel 29).

In the All JIA safety analysis set, overall, 15% of patients experienced categorical increase (according to NCEP criteria) to high cholesterol, 9.3% increased to high LDL-cholesterol, and 11% decreased to low HDL cholesterol. Overall, 23.8% of patients experienced a categorical increase (according to NCEP criteria) to high triglyceride levels.

Panel 29 Lipid changes in the placebo-controlled period of study JAHV

Treatment Period	PC DBW	
Treatment	**PBO**	**BARI**
N	81	82
PYE	29.4	41.4
	n/NAR (%)	**n/NAR (%)**
Lipid effects		
Total cholesterol NCEP criterion Borderline high (170-199 mg/dL) or high (≥200 mg/dL)	7/22 (31.8)	17/36 (47.2)
Total cholesterol NCEP criteria High (≥200 mg/dL)	3/26 (11.5)	6/41 (14.6)
LDL-Cholesterol NCEP Criteria borderline High (110 to 129 mg/dL) or High (≥130 mg/dL)	5/29 (17.2)	6/36 (16.7)
LDL-Cholesterol NCEP Criteria High (≥130 mg/dL)	3/32 (9.4)	5/43 (11.6)
HDL-Cholesterol NCEP Criteria Decrease to Borderline High (40 to 45 mg/dL) or Low (less than 40 mg/dl)	4/27 (14.8)	4/28 (14.3)
HDL-Cholesterol NCEP Criteria Decrease to Low (less than 40 mg/dL)	4/37 (10.8)	3/37 (8.1)
Triglycerides NCEP criterion borderline high (0-9 years of age: 75-99 mg/dL, 10-19 years of age:90-129 mg/dL) or high (0-9 years of age: ≥100 mg/dL, 10-19 years of age: ≥130 mg/dL)	15/31 (48.4)	9/24 (37.5)
Triglycerides NCEP criteria high (0-9 years of age: ≥100 mg/dL, 10-19 years of age: ≥130 mg/dL)	9/39 (23.1)	5/36 (13.9)

Abbreviations: BARI = baricitinib; DBW = double-blind withdrawal; HDL = high density lipoprotein; LDL = low density lipoprotein; N = number of patients; n = number of patients in the specified category; NAR = number of patients at risk for the specified abnormality in each treatment group; NCEP = National Cholesterol Education Program; PBO = placebo; PC = placebo-controlled; PYE = patient-year exposure.

Creatine phosphokinase

In the placebo-controlled period, 13 patients (23.6%) had any CTCAE grade increase in CPK (reflecting an increase in CPK) in the baricitinib treatment group and 7 patients (25%) in the placebo treatment group. Most increases were to Grade 1 or 2, 3 patients had increases to Grade ≥3, 1 in the baricitinib treatment group and 2 in the placebo treatment group (Grade 4). In the baricitinib treatment group 1 patient (1.2%) reported muscle spasm (PT) but the patient had no elevated CPK levels at the time of the reported muscle symptoms.

In the All JIA safety analysis set, 47 patients (33.8%) had any CTCAE grade increase of CPK (Panel 30). Nine patients (4.1%) had CTCAE grade increase to Grade ≥3 and of those patients, 3 patients (1.4%) had an increase to Grade ≥4. No additional muscle symptom AEs were reported.

Panel 30 CPK changes in the All JIA safety set (JAHV and JAHX)

N	220	
PYE	325.7	
CPK Change	**NAR**	**n (%)**
Any CTCAE increase in CPK	219	74 (33.8)
Increase to Grade ≥1 (>1× ULN)	207	71 (34.3)
Increase to Grade ≥2 (>2.5× ULN)	219	19 (8.7)
Increase to Grade ≥3 (>5× ULN)	219	9 (4.1)
Increase to Grade ≥4 (>10× ULN)	219	3 (1.4)
TEAEs potentially related to muscle symptoms- Lilly-Defined PTs	NA	1 (0.5)

Abbreviations: CPK = creatine phosphokinase; CTCAE = Common Terminology Criteria for Adverse Events; IR = incidence rate; JIA = juvenile idiopathic arthritis; N = number of patients in the analysis population; n = number of patients in the specified category; NA = not applicable; NAR = number of patients at risk; PT = preferred term; PYE = patient-year exposure; TEAE = treatment-emergent adverse event; ULN = upper limit of normal.

Haematology

In the placebo-controlled period, 11 patients (28%) had any CTCAE grade increase of haemoglobin (reflecting a decrease in haemoglobin) in the baricitinib treatment group and 8 patients (22%) in the placebo group (Panel 31). Mean change from baseline to final post-baseline value for haemoglobin was 0.148 mmol/L-Fe in the baricitinib treatment group, compared with -0.041 mmol/L-Fe in the placebo group. Treatment emergent events of low haemoglobin and low haematocrit were observed for 9 (17%) and 7 (10%) patients in the baricitinib treatment group and for 6 (12%) and 7 (11%) patients in the placebo group. In the All JIA safety analysis set, 51 patients (23%) had any CTCAE grade increase of haemoglobin (reflecting a decrease in haemoglobin). All increases were to Grade 1 or 2, no increases to Grade ≥3 was observed. Treatment emergent cases of low haemoglobin and low haematocrit were observed for 43 (28%) and 43 (24%) of patients while on baricitinib. Seven patients (3.2%, IR: 2.2) reported TEAEs of anaemia, 3 patients (1.4%, IR: 0.9) reported iron deficiency anaemia and 1 reported microcytic anaemia (0.5%, IR: 0.3). None of the anaemia events were reported as severe TEAE or SAE. No patient permanently discontinued or temporarily interrupted baricitinib due to an event of anaemia.

In the placebo-controlled period (Panel 31), 10 patients (24%) had any CTCAE grade increase in neutrophils (reflecting a decrease in neutrophil counts) in the baricitinib treatment group and 6 patients (21%) in the placebo group. No patient had an increase to Grade 4 or higher in the baricitinib treatment group. Mean decrease from baseline to final post-baseline value for neutrophil counts was higher (-1.041 × 10^9/L) in the baricitinib treatment group compared with placebo (0.007 × 10^9/L). In the All JIA safety analysis set, 60 patients (27%) had any CTCAE grade increase in neutrophils (reflecting a decrease in neutrophil counts) in the All JIA safety analysis set. The patient with observed with CTCAE grade 4 was observed with low absolute and segmented neutrophil count (Study Day 159). Baricitinib was interrupted first for 6 days (Study Day 143), then for 9 days (Study Day 160). Baricitinib was resumed (Study Day169), neutrophil count returned to normal level (Study Day 234).

In the placebo-controlled period (Panel 31), 10 patients (18%) had any CTCAE grade increase in lymphocytes (reflecting a decrease in lymphocyte counts) in the baricitinib treatment group and four patients (6.7%) in the placebo group. In the baricitinib treatment group, no patient had increase to Grade ≥3. Mean change from baseline to final post-baseline value for lymphocytes was small, -0.073 ×

10^9/L in the baricitinib treatment group and -0.16 × 10^9/L in the placebo treatment group. In the All JIA safety analysis set, 42 patients (19%) had any CTCAE grade increase in lymphocytes (reflecting a decrease in lymphocyte counts. Most CTCAE increases were to Grade 1 or 2, 2 patients (0.9%) had increase to Grade 3, and no patient had an increase to Grade 4.

Platelet counts (Panel 31) are discussed further above in the report.

Panel 31 Summary of haematological changes in the placebo-controlled period of study JAHV

Treatment Period	PC DBW	
Treatment	PBO	BARI
N	81	82
PYE	29.4	41.4
	n/Nb (%)	n/Nb (%)
Haematologic changes		
Haemoglobin decreased		
Any CTCAE grade increase	8/36 (22.2)	11/39 (28.2)
Increase to CTCAE grade ≥3 (Hb <8.0 g/dL)	0/36	0/39
Neutrophil count decreased		
Any CTCAE grade increase	6/28 (21.4)	10/42 (23.8)
Increase to CTCAE grade ≥3 (<1.0 × 10^9/L)	0/28	1/42 (2.4)
Lymphocyte count decreased		
Any CTCAE grade increase	4/60 (6.7)	10/56 (17.9)
Increase to CTCAE grade ≥3 (<0.5 × 10^9/L)	0/60	0/56
Platelet count increased		
Thrombocytosis ≤400 × 10^9/L to >400 × 10^9/L	1/12 (8.3)	9/30 (30.0)
Thrombocytosis ≤600 × 10^9/L to >600 × 10^9/L	1/15 (6.7)	1/35 (2.9)

Abbreviations: BARI = baricitinib; CTCAE = Common Terminology Criteria for Adverse Events; DBW = double-blind withdrawal; Hb = haemoglobin; N = number of patients; n = number of patients in the specified category; Nb = number of patients in the baseline category and that have at least 1 post-baseline measurement; PBO = placebo; PC = placebo-controlled; PYE = patient-year exposure.

Note: Percentages for CTCAE increases are based on number of patients at risk for specified abnormality.

2.6.8.5. Safety in special populations

The frequencies and IRs of TEAEs were similar across age groups except for the youngest group of patients (aged ≥2 to <6 years). The TEAEs in the youngest age group were:

- A 2-year-old female with mild anaemia.
- A 3-year-old female with mild events of: nasopharyngitis, herpangina, upper respiratory tract infection, bronchitis, nasopharyngitis, and nail injury.
- A 5-year-old male who reported mild Pharyngitis.
- A 5-year-old female who reported mild Respiratory tract infection. Seven months later, the patient reported moderate transaminasaemia that was described as resolving. Concomitantly, the patient reported mild COVID-19.
- A 2-year-old female who reported mild Respiratory tract infection and 8 months later reported mild transient neutropenia.
- A 5-year-old female who reported mild throat infection and 4 months later reported mild ankle pain.

Overall, most TEAEs were mild or moderate in severity in all age groups, and a few patients permanently discontinued baricitinib due to AEs across all groups while no patients discontinued in the age group ≥2 to <6 years (Panel 32). No SAEs were reported in the youngest age group (≥2 to <6 years) and the frequency of SAEs was similar across the other age groups. No deaths have been reported.

Panel 32 Overview of AEs by age group in the All JIA safety set (JAHV and JAHX)

Age Group	≥2 to <6 years			≥6 to <9 years			≥9 to <12 years			≥12 to <18 years		
N	6			9			30			175		
PYE	6.4			13.0			37.1			269.1		
	n	%	IR	n	%	IR	n	%	IR	n	%	IR
Total TEAEs	6	100	373.3	8	88.9	183.9	25	83.3	231.5	156	89.1	244.2
TEAE by severity												
Mild	5	83.3	181.4	4	44.4	45.6	11	36.7	47.0	69	39.4	36.2
Moderate	1	16.7	16.3	3	33.3	28.8	12	40.0	45.3	73	41.7	39.0
Severe	0	0	0	1	11.1	8.1	2	6.7	5.4	14	8.0	5.4
SAEs	0	0	0	1	11.1	8.1	3	10.0	8.3	18	10.3	7.0
Deaths	0	0	0	0	0	0	0	0	0	0	0	0
Infections and infestations SOC	5	83.3	141.9	4	44.4	50.0	15	50.0	60.1	96	54.9	55.9
Discontinuation from study due to AE	0	0	0	1	11.1	8.1	2	6.7	5.3	6	3.4	2.2

Abbreviations: AE = adverse event; IR = incidence rate; JIA = juvenile idiopathic arthritis; N = number of patients in the analysis population; n = number of patients in the specified category; PYE = patient-year exposure; TEAE = treatment-emergent adverse event; SAE = serious adverse event; SOC = system organ class.

Serious infections have only been reported in patients aged≥9 years: 1 infection-related SAE was reported in 1 patient in the group aged ≥9 to <12 years (3.3%, IR: 2.8), and 4 infection-related SAEs were reported in 4 patients in the group aged 12 to <18 years (2.3%, IR: 1.5).

Female and male

Out of 220 patients there were 68 (30.9%) male patients and 152 (69.1%) female patients. The number of patients with at least one TEAE was 82% among females and 77% among males. The number of patients with infections was 58% among females and 47% among males. Urinary tract infection was reported in 9 (5.9%) female patients and for 1 (1.5%) male patient.

Weight class

Out of 220 patients there were 29 (13.2%) patients with a weight of <30 kg, and 191 (86.8%) patients with a weight of ≥30 kg (Panel 33). A similar proportion of patients weighing ≥30 kg as compared with patients weighing <30 kg had TEAEs (83% versus 80%) and events in the Infections and infestations SOC (52% versus 55%). Twenty-one SAEs were reported in patients who weighed ≥30 Kg, and 1 SAE was reported in children who weighed <30 kg.

Panel 33 Serious Adverse Events by weight class in the All JIA safety set (JAHV and JAHX)

Weight Group	<30 kg			≥30 kg		
N	29			191		
PYE	38.9			286.8		
	N	%	IR	n	%	IR
Patients with ≥1 SAE	1	3.4	2.6	21	11.0	7.7
Musculoskeletal and connective tissue disorders	0	0	0	9	4.7	3.2
Arthralgia	0	0	0	2	1.0	0.7
Joint effusion	0	0	0	2	1.0	0.7
Juvenile idiopathic arthritis	0	0	0	2	1.0	0.7
Infections and infestations	0	0	0	5	2.6	1.8
Gastrointestinal disorders	1	3.4	2.6	3	1.6	1.0
Ileus	1	3.4	2.6	0	0	0
Injury, poisoning, and procedural complications	0	0	0	2	1.0	0.7
Respiratory, thoracic, and mediastinal disorders	0	0	0	2	1.0	0.7

Abbreviations: IR = incidence rate; JIA = juvenile idiopathic arthritis; N = number of patients in the analysis population; n = number of patients in the specified category; PYE = patient-year exposure; SAE = serious adverse event.

There were 138 patients with TE infections in the All JIA safety analysis set (Panel 34). Similar proportion of patients weighing ≥30 kg reported at least 1 infection-related TE compared with patients weighing <30 kg. All serious infections and Herpes zoster were reported in the patient group who weighed ≥30 kg. No confirmed OI was reported in any groups.

Panel 34 Treatment-emergent infections by weight class in the All JIA safety set (JAHV and JAHX)

Weight Group	<30 kg			≥30 kg		
N	29			191		
PYE	38.9			286.8		
	n	%	IR	n	%	IR
Patients with ≥1 TE infection	17	58.6	88.8	121	63.4	74.3
Serious infections	0	0	0	5	2.6	1.8
Infections that led to						
Permanent discontinuation from study drug	0	0	0	0	0	0
Temporary interruption from study drug	2	6.9	5.5	33	17.3	12.5
Confirmed TE Opportunistic infection	0	0	0	0	0	0
TE Herpes zoster	0	0	0	4	2.1	1.4
TE Herpes simplex	1	3.4	2.7	3	1.6	1.0

Abbreviations: IR = incidence rate; JIA = juvenile idiopathic arthritis; N = number of patients in the analysis population; n = number of patients in the specified category; PYE = patient-year exposure; TE = treatment emergent.

2.6.8.6. Discontinuation due to adverse events

Permanent discontinuation

In the All JIA safety analysis set, 9 patients (4.1%, IR: 2.8) had an AE that led to permanent study drug discontinuation. Two events (Bronchospasm and Pulmonary embolism already discussed above in the case descriptions) were reported as SAEs. Juvenile idiopathic arthritis (PT) was reported by 2 patients as leading to permanent study drug discontinuation (Panel 35). All other AE PTs and all SAE PTs resulting in discontinuation of baricitinib were single events, these included neutropenia, asthma, psoriasis, and liver injury.

Panel 35 Adverse events leading to permanent discontinuation of baricitinib in the All JIA safety data set

	All JIA Safety Analysis Set			
N	220			
PYE	325.7			
System Organ Class **Preferred Term**	**n**	**%**	**IR**	
			Estimate	**95% CI**
Patients with ≥1 AE	9	4.1	2.8	1.3, 5.2
Respiratory, thoracic, and mediastinal disorders	3	1.4	0.9	0.2, 2.7
Asthma	1	0.5	0.3	0, 1.7
Bronchospasm	1	0.5	0.3	0, 1.7
Pulmonary embolism	1	0.5	0.3	0, 1.7
Musculoskeletal and connective tissue disorders	2	0.9	0.6	0.1, 2.2
Juvenile idiopathic arthritis	2	0.9	0.6	0.1, 2.2
Blood and lymphatic system disorders	1	0.5	0.3	0, 1.7
Neutropenia	1	0.5	0.3	0, 1.7
Hepatobiliary disorders	1	0.5	0.3	0, 1.7
Liver injury	1	0.5	0.3	0, 1.7
Nervous system disorders	1	0.5	0.3	0, 1.7
Headache	1	0.5	0.3	0, 1.7
Skin and subcutaneous tissue disorders	1	0.5	0.3	0, 1.7
Psoriasis	1	0.5	0.3	0, 1.7

Abbreviations: AE =adverse event; CI = confidence interval; IR = incidence rate; JIA = juvenile idiopathic arthritis; N = number of patients in the analysis population; n = number of patients in the specified category; PYE = patient-year exposure.

Temporary discontinuation

In the placebo-controlled period, temporary interruptions occurred in 4 (4.9%) patients in the placebo group (all due to infections) and in 6 (7.3%) patients in the baricitinib group (4 infections, lymphopenia, neutropenia, gastritis and hypertransaminaseamia).

In the All JIA safety set, 57 patients (26%) interrupted baricitinib treatment due to AEs at least once (IR: 20.3/100PY), and 98.2% of patients resumed baricitinib following a temporary interruption. Events in the Infections and infestations SOC (n = 35, 15.9%, IR: 11.6) were responsible for most of the temporary interruptions of baricitinib.

2.6.8.7. Post marketing experience

Baricitinib was first authorised on 13 February 2017 in the EU for the treatment of moderately to severely active RA in adult patients. As of February 2022, baricitinib had been authorised in 76 countries for the treatment of moderately to severely active RA in adult patients, including EU. The PSUR 10 (DLP on 13 February 2022) is the latest PSUR available at the time of the DLP for this JIA extension of indication application.

Prompted by the available data from the ORAL Surveillance study (tofacitinib) and from Study B023 (baricitinib), on 11 February 2022, European Medicines Agency (EMA) 's safety committee, Pharmacovigilance Risk Assessment Committee (PRAC), started a review of the safety of JAK inhibitors used to treat several chronic inflammatory disorders (RA, psoriatic arthritis, JIA, ankylosing spondylitis, ulcerative colitis, AD, and alopecia areata). Olumiant was part of the products reviewed in the referral. On 23 January 2023, CHMP endorsed the measures recommended by the PRAC to minimise the risk of serious side effects with JAK inhibitors used to treat several chronic inflammatory disorders. These side effects include cardiovascular conditions, blood clots, cancer and serious infections.

Off-label use in children or adolescents is minimal based on the very few safety reports for paediatric patients (n = 4, reporting rate of 0.006 per 100 PY during the latest PSUR-PBRER 10 interval), and the most recent analysis from Study I4V-MC-B016 in the UK (as of February 2022), indicating that 0.76% of the patients (n = 11 of 1444 patients) were less than 18 years of age.

2.6.9. Discussion on clinical safety

Clinical studies

A randomised withdrawal design with an open-label lead-in period is an acceptable design for evaluating efficacy and safety in children, given that it can be extrapolated from the experience in adults.

Exposure

A total of 220 patients was exposed to any dose of baricitinib in the JIA clinical trial program; 171 patients were exposed to baricitinib for at least 52 weeks. Although there is a relatively large number of patients included and over 100 patients were exposed for at least one year, the safety experience in the youngest age group between 2 and 6 and between 6 and 9 years is limited. Most patients were aged between 9 - 12 (n=30, 14%) and between 12 - 18 (n=175, 80%) years old; only a few patients were between 2 – 6 (n=6) and between 6 – 9 (n=9) years old (see section 'Special populations' further below). Out of 220 patients there were 29 (13%) patients with a weight of <30 kg, and 191 (87%) patients with a weight of ≥30 kg. Please, note that the posology proposed for the SmPC is weight-based rather than age-based.

Common adverse events

Seen over the open-label as well as the randomised withdrawal periods, the most frequently occurring TEAEs were generally in line with the ADRs known for baricitinib. Upper respiratory tract infection, oropharyngeal pain, headache, abdominal pain and rash were more common when on baricitinib than if on placebo.

In the 12-week open-label period, most (57%) patients had at least 1 TEAE, and in the withdrawal phase, the proportion of patients with at least 1 TEAE was larger in the baricitinib group as compared to the placebo group (66% versus 47%). The occurrence of severe and serious AEs and of discontinuations due to AEs was low. In the open-label periods, 57% of patients had at least one TEAE, which in 4 cases (1.8%) was a severe AE and in 6 cases (2/7%) was a SAE; two (0.9%) patients discontinued due to an AE. In the placebo-controlled period, 47% (38/81) of patients in the placebo group had at least 1 TEAE, which was 66% (54/82) in the baricitinib group. In the placebo group, 2 patients (2.5%) had at least one severe AE and also 2 patients in the baricitinib group. No deaths occurred; there were 3 patients (3.7%) in the placebo group and 4 patients (4.9%) in the baricitinib group with at least one SAE. Discontinuations due to AEs were infrequent in the placebo (n=2) and baricitinib (n=1) groups. In the All JIA safety set using all available follow-up data, the most common TEAEs were similar to those already seen in the JAHV trial periods. Also, cases of herpes simplex (n=4, 1.8%) and herpes zoster (n=4, 1.8%), gastroenteritis (n=5, 2.3%), and acne (n=9, 4.1%) started to emerge. Therefore, when analysing all available safety data, the occurrence and pattern of AEs is in line with the known safety profile (ADRs) of baricitinib, including cases of herpes simplex and herpes zoster, gastroenteritis and acne. The frequent occurrence of TEAEs that also are manifestations of JIA (arthralgia, synovitis, etc.), are valued as related to the disease activity, not as potential ADR of baricitinib. Musculoskeletal manifestations not attributable to JIA did not point to a disbalance, and neither did so in placebo-controlled trials in AA and AD. It also is considered that in general, drop-out due to flare is a competing outcome for the occurrence of (mild to moderate) manifestations of JIA

over time. This may explain a seemingly higher occurrence of JIA manifestations in the baricitinib treated group, as compared to placebo.

Upper respiratory tract infections, herpes zoster and herpes simplex, gastroenteritis, urinary tract infections, pneumonia, folliculitis, swelling of the face and urticaria, headache, DVT and PE, nausea, abdominal pain and diverticulitis, rash and acne, weight increased, are known clinical (non-laboratory) ADRs of baricitinib. For the SmPC, the Applicant does not propose to add new ADRs, which can be agreed upon. The Applicant proposes to adapt frequencies based on the withdrawal period of the pivotal trial: headache was very common (11 %), neutropenia < 1 000 cells/mm^3 was common (2.4 %), and pulmonary embolism was common (1.2 %), which was acceptable to CHMP.

Serious adverse events

Several patients had SAEs while being treated with baricitinib, but not all cases are attributable to baricitinib. The SAEs of infections (5), gastroenteritis, headache and pulmonary embolism are known ADRs of baricitinib; all patients involved recovered upon discontinuation of baricitinib. The other cases, including the SAE of hepatic cytolysis and SAEs of arthralgia and synovitis etc., are considered unrelated. The case of PE is peculiar, due to the patient's young age. It is acknowledged that the patient had multiple risk factors in developing PE, despite young age, though it cannot be excluded that baricitinib contributed to its causation. Because it cannot be excluded that baricitinib contributed to its causation, CHMP endorses mentioning the case in section 4.8 of the SmPC.

In the All JIA safety set, 22 (10%) patients had ≥1 SAE, and most (n=9) SAEs were reported in the Musculoskeletal and connective tissue disorders SOC (arthralgia, joint effusion, juvenile idiopathic arthritis, other manifestations). As discussed further above, it is considered that the occurrence of JIA manifestations are not to be regarded as ADRs of baricitinib.

Adverse events of special interest

AESI's that were considered for this report were: infections, MACE, VTE, and malignancies, in line with the concerns that gave rise to the Art. 20 JAK referral, and growth and fractures following concerns about a possible effect of JAK inhibition on bone metabolism. Response to vaccination is of interest to the paediatric population; it is recommended to bring all vaccinations up to date before starting baricitinib. The addition of the recommendation to bring all vaccinations up to date before starting baricitinib is reflected in section 4.4 of the SmPC and in the additional risk minimisation measure materials in Annex II and Part V of the RMP.

Infections were a frequent AE and were more common in the baricitinib group as compared to placebo; serious infections did infrequently occur. Herpes zoster and herpes simplex occurred in some patients, but opportunistic infections did not occur. All infections and serious infections resolved, and in many cases and in all serious cases, baricitinib was temporarily interrupted. Infections are a known ADR of baricitinib but appeared to be manageable in the paediatric population. Younger children may be more liable to infection, and this is discussed in the section 'Special populations' further below.

There was no positively adjudicated MACE or arterial thrombotic event reported in the JIA clinical trial programme. One patient had developed PE while on baricitinib, which is discussed in the section on SAEs. The patient had a platelet level >ULN before the event, and platelet levels reduced to a normal level about 30 days after discontinuing baricitinib. About one-third of patients on baricitinib had platelet levels >400 × 10^9/L. There was no malignancy reported in the JIA clinical trial programme.

Fractures did occur in 7 patients on baricitinib, commonly distal fractures. There was no difference between baricitinib and placebo, but the sample size and exposure length is limited for a good comparison of fracture occurrence. The observed IR of fracture for the All JIA safety analysis set is within the range of the general childhood population (IR: 1.2 to 3.6 per 100 PY). Additionally, all

patients who reported a fracture were 12 to 15 years of age at the time of event, which is a 'peak age' for fractures. The distribution of upper and lower extremity fractures is in line with what can be expected in the healthy population (Burnham et al. 2006). Considering that patients with JIA are at an approximate 3-fold increased risk of fracture compared to a similar aged non-JIA population (Burnham et al 2006), the observed IR is lower than what could be expected in children with JIA for this age group. Based on the average z-scores and graphical displays of growth over time, there is no indication of abnormal growth on a group level. The non-clinical data in juvenile rats showed an effect on bone metabolism in juvenile rats, though at doses above clinical exposure. However, data with longer follow-up time are needed to evaluate growth and skeletal development against reference standards, long-term safety study JAHX was added to the RMP. Bone fractures in baricitinib-treated patients will be monitored through routine surveillance practice.

Laboratory findings

The analysis of laboratory values confirms that known ADRs of baricitinib may also occur in the paediatric population; it is considered that, based on the current data, for the paediatric population, there are no additional ADRs in laboratory values.

The developments of blood lipids in paediatric patients basically followed the pattern seen in adults; mean increases in total cholesterol, LDL- and HDL cholesterol were higher in the baricitinib group, as compared to the placebo group. CPK increase to more than 5 x ULN is an ADR for baricitinib. In the placebo-controlled period, increases in CPK were as common in the baricitinib group as in the placebo group, large increases were uncommon and there were no patients with related muscle symptoms/myalgia. Thrombocytosis > 600 x 10^9 cells/L and neutropenia < 1 x 10^9 cells/L are ADRs of baricitinib. In the placebo-controlled period, a grade≥3 increase in ANC occurred in 1 patient on baricitinib; platelets increase was more frequent on baricitinib for increases <600 x 10^9/L. ALT and AST levels increase 3 or more times the ULN are recognised as ADRs for baricitinib. Increases in liver enzymes were infrequent in the placebo-controlled period, and all cases recovered in the All JIA data set. All 6 patients with hepatic events used other medications with possible hepatotoxic effects, such as MTX and/or NSAIDs. For both patients with hepatic cytolysis, ALT and AST returned to normal levels without baricitinib interruption, and both recovered.

The number of patients receiving booster vaccinations of tetanus, diphtheria, and acellular pertussis vaccine and/or pneumococcal conjugate vaccine was minimal (n = 6), no conclusions can be made.

Subgroups

No important differences in the occurrence of AEs appeared between females and males. In the clinical development program, the posology was age based: patients <9 years old received 2 mg and patients ≥9 years received 4 mg. The posology proposed in the SmPC however is weight based: patients <30 kg will receive 2 mg and patients ≥30 kg will receive 4 mg. It however appears that for both weight-categories, the lower weight patients will have relatively high exposures (see Pharmacokinetics discussion). According to the available data, it does not seem that patients <30 kg are at an increased risk for adverse events, as compared to heavier patients. However, data in patients <12 years old and <30 kg are limited in number. Therefore, safety follow-up study JAHX in paediatric patients with JIA was included in the RMP. The MAH will include safety analyses of patients <12 years of age and 10 to <20 and 20 to <30 kg weight subgroups.

Discontinuations

Permanent discontinuation and temporary discontinuation of baricitinib was infrequent, usually associated with events that are known as ADR.

2.6.10. Conclusions on the clinical safety

Based on the available data, the safety profile of baricitinib in the doses of 1mg, 2 mg and 4 mg is acceptable in the paediatric population of patients with JIA. In the lower age (<9 years) and weight (<30 kg) categories, the number of patients is low, and in patients <20 kg the exposure is higher than in adults. Long-term safety in these groups will be followed post-marketing as reflected by the updated protocol of Study I4V-MC-JAHX as a Category 3 PASS of the RMP. From the non-clinical and available clinical data, there do not appear to be risks regarding bone safety, skeletal development or growth, but more data should be collected over a longer follow-up time in the post-marketing setting. Responses to vaccination is of interest for the paediatric population. Therefore, the RMP is updated include “Long-term safety in pediatric patients including growth and bone development, maturation and pubertal development and adverse response to vaccination” as missing information in the list of safety concerns. The addition of the recommendation to bring all vaccinations up to date before starting baricitinib is reflected in section 4.4 of the SmPC and in the additional risk minimisation measure materials in Annex II and the RMP.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table SVIII.1. Summary of Safety Concerns

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

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

2.7.2. Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
I4V-MC-B011: Retrospective Cohort Study to Assess Safety of Baricitinib in Nordic	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	Important identified risks: • Herpes zoster • VTE Important potential risks: • Serious and opportunistic infections (including	For RA study: Study progress reports	For RA study: Annually in PBRER/PSUR submitted in April of each year

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
countries (Ongoing)	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; liver injury; and all-cause mortality. Secondary Objectives: 3. To monitor the incidence rates of the aggregate outcomes of serious infections overall, MACE, malignancies overall, and VTE in very elderly patients, that is, ≥75 years of age. 4. To assess the effectiveness of risk minimisation activities by describing the pattern of use of baricitinib among patients with AD and the occurrence of pregnancy, active tuberculosis or active viral hepatitis, and the monitoring of lipid levels in relation to	tuberculosis, *Candida* infections, PML) • Potential for DILI • MACE as an outcome of hyperlipidaemia • Malignancy (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers) • Foetal malformation following exposure in utero • Myelosuppression (agranulocytosis) • Myopathy including rhabdomyolysis • GI perforation Missing information: • Long-term safety • Use in very elderly (≥75 years)	Final study report (Objectives 1-3*)* For AD Study: Study progress reports Final report for Objective 4, AD cohort Final Report	31 December 2027 For AD Study: Annually in PBRER/ PSUR submitted in April of each year To be determined based on at least 24 months of data in at least 50% of the discrete healthcare databases 31 December 2028

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	baricitinib use in routine clinical care.			
I4V-MC-B012 Observational post marketing Surveillance in 3 European Registries (Ongoing)	Primary Objectives: 1. To monitor the incidence rate and profile of the following aggregate outcomes of serious infections (including herpes zoster) and opportunistic infections (including tuberculosis, *Candida* infections, and PML), MACE, malignancies (including lymphoma and typically virus-induced malignancies, such as cervical and many oropharyngeal cancers), and VTE among patients with long-term exposure to baricitinib compared to patients with long-term exposure to other medications used for moderate-to-severe RA, as possible given the data available in the BSRBR, RABBIT, and ARTIS registries. 2. To describe the occurrence of the following individual outcomes: lymphoma, herpes zoster, opportunistic infections, rhabdomyolysis, agranulocytosis, PML, GI perforations, and evidence of DILI.	Important identified Risks: • Herpes zoster • VTE Important potential risks: • Malignancies (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers) • Serious and opportunistic infections (including Tuberculosis, *Candida* infections, PML), • Myelosuppression (agranulocytosis) • Myopathy including rhabdomyolysis • Potential for DILI • GI perforation • MACE as an outcome of hyperlipidaemia	Study progress reports Final study report	Annually in PBRER/ PSUR submitted in April of each year 31 March 2024

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
I4V-MC-B025: Survey to assess the effectiveness of the baricitinib additional risk minimisation measures (Planned)	1. To assess the understanding of and adherence to the key risk minimisation messages and required mitigating actions in the updated HCP Educational Material and PAC among a sample of dermatologists and rheumatologists 2. To assess the effectiveness of a DHPC distributed to communicate changes in SmPC	Important identified risks • Herpes zoster • VTE Important potential risks: • Serious and opportunistic infections (including tuberculosis, *Candida* infections, PML) • MACE as an outcome of hyperlipidaemia • Foetal malformation following exposure in utero • Malignancy	Protocol submission Final study report	25 April 2023 Six months after the end of data collection; estimated 30 April 2025
I4V-MC-JAJA and I4V-MC-JAJD These studies are reported jointly for reasons described in Section III.2. (Ongoing)	Study JAJA: Primary objective: 1. To compare baricitinib (combined dose groups) to TNF inhibitors with respect to VTE Secondary objectives: 1. To compare baricitinib (combined dose groups) to TNF inhibitors with respect to key safety outcomes 2. To compare each baricitinib dose to TNF inhibitors with respect to key safety outcomes Study JAJD: Primary objective: 1. To compare the risk of VTE among patients with RA treated with baricitinib (combined 2- and 4-mg dose groups) to similar patients treated with TNF inhibitors Secondary objectives: 1. To compare the risk of key safety outcomes among patients with RA treated with baricitinib (combined 2- and 4-mg dose groups) to similar patients treated with TNF inhibitors 2. To compare the risk of key safety outcomes among patients with RA	Important identified risks • VTE Important potential risks: • MACE • Opportunistic infection • Serious infection • Malignancy	Study progress reports Start of data collection End of data collection Final study report	Included annually in Baricitinib PBRER/ PSUR 25 April 2019 (JAJA), 13 February 2020 (JAJD). 30 September 2027 31 March 2028

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	treated with each baricitinib dose to similar patients treated with TNF inhibitors			
Drug utilisation study to assess prescribing patterns of baricitinib (Planned)	This study aims to measure the effectiveness of newly updated prescribing recommendations by evaluating prescribing behaviours	Important identified risks: • VTE Important potential risks: • MACE • Opportunistic infection • Serious infection • Malignancy	Protocol submission Final study report	25 April 2023 Within 12 months of end of data collection, estimated 30 December 2027
I4V-MC-JAHX (Ongoing)	Primary objective: To evaluate the long-term safety and tolerability of baricitinib in patients with JIA or systemic JIA. Secondary objective: To evaluate the long-term efficacy of baricitinib in children with JIA or sJIA, ERA or JPsA, and the potential effects of baricitinib on the cellular and humoral immune system	Missing information • Long-term safety in paediatric patients including growth and bone development, maturation and pubertal development, and adverse response to vaccination	Study report (JAHV cohort) Final study report (including both JAHV and JAHU)	04 April 2028 31 March 2031

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

2.7.3. Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Herpes zoster	[Routine risk minimisation	Routine pharmacovigilance

	measures:] SmPC Section 4.8 • SmPC section 4.4 recommends that if an infection develops, the patient should be monitored carefully, and Olumiant should be temporarily interrupted and not be resumed until the infection resolves. There is a further recommendation that, prior to starting treatment, all patients including patients with JIA, be brought up to date with all immunisations. PIL sections 2 and 4 PL Section 2 advises that the patient should tell their doctor if they develop signs of shingles. [Additional risk minimisation measures:] • Health care Professional Educational Material • Patient Alert Card	activities beyond adverse reactions reporting and signal detection • Herpes zoster follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to monitor the incidence of herpes zoster in patients exposed to baricitinib RA: • EU registries • Nordic health care study AD: • Nordic health care study
VTE	[Routine risk minimisation measures:] SmPC Sections 4.2, 4.4 and 4.8 (DVT and PE) PIL Section 2 SmPC Section 4.2 states that a dose of 2 mg once daily is recommended for patients at higher risk of VTE, MACE, and malignancy, for patients aged ≥65 years and for patients with a history of chronic or recurrent infections. SmPC Section 4.4 advises that in patients with cardiovascular or malignancy risk factors, baricitinib should only be used if no suitable treatment alternatives are available. In patients with known VTE risk factors other than cardiovascular or malignancy	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: • EU registries • Nordic health care study

	risk factors, baricitinib should be used with caution. VTE risk factors other than cardiovascular or malignancy risk factors include previous VTE, patients undergoing major surgery, immobilisation, use of combined hormonal contraceptives or hormone replacement therapy, and inherited coagulation disorder. If clinical features of VTE occur, treatment should be discontinued and patients should be evaluated promptly and appropriately treated. PL Section 2 advises patients: • To talk to their doctor or pharmacist before and during treatment if they have previously had a VTE or if they develop symptoms of VTE • Olumiant should be used with caution in patients with risk factors for VTE That treatment should be discontinued if clinical symptoms of VTE occur. [Additional risk minimisation measures:] • Health care Professional Educational Material • Patient Alert Card • DHPC	• Randomised, controlled post-authorisation safety studies in US (JAJA/JAJD) AD: • Nordic health care study
Malignancies (including lymphoma and typically virus-induced malignancies, such as cervical and many oropharyngeal cancers)	[Routine risk minimisation measures:] SmPC Sections 4.2 and 4.4 PIL section 2 SmPC Section 4.2 states that a dose of 2 mg once daily is recommended for patients at higher risk of VTE, MACE, and malignancy, for patients aged ≥65 years and for patients with a history of chronic or recurrent infections. SmPC Section 4.4 advises that in patients over 65 years of age, patients who are current or past long-time smokers, or	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:

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

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

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

GI Perforations	[Routine risk minimisation measures:] None [Additional risk minimisation measures:] None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Fistula and/or GI perforation follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to monitor the incidence of GI perforations in patients exposed to baricitinib RA: • EU registries • Nordic health care study AD: • Nordic health care study
MACE (as an outcome of hyperlipidaemia)	[Routine risk minimisation measures:] SmPC Sections 4.2, 4.4 and 4.8 (hypercholesterolaemia and hypertriglyceridaemia) PIL Section 2 and 4 SmPC Section 4.2 states that a dose of 2 mg once daily is recommended for patients at higher risk of VTE, MACE, and malignancy, for patients aged ≥65 years and for patients with a history of chronic or recurrent infections. SmPC Section 4.4 advises that lipid parameters should be assessed at 12 weeks following treatment initiation and thereafter according to international guidelines for hyperlipidaemia. Moreover, SmPC Section 4.4 advises that in patients over 65 years of age, patients who are current or past long-time smokers, and patients with a history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, baricitinib should only be used if no suitable treatment alternatives are available.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Cardiac disorders follow-up form • Cerebrovascular accident follow-up form • Mortality follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to compare the incidence of hyperlipidaemia and MACE among patients exposed to baricitinib: RA: • EU registries • Nordic health care study • Randomised, controlled post-authorisation safety studies in US (JAJA/JAJD) AD • Nordic health care study

	PL Section 2 advises patients that they may need blood tests while taking Olumiant to check if they have a high cholesterol level. [Additional risk minimisation measures:] • Health care Professional Educational Material (lipid monitoring) • Patient Alert Card • DHPC	
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 their doctor or pharmacist for advice before taking the medicine • States that patients should use an effective method of contraception to avoid becoming pregnant during treatment and for at least 1	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 health care study

	week after the last Olumiant treatment • States that patients must tell their doctor if they become pregnant as Olumiant should not be used during pregnancy [Additional risk minimisation measures:] • Health care Professional Educational Material • Patient Alert Card	
Long-term safety	[Routine risk minimisation measures:] SmPC Sections 4.4 and 4.8 (hypercholesterolaemia and hypertriglyceridaemia) PL Sections 2 and 4 No additional recommendations are included in the SmPC or PL other than those already stated for malignancy and MACE. [Additional risk minimisation measures:] None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Cardiac disorders follow-up form • Cerebrovascular accident follow-up form • Mortality follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to monitor long-term safety in patients exposed to baricitinib RA: • EU registries • Nordic health care study AD: • Nordic health care study
Use in very elderly (≥75 years)	[Routine risk minimisation measures:] SmPC Sections 4.2, 4.4 (lymphocytosis) and 5.2 PIL section 3 SmPC Section 4.2 states that • clinical experience in patients, ≥75 years is very limited. • a dose of 2 mg once daily is recommended for patients at higher risk of VTE, MACE, and malignancy, for patients aged ≥65 years and for patients with a history of chronic or recurrent infections.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Observational post-marketing safety studies to monitor the incidence of use in very elderly (≥75 years) in patients exposed to baricitinib: RA: • Nordic health care study AD: • Nordic health care study

	[Additional risk minimisation measures:] None.	
Use in patients with evidence of hepatitis B or hepatitis C infection	[Routine risk minimisation measures:] SmPC Section 4.4 PL Section 2 SmPC Section 4.4 recommends that screening for viral hepatitis should be performed before starting treatment and that if the test is positive, a liver specialist should be consulted Section 2 of the PL advises patients to speak to their doctor if they have, or have previously had, hepatitis B or C. [Additional risk minimisation measures:] None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: hepatic disorders follow-up Additional pharmacovigilance activities: None
Use in patients with a history of or current lymphoproliferative disease	[Routine risk minimisation measures:] SmPC Section 4.4 PL Section 2 PL Section 2 advises patients to tell their doctor or pharmacist before and during treatment if they have cancer. [Additional risk minimisation measures:] None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Use in patients with active or recent primary or recurrent malignant disease	[Routine risk minimisation measures:] PIL Section 2 PL Section 2 advises patients to tell their doctor or pharmacist before and during treatment if they have cancer. [Additional risk minimisation measures:] None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Long-term safety in paediatric patients including growth and bone	[Routine risk minimisation measures:] SmPC Section 4.2 PIL Section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

development, maturation and pubertal development, and adverse response to vaccination	SmPC Section 4.2 states • the safety and efficacy of baricitinib in children aged 0 to 2 years have not yet been established. No data are available. • the safety and efficacy of baricitinib in children less than 18 years of age with AD or AA have not yet been established. No data are available. PL Section 2 advises that Olumiant is not for use in children and adolescents younger than 2 years of age. It also advises that Olumiant is not for use in children and adolescents younger than 18 years old for AD and AA, because there is no information on use in these diseases. [Additional risk minimisation measures:] None	None Additional pharmacovigilance activities: • Long-term extension in children with JIA (Study JAHX)

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

2.7.4. Conclusion

The CHMP considered that the risk management plan version 20.2 is acceptable.

2.7.5. Pharmacovigilance system

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

2.7.6. Periodic Safety Update Reports submission requirements

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

2.8. Product information

2.8.1. User consultation

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

The proposed indication for baricitinib is: 'for the treatment of active juvenile idiopathic arthritis in patients 2 years of age and older who have had an inadequate response or intolerance to one or more prior conventional synthetic or biologic disease-modifying antirheumatic drugs (DMARDs):

- Polyarticular juvenile idiopathic arthritis (polyarticular rheumatoid factor positive [RF+] or negative [RF-], extended oligoarticular),

- Enthesitis related arthritis, and

- Juvenile psoriatic arthritis.

Baricitinib may be used as monotherapy or in combination with methotrexate.'

The proposed dose of baricitinib is "4 mg once daily for patients weighing 30 kg or greater. For patients weighing less than 30 kg, the recommended dose is 2 mg once daily. The dose should be reduced by half for patients with renal dysfunction or who use strong OAT3 inhibitors."

3.1.1. Disease or condition

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of diseases characterised by arthritis of unknown origin with onset before age of 16 years, persisting for more than 6 weeks. The currently used ILAR classification distinguishes the following JIA categories: systemic arthritis, polyarthritis rheumatoid factor (RF) negative, polyarthritis RF positive, oligoarthritis, psoriatic arthritis, enthesitis-related and undifferentiated arthritis.

The subcategories of JIA in the proposed indication follow the ILAR categories, which is in line with the EMA Guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis (EMA/CHMP/239770/2014 Rev. 2).

Baricitinib is a JAK1/JAK2 inhibitor demonstrating selectivity for and inhibition of JAK1 and JAK2 with lower potency towards inhibition of JAK3 or TYK2 (Fridman et al. 2010). Inflammatory cytokines, such as IL-6, which transduces cell signalling through the JAK/STAT pathway (Rawlings et al. 2004), and TNF, whose expression is reduced by inhibition of JAK1 and JAK2, are considered to be associated with the pathology of JIA (Ravelli and Martini 2007).

The aim of treatment of JIA is rapid suppression of inflammation, prevent occurrence of flares, reduce pain and maximise physical function, and promote normal growth and development. The ultimate

treatment goal is induction of clinical remission or attainment of minimal disease activity or inactive disease.

3.1.2. Available therapies and unmet medical need

Nonsteroidal anti-inflammatory drugs (NSAIDs) are considered a first–line treatment option in most cases of newly diagnosed JIA, followed by intra-articular glucocorticosteroids and conventional disease modifying antirheumatic drugs (DMARDs), including methotrexate and sulfasalazine. However, a substantial proportion of patients do not achieve an adequate response to these therapies (Ringold et al. 2013; Hinze et al. 2015; Ravelli 2016). Biologic agents approved for RA in the last decades have been added to the treatments available to children with JIA (Lovell et al. 2000; Ruperto et al. 2010b; Brunner et al. 2015). These treatments include TNF-inhibitors (adalimumab, etanercept, infliximab), tocilizumab, secukinumab, abatacept. The only JAK-inhibitor approved for JIA up to now is tofacitinib.

Although the biological treatments have led to clinical improvements, many patients do not respond and do not achieve long-lasting remission (Hinze et al. 2015; Onel et al. 2022). There still is a medical need for effective and safe treatments for the different forms of JIA.

3.1.3. Main clinical studies

The baricitinib clinical development programme for JIA includes one pivotal Phase 3 study (IV-MC-JAHV) and 1 supportive long-term extension study (IV-MC-JAHX); the long-term extension study is still ongoing. Dosing for JIA was based on PK/PD modelling of data in RA; the intended doses of 4 mg and 2 mg, based on body weight, were tested in the PK phase of the pivotal study JAHV. As half doses are needed for patients with decreased renal function or using strong OAT3 inhibitors, the Applicant submitted a grouping line extension application to introduce the 1 mg tablet.

Study JAHV is a double-blind, randomised (1:1) withdrawal, placebo-controlled study to evaluate the safety, efficacy, pharmacokinetics, acceptability, and palatability of baricitinib and the ability to mount primary and secondary immune response during baricitinib treatment in children from 2 years to less than 18 years of age with JIA. Included were patients with polyarticular JIA (n=143), extended oligoarticular JIA (n=16), ERA (n=50), and juvenile PsA (n=10). There were n=6 patients between 2-6 years, n=9 between 6-9 years, n=30 between 9-12 years, and n=175 between 12-18 years of age. To confirm or adapt the intended dose, 5-8 patients per age cohort were included in a 2-week PK phase. Next, the study proceeded with the intended doses with a 12-week open-label phase, after which responders (>30% response in PedACR) were randomised to placebo or continuation with baricitinib for up to 32 weeks. In this double-blind phase, the primary outcome was time-to-flare (worsening of ≥ 30% in at least 3 of the 6 PedACR core criteria for JIA and an improvement of ≥30% in no more than 1 of the criteria). Patients having a flare were considered drop-out and could continue in the ongoing long-term follow-up study JAHX, with open-label treatment with baricitinib.

3.2. Favourable effects

In the open-label period of study JAHV, a total of 167 (76%) patients reached a PedACR30 response at Week 12. The proportion of patients with a PedACR50 response was 64%, with PedACR70 was 46%, with PedACR90 response was 20%, and a PedACR100 response was reached in 10%. Decreases were also seen in the 6 PedACR components, including CHAQ disability, and in CHAQ Pain, JADAS-27 score, amongst others.

The primary outcome of the pivotal study JAHV was met. During the randomised withdrawal part of the

trial, patients receiving baricitinib were significantly less likely to experience disease flare when compared with those receiving placebo (hazard ratio = 0.241, p-value: <.001). By the end of the withdrawal period at week 44, 14 (17%) patients receiving baricitinib had a disease flare as compared to 41 (51%) patients receiving placebo. The survival curves of time-to-flare clearly separated the placebo group from the baricitinib group.

The treatment effect in time-to-flare was present in three of the included JIA subtypes, but not in the small (n=7) juvenile PsA group where no flares occurred.

- In the subgroup of patients with polyarticular JIA, the proportion of patients with a flare was 51% (26/51) for placebo and 18% (10/57) for baricitinib (p<0.001).

- In the subgroup of patients with extended oligoarticular JIA, the proportion of patients with a flare was 71% (5/7) for placebo and 20% (1/5) for baricitinib (p=0.24).

- In the subgroup of patients with ERA, the proportion of patients with a flare was 50% (10/20) for placebo and 19% (3/16) for baricitinib (p=0.083).

- In the subgroup of patients with juvenile PsA, no patients flared in the placebo group (n=3) nor in the baricitinib group (n=4).

A total of 67% of patients receiving baricitinib, and 38% of patients receiving placebo reached a PedACR30 response (p<.001), while 63% of patients receiving baricitinib, and 37% of patients receiving placebo reached a PedACR50 response (p=0.002). The improvements in the 6 components of the PedACR response criteria were all numerically larger in the baricitinib group, as compared to the placebo group (not tested for significance).

At week 44, there were 11 (14%) patients with inactive disease in the placebo group and 19 (23%) in the baricitinib group (p=0.11). At week 44, the mean (SE) change in JADAS-27 was -9.9 (1.0) in the placebo group and -14.2 (1.0) in the baricitinib group (p=0.001). At week 44, the mean (SE) change in CHAQ pain severity was -16.7 (3.2) in the placebo group and -29.7 (3.3) in the baricitinib group (p=0.003). In CHQ-PF50 Physical function Summary Sore, at week 44 the mean (SE) change from baseline was 10.5 (1.7) in the placebo group and 16.5 (1.7) in the baricitinib group (p=0.009).

In patients with juvenile PsA, at week 44 the mean (SE) change from baseline in PASI score was -0.8 (0.4) in the patients (n=3) on placebo and -1.2 (0.3) in patients (n=4) on baricitinib (p=0.57). In patients with juvenile PsA or with ERA, at week 44 the mean (SE) change in SPARCC enthesitis index was -1.9 (0.2) in the placebo (n=23) group and -1.5 (0.3) in the baricitinib (n=20) group (p=0.21). The mean (SE) change in JSpADA index was -1.5 (0.3) in the placebo (n=23) group and -2.6 (0.3) in the baricitinib (n=20) group (p=0.019).

Subgroup analysis for time-to-flare showed that the majority of treatment effects (hazard ratios) were between 0,22 – 0,30 with p-values <0.001, over subgroups of: prior biological DMARD use (yes/no), MTX use at baseline (yes/no), baseline ESR elevated (yes/no), JIA subtype (polyarticular and extended oligoarticular/juvenile PsA and ERA), female/male, age (⩾9 / <9), region EU, corticosteroid use at baseline (yes/no), weight class (⩾30 kg/<30 kg).

When analysing maintenance of effect, the proportion of patients who achieve PedACR30/50/70/90/100 response using their baseline values in study JAHV showed that after 48 weeks (n=126), 89% have at least PedACR30, while 81% have PedACR50 and 66% PedACR70, PedACR90 is reached by 49%.

3.3. Uncertainties and limitations about favourable effects

The study design, with an open-label phase and a randomised placebo-controlled withdrawal phase, makes it more difficult to evaluate the clinical relevance of the treatment effect of baricitinib, as compared to placebo. However, this approach is accepted for studies in the paediatric population including JIA (EMA/CHMP/239770/2014 Rev. 2).

The dose that was derived from the PK modelling in RA adults was: 4 mg for children aged 9 years and above and adolescents up to 18 years and 2 mg for children less than 9 years of age, and this dose regimen was carried forward in pivotal trial JAHV and open-label extension trial JAHX. However, the dose proposed in the SmPC is weight based: 4 mg for patients ⩾30 kg and 2 mg for patients <30 kg for patients aged 2-18 years. The dose proposal was based on PopPK modelling, which is an acceptable approach. However, based on the provided PopPK data, the C_{max} is higher in paediatric patients with juvenile idiopathic arthritis weighing <20 kg with the current posology of 2 mg once daily compared to the currently treated adult patients. A lower dose (e.g. 1 mg) would however compromise efficacy in this subgroup. Considering this, it was acceptable to propose 2 mg dose daily for patients weighing <30 kg. The longer-term safety data of this subgroup will be provided in a category 3 PASS.

The suspension used in the study is not yet approved nor submitted for marketing authorization. The Applicant provided the data that supports dissolving tablets in water for those patients who are not able to swallow tablets (sections 4.3 and 6.6 of SmPC), this is acceptable. Bioequivalence between the suspension used in the clinical study and the 4 mg tablets has been demonstrated in study JAGU.

3.4. Unfavourable effects

A study in juvenile rats supports an assessment of safety in children aged 1 and up and has identified the bone as a target organ. Bone findings from the juvenile toxicity study in rats and reproductive toxicity studies in rabbits and rats suggest that skeletal concerns were only noted at exposures that are unlikely to be clinically relevant (>24x).

A total of 220 patients was exposed to any dose of baricitinib in the JIA clinical trial program; 171 patients were exposed to baricitinib for at least 52 weeks.

In the 12-week open-label period, most (57%) patients had at least 1 TEAE, and in the withdrawal phase, the proportion of patients with at least 1 TEAE was larger in the baricitinib group as compared to the placebo group (66% versus 47%).

The occurrence of severe and serious AEs and of discontinuations due to AEs was low. In the open-label periods, 4 cases (1.8%) had a severe AE and 6 cases (2/7%) had a SAE; two (0.9%) patients discontinued due to an AE. In the placebo-controlled period, In the placebo group, 2 patients (2.5%) in the placebo group and 2 patients in the baricitinib group had at least one severe AE. There were 3 patients (3.7%) in the placebo group and 4 patients (4.9%) in the baricitinib group with at least one SAE. Discontinuations due to AEs were infrequent in the placebo (n=2) and baricitinib (n=1) groups.

In the open-label period, most TEAEs occurred in the SOCs of infections and infestations (25%), gastrointestinal disorders (15%), and investigations (12%), but also in the SOC for musculoskeletal and connective tissue disorders (11%). The most frequently occurring TEAEs were: nasopharyngitis (8.6%), headache (6.4%), arthralgia (5.5%), nausea (5%), upper respiratory tract infection (5%), (upper) abdominal pain (5%), vomiting (4.5%).

In the randomised-withdrawal period, in most SOCs the occurrences of TEAEs were numerically higher for baricitinib as compared to placebo: infections and infestations (38% versus 19%), investigations

(17% versus 2.5%), musculoskeletal and connective tissue disorders (16% versus 10%), gastrointestinal disorders (15% versus 6.2%). The single TEAEs that were numerically more common in the baricitinib group as compared to placebo were: upper respiratory tract infection (11% versus 1.2%), oropharyngeal pain (13% versus 3.4%), headache (11% versus 3.7%). But also clusters of abdominal pain (6.9% versus 17%) and rash (9.8% versus 3.4%) were more common the baricitinib group as compared to the placebo group. There was no difference between baricitinib and placebo in the occurrence of fractures (n=2 versus n=1), over this period. In the randomised-withdrawal period, 3 (3.7%) patients in the placebo group had an SAE and 4 (4.9%) patients in the baricitinib treatment group had an SAE (COVID-19, Gastroenteritis, Headache, and Pulmonary embolism).

Comparing All JIA data with the baricitinib period, the occurrence of TEAEs (IR 242 versus 254), SAEs (IR 7.1 versus 7.1) and of discontinuations due to AEs (2.8 versus 2.4) was similar. In the All JIA data set, the most common TEAEs were similar to those already seen in the JAHV trial periods. Also, cases of herpes simplex (n=4, 1.8%) and herpes zoster (n=4, 1.8%), gastroenteritis (n=5, 2.3%), acne (n=9, 4.1%) started to emerge. In the All JIA safety set, 22 (10%) patients had ≥1 SAE, most (n=9) SAEs were musculoskeletal in nature (arthralgia, joint effusion, juvenile idiopathic arthritis, other manifestations). The other SAEs included: appendicitis, Bartholin's abscess, soft tissue abscess, hepatic cytolysis, decreased appetite, ileus, bronchospasm, haematochezia, pulmonary embolism, amongst others; all these SAEs were single cases.

Out of 220 patients, there were 29 (13%) patients with a weight of <30 kg. A similar proportion of patients weighing ≥30 kg as compared with patients weighing <30 kg had TEAEs (83% versus 80%) and events in the Infections and infestations SOC (52% versus 55%). Twenty-one SAEs were reported in patients who weighed ≥30 kg, and 1 SAE was reported in children who weighed <30 kg (Ileus, considered unrelated). All serious infections and Herpes zoster were reported in the patient group who weighed ≥30 kg.

No SAEs were reported in the youngest age group (≥2 to <6 years), and the frequency of SAEs was similar across the other age groups. The frequencies and IRs of TEAEs were similar across age groups except for the youngest group of patients (aged ≥2 to <6 years).

There were no cases of MACE, malignancy, or DVT, there was 1 case of PE and 5 cases of serious infections. The available data on growth and skeletal development did not show abnormalities.

3.5. Uncertainties and limitations about unfavourable effects

Although there are a relatively large number of patients included and over 100 patients were exposed for at least one year, the safety experience in the youngest age group between 2 and 6 and between 6 and 9 is limited. Most patients were between 12 - 18 (n=175, 80%) years old; only few patients were between 2 – 6 (n=6) and between 6 – 9 (n=9) years old. There were 29 (13%) patients with a weight of <30 kg. The posology proposed for the SmPC is weight-based (2mg if <30kg, 4mg if ⩾30kg). As exposure, notably C_{max}, is higher in children <20 kg on 2 mg, as compared to adults on 4 mg, safety in this subgroup was included in the post-marketing long term safety analyses that have been included in the RMP.

A randomised withdrawal design with an open-label lead-in period is acceptable for evaluating efficacy and safety in children, given that it can be extrapolated from the experience in adults. The bone safety/growth and long-term safety in children and adolescents will be followed-up in a Category 3 PASS of the RMP.

3.6. Effects Table

Panel 36 Effects Table for Olumiant (baricitinib) in the treatment of juvenile idiopathic arthritis (data cut-off: 16 March 2022).

Effect	Short Description	Unit	Placebo	Baricitinib	Uncertainties/ Strength of evidence	References
Favourable Effects						
Time to flare	>30% worsening in PedACR definition.	%	51	17	SoE: HR (95%CI)=0.24 (0.13-0.45) Unc: withdrawal design	JAHV
PedACR50	≥50% improvement	%	37	63	SoE: p<0.002; supported by improvements in all 6 components Unc: not totally independent from flare	
Inactive disease	Absence of (specified) clinical manifestations	%	14	23	Unc: p=0.11; not totally independent from flare	
Unfavourable Effects						
SAEs	Serious Adverse Events	%	3.7	4.9	SoE: including serious infections	
Infections		%	19	38	SoE: also in open-label period and follow-up the most common AE.	

Abbreviations: PedACR: Paediatric American College of Rheumatology response criteria/flare criteria.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Overall, it is considered that baricitinib is effective in the treatment of JIA, and that the effects are of clinical relevance and apply to all 4 subtypes of JIA studied.

The initially proposed indication included “baricitinib may be used as monotherapy or in combination with conventional synthetic DMARDs”. Because most participants used methotrexate concomittantly, the CHMP requested the Applicant to change it “as monotherapy or in combination of methotrexate”,

which the MAH agreed. Regarding disease activity as well as considering treatment history, the study population was in line with the target population.

Based on the provided PopPK data, the C_{max} is higher in paediatric patients with juvenile idiopathic arthritis weighing <20 kg with the current posology of 2 mg once daily compared to the currently treated adult patients. This could lead to additional safety issues. It is considered that the sample size of the risk groups is too small to exclude additional toxicity due to higher exposure, although the safety data that are available are reassuring. Long-term safety will be followed in a Category 3 PASS of the RMP, especially also in the lower weight and younger age groups.

The primary outcome of the pivotal study JAHV was met: during the randomised withdrawal part of the study, patients on baricitinib were less likely to get a flare than patients on placebo (17% versus 51%, with a hazard ratio of 0.24, p<0.001). It is supportive for the proposed indication that the treatment effect in time-to-flare was present in three of the JIA subtypes, although not in the small juvenile PsA group where no flares occurred. There were trends supportive of improvement for patients with psoriasis, enthesis and axial spondyloarthritis, although these subgroups were smaller and between-group differences were not always statistically significant. The results in time-to-flare (primary outcome) and PedACR30 response were consistent over subgroups, including JIA subtype (polyarthritis, extended oligoarthritis, juvenile PsA, ERA), for age groups/dose groups, weight groups, for patients with or without concomitant methotrexate, amongst others. The absence of flares in the jPsA group may be a chance finding. Juvenile PsA is known to come with flares, and flares in this subgroup did occur in a similar trial with an IL-17 inhibitor or placebo (Cosentyx SmPC), for example. Overall results should normally be extrapolatable to JIA subgroups in accordance with the EMA guideline on JIA.

Besides the prevention of flares, the treatment goals in JIA include the reduction of disease activity and ultimately reaching inactive disease/remission. The difference between baricitinib and placebo in occurrence of flare is considered clinically relevant, which is notably supported by clinically relevant proportions of patients with a PedACR30, (50, 70 or 90), large reductions in the joint counts of -7 (active) to -4 (limited ROM) that remain when staying on baricitinib in the withdrawal phase, a mean change of -12 in JADAS-27 that exceeds the estimated MID of -5.5 (Bulatovic 2013), a change of ~0.5 in CHAQ disability index (range 0-3) which is supported by the change in CHQ-PF50 Phs, average changes >20 mm on Parent's global assessment of well-being and CHAQ assessment of pain. By the end of the randomised withdrawal phase, there were numerically somewhat more patients with inactive disease in the baricitinib group (23%) as compared to the placebo group (14%), which illustrates that reaching remission in JIA is difficult to reach. In the long-term follow-up study JAHX, the proportions of patients with low disease activity/inactive disease increased over time.

When analysing all available safety data, the occurrence and pattern of AEs are in line with the known safety profile (ADRs) of baricitinib, including cases of herpes simplex and herpes zoster, gastroenteritis and acne. The occurrence of severe and serious AEs and discontinuations due to AEs was low.

Surprisingly, the occurrence of musculoskeletal TEAEs was higher in the baricitinib group than in the placebo group; mainly mild arthralgia and mild synovitis. This is not considered to be causal but driven by selection by drop-out due to flare in the placebo group.

In the All JIA safety set using all available follow-up data, the occurrence of and pattern of TEAEs, SAEs and discontinuations were basically similar to the baricitinib period in the randomised withdrawal phase and in line with what is known for baricitinib, also in the youngest and lowest weight children. However, numbers were small and safety in these groups will be solved with the inclusion of a Category 3 PASS of the RMP. Although the baricitinib exposure of the randomised withdrawal period is

included in the All JIA data, and comparing IRs with different lengths of exposure is generally difficult, it is considered that there is no tendency that AEs would accumulate over time.

MACE, DVT, and malignancies did not occur, while PE occurred in 1 case, and serious infections occurred in 5 cases. It is considered that due to the age range of the target population, these patients usually do not collect risk factors that rise the propensity for MACE, VTE and malignancies. From the non-clinical and available clinical data, there do not appear to be risks regarding bone safety, skeletal development or growth, but more data should be collected over a longer follow-up time in the post-marketing setting.

3.7.2. Balance of benefits and risks

Baricitinib is effective for the treatment of JIA. The primary outcome of the pivotal study JADV was met: patients on baricitinib were less likely to get a flare than patients on placebo. The difference between baricitinib and placebo is clinically relevant and supported by the results of secondary outcomes. Over 1 – 2 years of treatment, it appears that in most patients, responses can be maintained without the occurrence of flares. The results in time-to-flare (primary outcome) and PedACR30 were basically consistent over subgroups, including JIA subtype (polyarthritis, extended oligoarthritis, juvenile PsA, ERA), for age groups/dose groups, weight groups, and for patients with or without concomitant methotrexate.

Based on the available data, the safety profile of baricitinib in the doses of 1mg, 2 mg and 4 mg is acceptable in the studied paediatric population of patients with JIA. However, especially in the lower age (<9 years) and weight (<30 kg) categories, the number of patients is low. In patients weighing <20 kg, exposure was higher than estimated for adults, but a lower strength in this weight group would compromise efficacy. Therefore, the proposed posology of 2 mg daily for patients weighing <30 kg is acceptable. Long-term safety in these children will be followed post-marketing in a Category 3 PASS, especially also if <20kg. From the non-clinical and available clinical data, there do not appear to be risks regarding bone safety, skeletal development or growth, but these risks have been included as missing information in the RMP and more data will be collected over a longer follow-up time in the post-marketing setting.

3.8. Conclusions

The overall benefit/risk balance of Olumiant new strength (1 mg) for the treatment of Juvenile idiopathic arthritis in patients 2 years of age and older who have had an inadequate response or intolerance to one or more prior conventional synthetic or biologic disease-modifying antirheumatic drugs (DMARDs): Polyarticular juvenile idiopathic arthritis (polyarticular rheumatoid factor positive [RF+] or negative [RF-], extended oligoarticular), Enthesitis related arthritis, and Juvenile psoriatic arthritis is positive.

4. Recommendations

- *Outcome*

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Olumiant new strength (1 mg), is favourable in the following indication:

Olumiant is indicated for the treatment of Juvenile idiopathic arthritis in patients 2 years of age and older who have had an inadequate response or intolerance to one or more prior conventional synthetic

or biologic disease-modifying antirheumatic drugs (DMARDs): Polyarticular juvenile idiopathic arthritis (polyarticular rheumatoid factor positive [RF+] or negative [RF-], extended oligoarticular), Enthesitis related arthritis, and Juvenile psoriatic arthritis. Baricitinib may be used as monotherapy or in combination with methotrexate.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Olumiant subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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.

An updated RMP should be submitted:

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

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

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

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

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

- Additional Patient Alert Cards

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

- Indication and posology statements provided to reinforce in whom baricitinib should be used
- That baricitinib increases the potential risk of infections. Patients should be instructed to seek immediate medical attention, if signs or symptoms suggesting infection appear. As there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes. Baricitinib should only be used in patients 65 years of age and older if no suitable treatment alternatives are available.
- That baricitinib use should be stopped in case of herpes zoster or any other infection that doesn't respond to standard treatment until the event resolves. Patients should not be immunised using live attenuated vaccines shortly before or during treatment with baricitinib.
- Prior to initiating treatment it is recommended that all patients, particularly paediatric patients, be brought up to date with all immunisations in agreement with local current immunisation guidelines
- Prescribers should screen the patients for viral hepatitis before commencing baricitinib treatment. Active tuberculosis should also be ruled out.
- That baricitinib use is associated with hyperlipidaemia; prescribers should monitor the patient's lipid parameters and manage the hyperlipidaemia, if detected.
- Baricitinib increases the risk of venous thrombosis and pulmonary embolism. Baricitinib should be used with caution in patients with known risk factors for DVT/PE other than cardiovascular or malignancy risk factors. Patients should be instructed to seek immediate medical attention if signs or symptoms of DVT/PE appear.
- That there is a potentially increased risk of MACE in patients with certain risk factors using JAK inhibitor treatment, including baricitinib. In patients 65 years of age and older , patients who are current or past long term smokers, and patients with other cardiovascular risk factors, baricitinib should only be used if no suitable treatment alternatives are available.
- That Lymphoma and other malignancies have been reported in patients receiving JAK inhibitors, including baricitinib. In patients over 65 years of age, patients who are current or past long term smokers, or with other malignancy risk factors (e.g. current malignancy or history of malignancy) baricitinib should only be used if no suitable treatment alternatives are available.
- That baricitinib is contraindicated in pregnancy as pre-clinical data showed reduced foetal growth and malformations. Physicians should advise women of child bearing potential to use contraception during treatment and for a week after its ending. If a planned pregnancy is considered, baricitinib treatment should be stopped.
- The purpose and use of the Patient Alert Card.

The patient alert card shall contain the following key messages:

- That treatment with baricitinib may increase the risk of infections, and viral reactivation which can become serious if not treated.
- Signs or symptoms of infections including general symptoms, and specifically tuberculosis and herpes zoster signs and symptoms; and a warning for the patients to seek immediate medical attention if signs or symptoms suggesting infection appear.
- Patients should seek immediate medical attention if signs and symptoms of myocardial infarction or stroke occur.
- That baricitinib should not be taken while pregnant and that women should inform their doctor should they become (or wish to become) pregnant.
- That baricitinib may cause a blood clot in the leg that may travel to the lungs; a description of signs and symptoms is provided, along with a warning for the patients to seek immediate medical attention if signs or symptoms suggesting a blood clot appear.
- That baricitinib may cause non-melanoma skin cancer and that the patients should talk to their doctor if new skin lesions appear during or after therapy or if existing lesions change appearance, tell your doctor.
- Contact details of the prescriber.
- That the Patient Alert Card should be carried by the patient at any time and to share it with other healthcare professionals involved in their treatment.

- Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
I4V-MC-B011: Retrospective Cohort Study to Assess Safety of Baricitinib in Nordic countries	For RA study: Final study report (Objectives 1-3*): 31 December 2027* For AD Study: Final Report: 31 December 2028
I4V-MC-B012: Observational post marketing Surveillance in 3 European Registries	Final study report: 31 March 2024
I4V-MC-B025: Survey to assess the effectiveness of the baricitinib additional risk minimisation measures	Final study report: Six months after the end of data collection; estimated 30 April 2025
Interventional post-authorisation safety studies (PASS): • I4V-MC-JAJA: A Randomized Active-Controlled Parallel-Group Phase 3b/4 Study of Baricitinib in Patients with Rheumatoid Arthritis	Final study report: 31 March 2028

Description	Due date
• I4V-MC-JAJD: A Randomized, Controlled Pragmatic Phase 3b/4 Study of Baricitinib in Patients with Rheumatoid Arthritis These studies are reported jointly for reasons described in Section III.2 of the RMP	
Drug utilisation study to assess prescribing patterns of baricitinib	Final study report: Within 12 months of end of data collection, estimated 30 December 2027
Interventional post-authorisation safety study (PASS): 14V-MC-JAHX Open-label extension study evaluating the long-term safety and tolerability of baricitinib in patients with JIA	Final study report: 31 March 2031

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

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/004/2022 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation concerning the following change(s):

Variations requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB
X.02.III	Annex I_2.(c) Change or addition of a new strength/potency	Line Extension	I, IIIA, IIIB and A

Extension application to introduce a new strength (1 mg film-coated tablet), grouped with a type II variation (C.I.6.a) in order to extend the indication to include treatment, as monotherapy or in combination with conventional synthetic disease modifying antirheumatic drugs (DMARDs), of active juvenile idiopathic arthritis (JIA) in patients 2 years of age and older who have had an inadequate response or intolerance to one or more prior conventional synthetic or biologic DMARDs, based on final results from the pivotal study JAHV (I4V-MC-JAHV); this is a multicentre, double-blind, randomised, placebo-controlled, medication-withdrawal Phase 3 study in children from 2 years to less than 18 years of age with JIA who have had an inadequate response or intolerance to treatment with at least 1 cDMARD or bDMARD. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. The guide for HCPs in the Annex II was updated to recommend paediatric patients are immunised prior to initiation of treatment.
Version 20.2 of the RMP has also been approved.