EMA/275928/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Olumiant

International non-proprietary name: Baricitinib

Procedure No. EMEA/H/C/004085/II/0046

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	Description	Planned date	Actual Date	Need for discussion[2]
☐	Start of procedure	11 Dec 2023	11 Dec 2023	☐
☐	CHMP Rapporteur Assessment Report	15 Jan 2024	15 Jan 2024	☐
☐	CHMP members comments	29 Jan 2024	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	01 Feb 2024	n/a	☐
☐	Start of written procedure	06 Feb 2024	06 Feb 2024	☐
☐	Request for supplementary information	08 Feb 2024	08 Feb 2024	☐
☐	Submission of MAH responses	05 Mar 2024	26 Feb 2024	☐
☐	Re-start of procedure	06 Mar 2024	06 Mar 2024	☐
☐	CHMP Rapporteur Assessment Report	20 Mar 2024	20 Mar 2024	☐
☐	CHMP members comments	25 Mar 2024	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	27 Mar 2024	n/a	☐
☐	Start of written procedure	02 Apr 2024	02 Apr 2024	☐
☐	Request for supplementary information	04 Apr 2024	04 Apr 2024	☐
☐	Submission of MAH responses	30 Apr 2024	25 Apr 2024	
☐	Re-start of procedure	01 May 2024	01 May 2024	☐
☐	CHMP Rapporteur Assessment Report	15 May 2024	15 May 2024	☐
☐	CHMP members comments	21 May 2024	21 May 2024	☐
☐	Updated CHMP Rapporteur Assessment Report	23 May 2024	23 May 2024	☐
☒	opinion	30 May 2024	30 May 2024	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Procedure resources	
Rapporteur:	Peter Mol

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eli Lilly Nederland B.V. submitted to the European Medicines Agency on 20 November 2023 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Update of section 5.1 of the SmPC, in order to add information on JIA-associated uveitis or chronic anterior antibody positive uveitis based on interim results from study I4VMC-JAHW; this is an open-label, active-controlled, safety, and efficacy study of oral baricitinib in patients from 2 years to less than 18 years old with active juvenile idiopathic arthritis-associated uveitis or chronic anterior antinuclear antibody-positive uveitis.

The requested variation proposed amendments to the Summary of Product Characteristics.

2. Overall conclusion and impact on the benefit/risk balance

The MAH provided interim-data to support this type II variation to update Section 5.1 of the SmPC for Olumiant (baricitinib) based on the Phase 3 Study I4V-MC-JAHW (JAHW). This study was conducted in line with the baricitinib PIP (EMEA-001220-PIP01-M07), and concerns an open-label and active-controlled study aimed at the evaluation of efficacy and safety of baricitinib when administered once daily (QD) to paediatric patients with active JIA-U or ANA-positive uveitis who have had an inadequate response to topical steroids and methotrexate (MTX) or biologic disease-modifying antirheumatic drugs (bDMARDs). A total of 29 patients from 2 – 18 years of age was included, who were stratified into two cohorts: The methotrexate inadequate responder (MTX-IR) cohort (n=10), and the biologic disease-modifying antirheumatic drug inadequate responder (bDMARD-IR) cohort (n=19). The first cohort was subsequently assigned to either adalimumab (n = 5) or baricitinib (n = 5), the latter to baricitinib. Dosing regimens were according the corresponding SmPC of baricitinib and adalimumab, i.e. baricitinib 2 mg in children 2 to <9 years old, baricitinib 4 mg in children 9 to <18 years old, adalimumab 20 mg in children < 30 kg, or adalimumab 40 mg in children ≥ 30 kg. The primary endpoint, which was not met, was the proportion of responders to baricitinib at Week 24; response was defined according to the SUN (standardisation of uveitis nomenclature) criteria as a 2-step decrease in the level of inflammation (anterior chamber cells) or decrease to zero through Week 24, in the eye most severely affected at baseline. Eight (33.3%) patients were baricitinib responders (7 bDMARD-IR and 1 MTX-IR), but the response rate between the two cohorts did not show statistical significance. The observed safety data were generally consistent with the established safety profile in the baricitinib polyarticular JIA population.

Based on the data of study Study I4V-MC-JAHW (JAHW), the MAH proposed to update Section 5.1 of the SmPC. The CHMP considered the inclusion of data from this paediatric study relevant for clinicians and patients. It is acknowledged this information comes from a non-authorised indication. However, in light of the paediatric regulation, its inclusion in the 5.1 sub-section, paediatric population, is considered relevant.

Study I4V-MC-JAHW (JAHW) was not considered a true randomised study. Ethical considerations and challenges in enrolling bDMARD naïve patients resulted in the deviation from a 1:1 randomisation ratio. However, the modified study design supports the MAH's conclusion that the study population is

reflective of the real-world patient population. Therefore, SmPC Section 5.1 includes no mention of the JAHW study as being a randomised study.

It was noted the TEAEs, oropharyngeal pain (n = 4, 16.7%) and pyrexia (n = 3, 12.5%) were observed in the JAHW study. However, considering the low patient years of exposure to baricitinib in this study, the sample size, and age of the population, these TEAEs were not added to SmPC section 4.8.

The MAH was requested to provide data regarding the potential impact of concomitant medication use on the response rate. However, since concomitant medication use was considerably lower in the bDMARD-IR baricitinib responders' group, the CHMP agreed that the concomitant use had no impact on the response rate.

Overall the CHMP agreed to reflect in section 5.1 of the SmPC the results as follows: The efficacy and safety of baricitinib were evaluated in 29 patients from 2 to < 18 years of age with active JIA-associated uveitis or chronic anterior antibody positive uveitis. MTX-IR (n = 10) were assigned to baricitinib (n = 5) or adalimumab (n = 5); bDMARD-IR (n = 19) were all assigned to baricitinib. Baricitinib was dosed 2 mg once daily for patients 2 to < 9 years old and 4 mg once daily for those 9 to < 18 years old, adalimumab dosing was 20 mg (if < 30 kg), or 40 mg (if ≥ 30 kg) once every two weeks. The primary endpoint was the proportion of patients with a 2 step decrease in the level of inflammation (anterior chamber cells) according to the SUN (standardisation of uveitis nomenclature) criteria or decrease to zero through week 24, in the eye most severely affected at baseline. Eight (33.3 %) patients were baricitinib responders (7 bDMARD-IR and 1 MTX-IR), but the response rate between the two cohorts did not show a statistical significance.

In addition, the ATC code for baricitinib is updated from L04AFA37 into L04AF02, to align with the latest version (2024-01-26) of the ATC/DDD index.

Finally, the CHMP had deferred the obligation to submit the results of studies with baricitinib in one or more subsets of the paediatric population, including atopic dermatitis. However, the MAH recently received approval for olumiant's extension of indication, in procedure EMEA/H/C/004085/II/0037, for paediatric patients (from 2 years of age and older) with moderate to severe atopic dermatitis. Therefore, the sub-section, paediatric population, of SmPC section 5.1, is updated as follows:

- "The European Medicines Agency has deferred the obligation to submit the results of studies with baricitinib in one or more subsets of the paediatric population in chronic idiopathic arthritis~~, atopic dermatitis~~ and alopecia areata (see section 4.2 for information on paediatric use).

The MAH noted a discrepancy in the JUVE-BASIS study information in section 5.1 of the SmPC. Therefore, the baseline characteristic sub-section is updated to correct for a 'typo' in the standard deviation for the mean age, corrected from 3.4 to 3.0.

The benefit-risk balance of Olumiant remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Update of section 5.1 of the SmPC in order to add information on JIA-associated uveitis or chronic anterior antibody positive uveitis based on interim results from study I4VMC-JAHW; this is an open-label, active-controlled, safety, and efficacy study of oral baricitinib in patients from 2 years to less than 18 years old with active juvenile idiopathic arthritis-associated uveitis or chronic anterior antinuclear antibody-positive uveitis.

☒ is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I are recommended.

Annex: Rapporteur’s assessment comments on the type II variation

4. Introduction

Juvenile idiopathic arthritis-associated uveitis (JIA-U) involves chronic inflammation of the uveal components of the eye, that is, the iris, choroid, and retina. Clinical manifestations may include redness, pain, photophobia, and blurred vision. The inflammation may extend to other ocular structures, potentially causing complications such as cataracts, glaucoma, or macular edema or even loss of vision if untreated. While in most cases, JIA precedes the development of uveitis, a minority of patients develop uveitis before the onset of JIA (Carlsson E., et al; 2021). Regular ophthalmologic screening is thus warranted.

The prevalence of JIA in developed countries is estimated between 16–150 per 100,000. The proportion of JIA patients developing uveitis is up to 30% of individuals positive for antinuclear antibodies (ANA) (Ravelli A., et al; 2005), and 10–20% across all sub-forms of JIA (Tappeiner C., et al; 2018).

Regarding pharmaceutical interventions, first-line treatment strategies for JIA-associated uveitis include topical glucocorticoids, and in the case of synechiae, mydriatic eye drops to prevent an increase in intraocular pressure and cataract development. If topical treatment fails to induce stable remission, systemic treatments are added (Carlsson E., et al; 2021), which need to be continued for at least two years after achievement of remission to reduce the risk of recurrence (Kalinina Ayuso., et al; 2011). Methotrexate (MTX) is a well-established first-line IMT in the management of JIA-associated uveitis (Heiligenhaus A., et al; 2007). Other disease modifying anti-rheumatic drugs (cDMARDs) have been considered for those with chronic anterior uveitis and JIA such as azathioprine, leflunomide, mycophenolate and cyclosporine; however, use of these agents are limited due to adverse effects and reports of refractory uveitis (Paroli MP., et al; 2022).

Biologic DMARDs have led to significant improvements in JIA-U treatment. Adalimumab (TNF-a inhibitor) has shown to reduce the risk of treatment failure by 75% relative to placebo in patients with JIA-U (Ramanan., et al; 2017). In a tocilizumab trial however, the primary endpoint was not met (APTITUDE trial; response rate 34% [95% CI 25–57], p=0·11) (Ramanan., et al; 2020).

Baricitinib is a JAK1/JAK2 inhibitor demonstrating selectivity for and inhibition of JAK1 and JAK2 with lower potency towards inhibition of JAK3 or TYK2. Janus kinases are a family of 4 protein tyrosine kinases (JAK1, JAK2, JAK3, and tyrosine kinase 2 [TYK2]) that play an important role in cytokine signal transduction (Fridman., et al. 2010). Baricitinib is currently approved for rheumatoid arthritis, atopic dermatitis, alopecia areata and JIA (polyarticular JIA, extended oligoarticular, enthesitis-related JIA, and juvenile psoriatic arthritis) in patients 2 years of age and older.

The etiology and pathogenesis of JIA-U and ANA-positive uveitis are still poorly understood; however, the aqueous humor of these patients contains elevated levels of a number of cytokines, including interleukin (IL)-2, IL-6, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α (Agrawal et al. 2014; Sijssens et al. 2007). Inflammatory cytokines, such as IL-6, which transduces cell signaling 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-U and ANA-positive uveitis (Sijssens., et al. 2007; Agrawal et al. 2014). Therefore, theoretically, inhibition of JAK-STAT signaling by baricitinib could target multiple cytokine pathways associated with JIA-U and ANA-positive uveitis.

The applicant has provided interim-data to support a type II variation to update Section 5.1 of the SmPC for Olumiant (baricitinib) with regard to the Phase 3 Study I4V-MC-JAHW (JAHW). Study JAHW, conducted in line with the baricitinib PIP (EMEA-001220-PIP01-M07), is open-label and active-controlled, and aimed at the evaluation of efficacy and safety of baricitinib when administered once daily (QD) to pediatric patients with JIA-U or ANA-positive uveitis who have had an inadequate response to topical steroids and methotrexate (MTX) or biologic disease-modifying antirheumatic drugs (bDMARDs).

5. Clinical Efficacy aspects

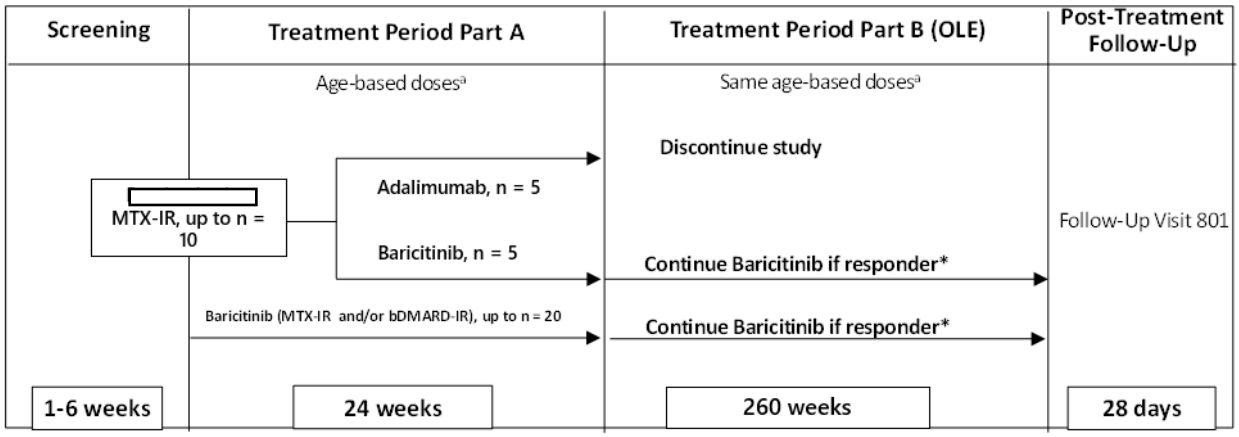
5.1. Methods

Study I4V-MC-JAHW (JAHW) is an open-label, active-controlled, Phase 3 trial to evaluate the efficacy and safety of baricitinib when administered once daily (QD) to patients 2 years to less than 18 years old with active JIA-U or chronic anterior ANA-positive uveitis without systemic features.

This study is conducted in 2 parts, Part A and Part B, and includes the following 4 periods (see also Figure 1):

- Screening period (from 1-6 weeks)
- Open-label treatment period – Part A (24 weeks)
- Open-label treatment period – Part B (260 weeks), and
- Post-treatment follow-up period (28 days after last dose of investigational product).

Figure 1 Study design for Clinical Protocol I4V-MC-JAHW



Abbreviations: bDMARD-IR = biologic disease-modifying antirheumatic drug-inadequate responder; MTX-IR = methotrexate-inadequate responder; n = number of patients; OLE = open-label extension.

[a] Patients ≥ 6 to <12 years old assigned to baricitinib have the option of receiving the oral suspension or tablets. Patients >12 years old assigned to baricitinib will receive tablets. Patients assigned to adalimumab weighing <30 kg will receive 20 mg, and those ≥30 kg will receive 40 mg.

Diagnosis and Main Criteria for Inclusion:

The study population included children from 2 to less than 18 years old with the following criteria at screening and baseline:

- Diagnosis of JIA-U or chronic ANA-positive uveitis without systemic features.
- Active anterior uveitis, defined as the Standardization of Uveitis Nomenclature (SUN) criteria grade ≥1+ at Visit 1 and Visit 2, despite prior treatment with adequate doses of topical steroid therapy and methotrexate (MTX).
- Inadequate response or intolerance to MTX. Patients considered to have inadequate response must have received MTX for at least 12 weeks before an inadequate response may be determined. Patients continuing MTX in the study must have been on a stable dose for at least 4 weeks prior to screening. Patients not continuing MTX during the study must have stopped MTX 4 weeks prior to screening.

Note: Protocol JAHW provides a 12-week period to establish if a patient is responding to prior treatment. Investigators relied on their training and clinical experience regarding the SUN criteria to determine if a patient had responded to prior treatment. Investigators also relied on their training and clinical experience to make a formal determination of intolerance. Specific examples of intolerance to MTX are gastrointestinal intolerance, laboratory enzyme elevations, but may include other elements deemed as appropriate by the investigator.

- Received topical corticosteroid eye drops at a stable dose for at least 2 weeks prior to screening (maximum of 4 drops per day per eye at screening).

The study excluded patients if they met any of the following criteria at screening and at baseline:

- Uveitis without a diagnosis of JIA or chronic anterior uveitis without positive ANA.
- A history or presence of any autoimmune inflammatory condition other than JIA.
- Contraindications to adalimumab as addressed in local product labelling or local clinical practice that would preclude the patient from participating in this study. Exception: Patients who were biologic disease-modifying antirheumatic drug-inadequate responders (bDMARD-IR) with a contraindication to adalimumab could be enrolled, as they were assigned to baricitinib.
- Increased intraocular pressure ≥ 25 mm Hg or that required treatment, including increases in medications, surgery, or hospitalisation, within 4 weeks prior to baseline that, in the opinion of the investigator, would pose an unacceptable risk to the patient if participating in the study.
- Intraocular surgery within the 3 months prior to screening (such as for cataract (s), glaucoma, or vitrectomy).

Prior/Concomitant Therapy

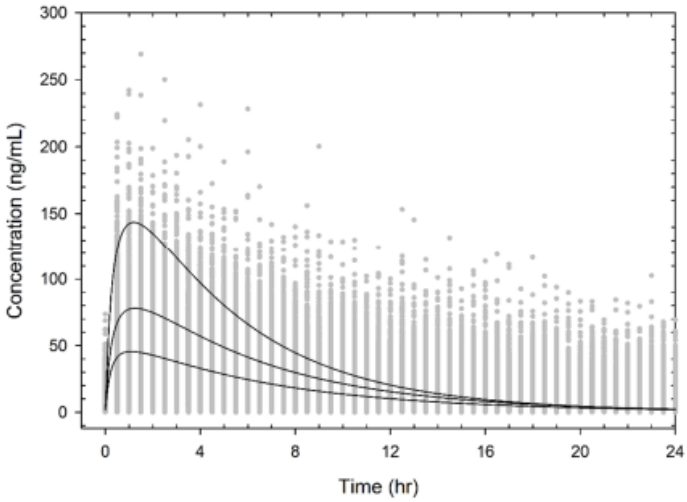
- Received treatment with any parenteral corticosteroid administered by intra articular, intramuscular, or intravenous injection within 4 weeks prior to Visit 2.
- Use of oral corticosteroids at average daily doses of greater than 10 mg/day or 0.2 mg/kg/day prednisone equivalent, whichever is less, or had done so within 2 weeks prior to screening. If continuing oral corticosteroids, patients had to be on a stable dose for 4 weeks prior to baseline.
- A depot peri ocular, peri ocular or intraocular corticosteroid injection within 30 days prior to Visit 2.
- Intraocular steroid implant within 6 months (e.g., Ozurdex) or 18 months (e.g., Iluvien) prior to Visit 2.
- Intraocular disease modifying agents, including anti vascular endothelial growth factor injections, within 30 days prior to Visit 2.The Screening Period was up to 42 days prior to baseline. At screening, the parent or legal guardian signed the informed consent form (ICF) and the patient signed the assent form (as appropriate) per local requirements prior to any study assessments, examinations, or procedures being performed.

Dose selection

All baricitinib doses were equivalent to 4-mg baricitinib exposure in adult rheumatoid arthritis (RA) patients, as previously established in patients with JIA in Study I4V-MC-JAHV through pharmacokinetic analyses. Predicted concentration-versus-time data in patients with RA were simulated using physiologically based pharmacokinetic (PBPK) modelling. The modelling predicted that baricitinib

concentrations in adolescents 12 to <18 years old and in children 6 to <12 years old would be expected to be similar to those in adults (Figure 2); therefore, these patients will initially receive the 4-mg QD dose in Study JAHW. Conversely, concentrations in children aged <6 years would be expected to be toward the higher end of the range observed in adults; therefore, these patients initially received a lower 2-mg QD dose.

Figure 2 Comparison of predicted steady-state concentrations of baricitinib in pediatric (solid lines) versus adults (gray dots) receiving 4-mg QD.



These graphs are overlay plots comparing model-predicted mean concentration–time curves in pediatric age groups to model-predicted plasma concentrations in adults. Solid lines are model-predicted mean concentrations in age groups 2 to <6 years (top line), 6 to <12 years (middle line), and 12 to <18 years (bottom line). These lines were developed using a physiologically-based pharmacokinetic (PK) model implemented with Simcyp®, based on adult data with adjustment for age. The gray dots indicate individual concentrations derived from simulations of the final population PK model for baricitinib in adult patients with rheumatoid arthritis.

Patients in the adalimumab group received weight-based doses of subcutaneously administered adalimumab, either 20 mg (if <30 kg) or 40 mg (if ≥ 30 kg), every 2 weeks.

Treatment with concomitant therapies during the study were permitted only as described below and in Table 1.

Table 1 Concomitant JIA Therapies

Drug Class	As Needed	Chronic Use	Conditions for Use During Part A
MTX[a]	No	Yes	• Maximum of 25 mg/m^2/week. • Stable dose is required for at least 4 weeks prior to screening. • Must continue on same dose throughout Part A. • May initiate, increase or decrease the dose, or discontinue during Part B.
csDMARDs other than MTX[a]	No	Yes	• Stable dose is required for at least 4 weeks prior to screening. • Must continue on same dose throughout Part A. • May initiate, increase or decrease dose, or discontinue during Part B. • Maximum of 2 concomitant csDMARDs (including MTX).
Mycophenolate mofetil	No	Yes	• Stable dose is required for at least 4 weeks prior to screening. • Must continue on same dose throughout Part A. • May initiate, increase or decrease the dose, or discontinue during Part B.
Topical steroid eye drops	No	Yes	• Maximum of 4 drops/day per eye at screening. • Stable dose is required for at least 2 weeks prior to screening. • In Part A, drops may be tapered between Week 4 through Week 20. • In Part B, drops may be tapered after Week 24 to any dose, including zero. • Formulation may not change during Part A, but may change during Part B.
Oral corticosteroids	No	Yes	• Maximum dose of 10 mg/day or 0.2 mg/kg/day prednisone equivalent, whichever is less. • Stable dose is required for at least 2 weeks prior to screening and 4 weeks prior to baseline. • Must continue on same dose throughout Part A, except for treatment of an AE. • May initiate, increase or decrease dose, or discontinue during Part B.
Intra-articular corticosteroid joint injections	No	No	• Maximum of 8 injections per year. • Maximum of 2 injections in a single session. • Not permitted within 4 weeks prior to Visit 2.
Intraocular corticosteroid injections	No	No	• Not permitted within 30 days prior to Visit 2. • Not permitted during Part A. • Permitted during Part B.
Systemic corticosteroids (other than oral and intra-articular)	No	Yes	• Not permitted during Part A. • Permitted during Part B at a maximum dose of 10 mg/day or 0.2 mg/kg/day prednisone equivalent, whichever is less.
Analgesics & NSAIDs	No	Yes	• Stable dose is required for at least 1 week prior to Visit 2. • Must continue on same dose throughout Part A, except for treatment of an AE. • May initiate, increase or decrease dose, or discontinue during Part B.

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

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

The primary efficacy endpoint of Study I4V-MC-JAHW (JAHW) was the proportion of responders at Week 24. Response was defined according to the Standardization of Uveitis Nomenclature (SUN) criteria as a 2-step decrease in the level of inflammation (anterior chamber cells) or decrease to zero through Week 24, in the eye most severely affected at baseline. The grading system considers factors such as the presence of cells in the anterior chamber, flare, vitreous haze, and the extent of peripheral anterior synechiae. For cells in the anterior chamber, values range from 0 (quiet) to 3+ (severe cells). Flare is graded from 0 (none) to 2+ (marked), while vitreous haze follows a similar scale. Peripheral Anterior Synechiae (PAS) are graded from 0 (none) to 4 (360 degrees) (Jabs DA,. Et al; 2005).

Statistical analysis

A Bayesian analysis was used to analyse the primary efficacy endpoint with posterior probability reported. The primary endpoint would be met, and the study would be considered positive if the probability of a treatment response in greater than 57% of patients exceeded 80%.

While Study JAHW included the adalimumab treatment group as an active reference arm, the study was not designed or powered for statistical comparisons between treatment groups. Therefore, comparisons of efficacy or safety data between the baricitinib and adalimumab treatment groups are not appropriate, and no statistical treatment comparisons were conducted.

Two interim analyses were performed to determine if the study should be stopped for futility when 10 and 20 baricitinib-treated patients completed 24 weeks of treatment, respectively, and also on the primary endpoint. At each of the interim analyses, the posterior probability of the treatment response rate being lower than 40% was calculated, and the study was to be stopped if this probability was more than 75% (otherwise the study would continue).

5.2. Results

Study JAHW has enrolled 30 patients until the interim data analysis. One patient was assigned to treatment but discontinued before receiving the investigational product. Twenty-four patients were exposed to either baricitinib 4 mg or 2 mg doses QD based on age group. All baricitinib doses were equivalent to 4 mg baricitinib exposure in adult RA patients. Five patients were exposed to adalimumab at either 20-mg or 40-mg doses based on weight, administered by subcutaneous injection every 2 weeks.

The planned interim analysis revealed that baricitinib only had marginal efficacy in the treatment of JIA-U. Therefore, and due to better treatment options that became available (adalimumab), the MAH proposed discontinuation of study enrolment which was agreed by PDCO (P/0063/2023 dated 03 March 2023). In line with the modifications approved by the PDCO, the current study design is as follows (Figure 1):

- patients receiving baricitinib in Part A who reached the primary endpoint as a baricitinib responder proceed to Part B for continued access to baricitinib, and
- all other patients are discontinued after Week 24. All patients receiving adalimumab during Part A are transitioned to commercial adalimumab with clinical standard of care maintained by the clinician.

Eight (33.3%) patients in the baricitinib group were responders at Week 24. Among the 8 responders in the baricitinib group, 7 (36.8%) were from the MTX-IR and/or bDMARD-IR cohort, and 1 (20.0%) was from the MTX-IR cohort. Four (80.0%) patients in the adalimumab reference group were responders at Week 24 (Table 2).

Table 2 SUN Grade of Cells in the Anterior Chamber Response Rate at Week 24 - Baricitinib mITT Population

Treatment Group	Baricitinib		
	Total N = 24	MTX-IR and/or bDMARD IR N = 19	MTX-IR N = 5
Response at Week 24			
n (%)	8 (33.3)	7 (36.8)	1 (20.0)
Posterior Probability of response rate >57%	1.03%	NA	NA

Abbreviations: bDMARD-IR = biologic disease-modifying antirheumatic drug-inadequate responder; mITT = modified intent-to-treat; MTX-IR = methotrexate-inadequate responder; N = number of patients in the analysis population; n = number of patients in the specified category; NA = not applicable; SUN = Standardization of Uveitis Nomenclature.

The posterior probability of the baricitinib treatment response rate exceeding 57% was 1.03%, which is less than the 80% probability threshold set for a successful study. Therefore, the primary efficacy endpoint was not met.

5.3. Efficacy discussion

Study JAHW is an open-label, active-controlled Phase 3 study in patients with active JIA-U or chronic ANA-positive uveitis without systemic features despite prior treatment with topical steroid therapy and MTX. Overall, the inclusion and exclusion criteria appear to be justified based on the study's objectives, the need to assess the investigational drugs in a specific patient population, and considerations for participant safety and data integrity.

During the randomization process before Part A, patients with a history of inadequate response to biologic disease-modifying antirheumatic drugs (bDMARD-IR) were deliberately excluded from being randomized to the adalimumab arm, being exclusively assigned to the baricitinib arm. Furthermore, this approach masks that Study JAHW is not a fully randomized study, as only a subset of patients had the opportunity to be assigned to the adalimumab group. It appears that the number of bDMARD-IR patients at baseline who were eligible only for randomization to the baricitinib group were 19 patients from the 30 enrolled patients at screening. The MAH acknowledged that both the original and modified studies did not randomise all patients on a 1:1 ratio in baricitinib and adalimumab, and randomisation was limited only to the MTX-IR patients (n=10). The MAH justified the deviation from a 1:1 randomization ratio based on ethical considerations and challenges in enrolling bDMARD naive patients. The modified study design supports the MAH's conclusion that the study population is reflective of the real-world patient population.

The primary outcome was a two point decrease in SUN criteria or decrease to zero at week 24. Considering the relapsing nature of JIA-U, the cut-off point of 24 weeks is appropriate. It is agreed that decrease of SUN score to zero is clinically important, however it is not clear if the minimal clinically meaningful difference (MCID) for SUN criteria is indeed the defined 2 points decrease stipulated as primary outcome. As this study has not met the primary objective, a more strict definition of the endpoint would not change the conclusions.

During Interim analysis after 24 weeks of treatment, the primary objective was not met. Overall, 8 patients from 24 total in baricitinib arm had met the primary outcome; 7/19 were bDMARD-IR patients. The disproportionality in response to baricitinib between bDMARD-IR and bDMARD naïve patients is noticeable. Despite the fact that numbers are too small to draw a firm conclusion, this still could be an indicator that patients can benefit from baricitinib, especially after failure to bDMARDs. This is supportive for inclusion of data in SmPC section 5.1.

Response rate to adalimumab was 80%, which is comparable to the results of adalimumab's clinical trial (decreased the risk of treatment failure by 75% relative to placebo (HR = 0.25 [95% CI: 0.12, 0.49])).

Long-term administration of concurrent medications such as MTX, csDMARDs, mycophenolate mofetil, topical and systemic steroids, and NSAIDs was permitted throughout the study. Data regarding the distribution of patients using concomitant medication in each study arm indicated that the concomitant medication usage was comparable between bDMARD naïve groups (baricitinib n=5 and adalimumab n=5) and higher in bDMARD-IR group (n=19 all in baricitinib group). At previous round it was unclear how many of the 7 bDMARD-IR responders on baricitinib had concomitant medications. In response to the remaining OC, the MAH has provided analysis on the effects of concomitant use on the final results, demonstrating that concomitant medication use between 7 bDMARD-IR baricitinib responders, has not impacted the response rate. Amendments to section 5.1 were applied accordingly.

6. Clinical Safety aspects

6.1. Methods – analysis of data submitted

The secondary objective(s) for Part A and B of the study were to evaluate the safety of baricitinib in children with JIA U or ANA positive uveitis by

- Adverse events (AEs) including serious adverse events (SAEs).
- Permanent discontinuation of investigational product due to Aes.
- Temporary interruption of investigational product.

Following variables used in this regard:

- Aes
- Treatment-emergent adverse events (TEAEs)
- Serious adverse events (SAEs)
- Adverse events of special interest
- Death
- Treatment interruption and study discontinuation
- Laboratory tests
- Vital Signs
- Growth and development

Descriptive analyses were applied to evaluate safety data.

6.2. Results

The safety population included 24 patients in the baricitinib group and 5 in the adalimumab group. Across both treatment periods, patients in the baricitinib group had 67.96 (SD: 64.34) mean weeks of exposure contributing to a total of 31.26 patient-years of exposure. Patients in the adalimumab group had 43.86 (SD: 34.87) mean weeks of exposure contributing to a total of 4.20 patient-years of exposure.

Across both treatment periods, 20 (83.3%) patients in the baricitinib group were reported with at least 1 TEAE. Most TEAEs were mild or moderate in severity. During Part A of the study, the most commonly reported TEAEs in the baricitinib treatment group were:

- Nausea, n = 4 (16.7%)
- Oropharyngeal pain, n = 4 (16.7%)
- Pyrexia, n = 3 (12.5%)
- Vomiting, n = 3 (12.5%)
- Headache, n = 3 (12.5%), and
- Abdominal pain upper, n = 3 (12.5%).

Table 3 Summary of Adverse Events in Study JAHW

	Study Part A		Study Parts A and B	
	Baricitinib N = 24 n (%)	Adalimumab N = 5 n (%)	Baricitinib N = 24 n (%)	Adalimumab N = 5 n (%)
Patients with ≥1 TEAE	20 (83.3)	4 (80.0)	20 (83.3)	4 (80.0)
TEAEs by severity[a]				
Mild	10 (41.7)	2 (40.0)	8 (33.3)	2 (40.0)
Moderate	7 (29.2)	1 (20.0)	9 (37.5)	1 (20.0)
Severe	3 (12.5)	1 (20.0)	3 (12.5)	1 (20.0)
Death	0	0	0	0
SAEs	2 (8.3)	1 (20.0)	2 (8.3)	1 (20.0)
Aes leading to permanent discontinuation of study treatment	1 (4.2)	0	1 (4.2)	0

Abbreviations: AE = adverse event; N = number of patients; n = number of patients in the specified category; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

A Patients with multiple occurrences of the same event are counted under the highest severity.

Note: Aes are reported based on treatment assignment at baseline. Patient I4V-MC-JAHW-184-30864 who started on adalimumab and is counted under the treatment column of adalimumab, has had 2 mild and non-serious Aes of increased eosinophil count (84 days after switching) and increased platelet count (168 days after switching) after switching from adalimumab to baricitinib at Week 24. Prior to switching to baricitinib, this patient reported 14 TEAEs while on adalimumab.

Note: The highest severity of 2 patients in the baricitinib group (I4V-MC-JAHW-346-31701 and I4V MC JAHW-443-30061) was reported as mild in study Part A and became moderate in study Part B.

Two (8.3%) patients treated with baricitinib were reported with SAEs of Uveitis (worsening of Uveitis) and Intentional overdose with paracetamol. Investigators determined that both SAEs were not related to the study treatment. No deaths occurred during the study. One patient in the baricitinib group permanently discontinued the study drug due to an adverse event of Uveitis (worsening of Uveitis).

Across both treatment periods, the most commonly reported TEAEs in the baricitinib group were:

- COVID-19, n = 5 (20.8%)
- Pyrexia, n = 5 (20.8%), and
- Nausea, n = 5 (20.8%).

There were no serious infections, confirmed opportunistic infections, major adverse cardiovascular events, venous thromboembolic events, arterial thrombotic events, malignancies, or nonmelanoma skin cancer.

There were no clinically meaningful findings or trends in weight, height, or body mass index. No clinically meaningful differences were observed among baricitinib-treated patients between their image-estimated bone age and their chronological age.

6.3. Safety discussion

Safety endpoints were secondary endpoints in JAWH study. No deaths were reported. One patient in baricitinib arm discontinued the treatment due to worsening of the uveitis. Considering that the study did not meet the efficacy endpoint, this is not unexpected. No opportunistic or serious infections were reported, which is reassuring.

With the exception of oropharyngeal pain (n = 4, 16.7%) and pyrexia (n = 3, 12.5%), the most frequently reported TEAEs are already documented in section 4.8 of the current SmPC version. The MAH explained that two of the oropharyngeal and one of the pyrexia cases were associated with upper respiratory tract infection, which is included as an ADR in section 4.8.

7. PRAC advice

Not applicable

8. Changes to the Product Information

As a result of this variation, section 5.1 of the SmPC is being updated to reflect the outcome of study I4VMC-JAHW.

9. Assessment of the responses to the 1st request for supplementary information

9.1. Major objections

NA

9.2. Other concerns

Clinical aspects

Question 1

Only a subset of patients had the opportunity to be assigned to the adalimumab group. It appears that the number of bDMARD-IR patients at baseline who were eligible only for randomization to the baricitinib group were 19 patients from 30 enrolled patients at screening (more than 63%). The MAH should justify the claim that study JAHW indeed is a randomised study. This discussion should address the deliberate exclusion of certain patient subgroups from randomization to specific treatment arms and how this might influence the overall randomization balance.

Summary of the MAH's response

The objective of Study JAHW was to evaluate the efficacy and safety of baricitinib when administered QD to paediatric patients with JIA-U or ANA+U who have had an IR to topical steroids and MTX or bDMARDs. The inclusion of patients with an IR or intolerance to MTX treatment (MTX-IR patients) was driven by physician and patient preference for an alternative oral therapeutic option for paediatric patients with JIA-U who are MTX-IR (Batchelor and Marriott 2015).

Study JAHW was designed to evaluate baricitinib across 2 distinct populations:

1. Patients that had developed an IR to MTX but were naïve to biologics. Adalimumab was included as an active reference and no formal statistical comparisons were planned (or conducted). These patients were randomised 1:1 to baricitinib and adalimumab.

2. Patients that had developed an IR to both MTX and bDMARDs. These patients were directly assigned to baricitinib.

Due to limited approved bDMARDs treatment options for patients with JIA-U/ANA+U, randomisation would have been unethical for MTX/bDMARDs-IR patients, as all patients would have already received adalimumab treatment and determined to have an IR prior to entering Study JAHW. As such, randomisation was limited to the MTX-IR patients. Lilly considers the resultant study population is reflective of the real-world JIA-U/ANA+U patient population.

As originally designed, Study JAHW randomisation scheme was as follows,

- At least 20 MTX-IR (but not bDMARD-IR) patients will be randomised to baricitinib and adalimumab in a 1:1 ratio.
- At least 10 and up to 30 MTX-IR and bDMARD-IR patients will be assigned to baricitinib.

During the conduct of Study JAHW, enrolment eligibility was linked to the open age-cohorts associated with Study JAHV (polyarticular JIA). As a result, the patients enrolled into Study JAHW entered in the following sequential age cohorts:

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

Patients entering Study JAHW that were inadequate responders to both MTX and bDMARDs tended to be older than MTX-IR only (11.6 years versus 6.6 years), as well as, carrying a uveitis diagnosis for a longer period of time (6.4 years versus 2.5-3.0 years).

As a result of the design and associated age-gated entry into the study, the initial patients that entered the study were inadequate responders to both MTX and bDMARDs. This reflects typical JIA-U patient progression (Heiligenhaus et al. 2019). It was not until Study JAHW was able to enrol patients younger than 9 years of age, that more patients with an IR to MTX were identified and able to be recruited into the study.

By 2022, Study JAHW investigators were struggling to recruit MTX-IR patients (even after investigators were able to enrol patients down to 2 years of age) as the use of adalimumab for treating uveitis had become an established part of uveitis treatment guidelines (Angeles-Han et al. 2019; Foeldvari et al. 2023). Therefore, investigators were no longer successful in offering patient or caregivers a clinical research programme with widespread availability and access to adalimumab (with a labelled indication). As a result, Lilly submitted a PIP modification request in October 2022 (EMEA-001220-PIP01-11-M07) to:

1. End further enrolment of patients into Study JAHW and discontinue the study.
2. Modify the PIP to clarify that the number of the so far enrolled patients into Study JAHW would meet the formal enrolment requirements for the study.
3. Provide patients assigned to baricitinib who had completed the primary endpoint as a responder with continued access to baricitinib.

The Paediatric Committee agreed with the proposed changes (EMA Decision P/0063/2023).

As a result of the modified PIP, the protocol for Study JAHW was revised to incorporate the modifications. At the cessation of enrolment efforts, 29 total patients had been recruited. A total of 19 patients with an IR to both MTX and/or bDMARDs were assigned to baricitinib treatment, while the 10 MTX-IR patients recruited were randomised 1:1 to baricitinib (n = 5) and adalimumab (n = 5).

Conclusion

Lilly believes the resultant JAHW study population is reflective of the real-world JIA-U/ANA+U patient population and meets both the original and modified PIP requirements. However, Lilly acknowledges that both the original and modified studies did not randomise all patients on a 1:1 ratio in baricitinib and adalimumab.

Although the original 20 patients target for the MTX-IR population was not reached, the 10 patients that were recruited were appropriately randomised to baricitinib (n = 5) and adalimumab (n = 5). The MTX/bDMARD-IR patients (n = 19) were correctly assigned to receive baricitinib.

Assessment of the MAH's response

From total 29 included patients, 19 were bDMARD-IR and were assigned to baricitinib, 10 were only MTX-IR and were randomised in 1:1 ratio to adalimumab and baricitinib. MAH justifies the deviation from a 1:1 randomization ratio based on ethical considerations and challenges in enrolling bDMARD naive patients. The modified study design supports the MAH's conclusion that the study population is reflective of the real-world patient population and no claims have been included in the suggested text of SmPC referring to JAHW study as a randomised study. Therefore, the issue is considered resolved.

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance

Question 2

The distribution of patients using concomitant medications in each study arm remains undisclosed. To address the potential impact of imbalances in concomitant medication usage on the outcomes, it is requested to present the data pertaining the utilization of concurrent medications within each group, accompanied by a discussion elucidating the implications for the observed results.

Summary of the MAH's response

Table 8.8 in the CSR entitled "Concomitant Medications Safety Population Study I4V-MC-JAHW" comprises a complete listing of concomitant medications taken by study participants in the trial.

Please refer to Appendix 1 for a more granular listing of concomitant medications administered during the Part A of the study which correlates to the primary endpoint.

As specified in Section 7.7 entitled "Concomitant Therapy" in Protocol JAHW, patients were required to report any other medications taken during the conduct of the study and principal investigators were advised to not start any new therapies unless required to treat AEs or for the treatment of an ongoing medical condition. Specific instructions regarding the use and dosing of topical ophthalmic corticosteroids are also provided in the protocol.

To address reviewers concerns regarding potential imbalances in regard to use of concomitant medications, please refer to the Table 1.1 which is a subset of Appendix 1 intended to focus on medications used to treat JIA/JIA-U and broken down by the 3 groups of interest:

- MTX-IR patients receiving baricitinib (n = 5),
- MTX-IR patients receiving adalimumab (n = 5), and
- bDMARD/MTX-IR patients (n = 19).

Some general observations regarding JIA/JIA-U concomitant medications taken by patients during Study JAHW Part A are available below:

- The listed biologics were initiated after a patient became non-responder and after investigational product was discontinued at the ETV. The biologic was reported because it was initiated prior to completion of V801 (thus captured as a concomitant medication since patient was still a trial participant). Because of the disease state and clinical consequences of non-responding patients, initiating alternative treatments immediately after ETV visit is allowed by protocol.
- A balanced number of patients in the MTX-IR groups was treated with corticosteroid eye drops. 5 in baricitinib group and 4 in adalimumab group.
- No patient in the MTX-IR groups received concomitant medications for glaucoma.
- No patient in the MTX-IR groups received adjunct/supplemental JIA-U treatments.
- No patient in the MTX-IR groups received NSAID/COX-2 inhibitors.

In conclusion, patients in the randomised MTX-IR group (baricitinib n = 5, adalimumab n = 5) received a balanced assortment of medications intended to treat or manage JIA-U. Patients in the baricitinib treatment assigned MTX/bDMARD-IR group (n = 19) tended to receive more ophthalmic corticosteroids, glaucoma treatments, and adjunctive/supplemental JIA/JIA-U treatments. These data reflect the longer duration of disease and standard of practice regarding STEP therapy for management of JIA-U (Foeldvari et al. 2023).

It is Lilly's view that the minor differences in utilisation rates of concomitant medications in the randomised MTX-IR groups did not result in an impact on responder rates. Because the patients in the MTX/bDMARD-IR group (n = 19) group were not randomised (that is, were directly assigned to baricitinib), the concomitant medication impact on responder rates is not applicable in terms of any potential imbalance.

Table 1.1. Focused JIA/JIA-U Concomitant Medications Safety Population Treatment Period Part A Study I4V-MC-JAHW

Therapeutic Group	Medication	Bari (MTX-IR Only) (N = 5)	Adalimumab (N = 5)	Bari (MTX-IR and/or bDMARD-IR) (N = 19)	Total (N = 29)
Antifolate Treatment					
	Methotrexate	3	2	5	10
Ophthalmic Treatments					
	Dexamethasone	3	2	5	10
	Prednisolone	1	2	6	9
	Triamcinolone	0	0	2	2
	Steroid Eye Drops (PI Compounded)	0	0	1	1
	Apraclonidine	0	0	1	1
	Brimonidine	0	0	1	1
	Brinzolamide	0	0	1	1
	Dorzolamide/timolol	0	0	1	1
	Timolol/travoprost	0	0	1	1
Biologics - Initiated After Patient Determined to be Non-responder					
	Infliximab	0	0	3	3
	Adalimumab	1	0	1	2
	Golimumab	0	0	1	1
Other Oral Treatments (JIA and JIA-U)					
	Leflunomide	0	0	2	2
	Acetazolamide	0	0	1	1
	Mycophenolic Acid	0	0	3	3
	Cyclopentolate	0	0	2	2
	Ibuprofen	0	0	4	4
	Naproxen	0	0	2	2
	Etoricoxib	0	0	1	1
	Indometacin	0	0	1	1

Assessment of the MAH's response

The applicant has provided requested data regarding concomitant medication use in different groups under barcitinib or adalimumab treatment. It appears that concomitant medication use was related to previous response to bDMARDs. As in bDMARD-IR patients had higher chance of using concomitant medications. This association is reasonable given that these patients have experienced uveitis for a more extended period. Additionally, the adalimumab group demonstrates a concomitant medication usage pattern comparable to the baricitinib bDMARD-naïve group.

The MAH has not conducted an analysis of the effects of concomitant use on the final results. It remains unclear how many of the 7 bDMARD-IR responders on baricitinib had concomitant medications. This lack of clarity introduces the possibility of overestimating the total response rate of 33.3% as asserted by the applicant. As a result, there is a request to either remove the 33.3% response rate from the proposed SmPC text or provide a justified explanation for its inclusion. Issue not resolved.

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance

Question 3

With the exception of oropharyngeal pain (n = 4, 16.7%) and pyrexia (n = 3, 12.5%), all the most frequently reported TEAEs are already documented in section 4.8 of the current SmPC version. The inclusion of these TEAEs in SmPC section 4.8 is requested, or appropriate justification should be provided otherwise.

Summary of the MAH's response

A total of 24 patients from 2 to 18 years of age or younger, were exposed to any dose of baricitinib in the active JIA-U or chronic ANA+U clinical trial programme, representing 9.28 patient years' exposure. During Part A of the study, 4 patients experienced the TEAE of oropharyngeal pain (16.7%) and 3 patients experienced the TEAE of pyrexia (12.5%). Furthermore, of the 4 patients with oropharyngeal pain, in 2 patients the TEAE was associated with an underlying upper respiratory tract infection (tonsillitis and throat infection). Similarly, of the 3 patients with pyrexia, in 1 patient the TEAE was associated with upper respiratory tract infection and bronchitis. Considering the low patient years' of exposure to baricitinib in this study (9.28 patient years of exposure), the sample size, and age of the population, these TEAEs do not represent a clinically significant concern. Additionally, the current SmPC includes text on TEAEs reported in the baricitinib clinical trial programmes (for example, Upper respiratory tract infections).

Based on these factors, Lilly contends that the TEAEs of oropharyngeal pain and pyrexia observed in Study JAHW should not be included in Section 4.8 of the SmPC.

Assessment of the MAH's response

The applicant has provided information regarding oropharyngeal pain and pyrexia cases in JAHW study. It is evident that the majority of these cases were associated with upper respiratory tract infections. This reduces the likelihood of a causal relationship between baricitinib and these adverse events. Consequently, there is no amendment to their inclusion in Section 4.8. Issue resolved.

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance

Question 4

For the purpose of thoroughness and more clarity, it is requested to adjust the wording as follow:

" The efficacy and safety of baricitinib were evaluated in 29 patients from 2 to < 18 years of age with active JIA-associated uveitis or chronic anterior antibody positive uveitis. ~~Patients were stratified into two cohorts, the m~~Methotrexate inadequate responders (MTX IR~~;) cohort (~~n = 10) were assigned to baricitinib (n = 5) or adalimumab (n = 5)~~;~~, and the~~ biologic disease-modifying antirheumatic drug inadequate responders (bDMARD IR~~;) cohort (~~n = 19) were all ~~. The bDMARD IR cohort was~~ assigned to baricitinib ~~(n = 19)~~. ~~The MTX IR cohort was assigned to baricitinib (n = 5) or adalimumab (n = 5, as a~~

~~reference arm only). Patients received either b~~Baricitinib was dosed 2 mg QD for patients ~~(~~2 to < 9 years old~~)~~, ~~baricitinib~~ and 4 mg QD for those ~~(~~9 to < 18 years old~~)~~, adalimumab dosing was 20 mg (if < 30 kg), or ~~adalimumab~~ 40 mg (if ≥ 30 kg) once every two weeks.

The primary endpoint was proportion of patients with ~~responders to baricitinib (both MTX IR and bDMARD IR) at week 24. Response was defined according to the SUN (standardisation of uveitis nomenclature) criteria as a~~ 2 step decrease in the level of inflammation (anterior chamber cells) according to the SUN (standardisation of uveitis nomenclature) criteria or decrease to zero through week 24, in the eye most severely affected at baseline. Eight (33.3 %) patients were baricitinib responders (7 bDMARD IR and 1 MTX IR), ~~however~~ was not statistically significant. ~~The observed safety data were consistent with the established safety profile in the baricitinib polyarticular JIA population.~~"

Summary of the MAH's response

Lilly agrees to adjust the wording of the SmPC as proposed. An updated SmPC is provided with this regulatory response. The last sentence should be slightly reworded though to improve understanding of the findings: "Eight (33.3 %) patients were baricitinib responders (7 bDMARD IR and 1 MTX IR), ~~however~~ but results were ~~was~~ not statistically significant."

Assessment of the MAH's response

The requested changes have been implemented. However, the adoption of the 33.3% response rate is contingent upon the response to the remaining OC. Issue partially solved.

10. Assessment of the responses to the 2nd request for supplementary information

10.1. Major objections

NA

10.2. Other concerns

Clinical aspects

It remains unclear how many of the 7 bDMARD-IR responders on baricitinib had concomitant medications. This lack of clarity introduces the possibility of overestimating the total response rate of 33.3% as asserted by the applicant. As a result, there is a request to either remove the 33.3% response rate from the proposed SmPC text or justify its inclusion.

Summary of the MAH's response

As discussed in Study I4V-MC-JAHW Protocol (Section 7.7 Concomitant Treatment), patients were required to enter the study with concomitant medications at a steady dose. During Part A, the dosages of concomitant treatment could only be adjusted for safety reasons, with the exception of topical corticosteroid eye drops. Corticosteroid eye drops were to be tapered over time as tolerated by the patients. Detailed information on tapering methodology is provided in the Protocol. If tapering was not tolerated, the number of drops could be adjusted back to the number received at screening.

To further address this question, Table 1.1 provides a summary of concomitant medication use for the 7 responders compared to the 12 non-responders in the study.

Table 1.1. Focused JIA/JIA-U Concomitant Medications bDMARD-IR Baricitinib Population Treatment Period Part A Study I4V-MC-JAHW

Therapeutic Group	Medication	Bari (bDMARD-IR) RESPONDER (N = 7)	Bari (bDMARD-IR) NON-RESPONDER (N = 12)	Total (N = 19)
csDMARDs				
	Methotrexate	0	5	5
	Cyclopentolate	0	2	2
	Leflunomide	0	2	2
	Mycophenolic Acid	0	3	3
Ophthalmic Treatments				
	Apraclonidine*	0	1	1
	Brimonidine*	0	1	1
	Brinzolamide*	0	1	1
	Dexamethasone**	1	4	5
	Dorzolamide/timolol*	0	1	1
	Prednisolone**	0	6	6
	Steroid Eye Drops** (PI Compounded)	0	1	1
	Timolol/travoprost*	0	1	1
	Triamcinolone**	1	1	2
Biologics - Initiated After Patient Determined to be Non-responder[a]				
	Adalimumab	0	1	1
	Golimumab	0	1	1
	Infliximab	0	3	3
Other Oral Treatments (JIA and JIA-U)				
	Acetazolamide	0	1	1
	Etoricoxib	1	0	1
	Ibuprofen	2	2	4
	Indomethacin	0	1	1
	Naproxen	1	1	2

Abbreviations: bari = baricitinib; bDMARD = biologic disease-modifying antirheumatic drug; csDMARD = conventional synthetic disease-modifying antirheumatic drugs; IR = inadequate response; JIA = juvenile idiopathic arthritis; JIA-U = JIA-associated uveitis; N = number of patients in the specified category; PI = principal investigator.

[a] Patients declared to be non-responders at Week 24 (primary endpoint) were discontinued from I4V-MC-JAHW and baricitinib but could start receiving biologics in the second part of the study.

*intraocular pressure lowering agents

**topical corticosteroid eye drops

When comparing the concomitant medications from the bDMARD-IR baricitinib responders (n = 7) with the ones from the non-responders (n = 12), data in Table 1.1 show that the use of concomitant medications among the 7 responders was minimal and that non-responding patients tended to utilize

them at a greater extent.

Given the distribution of concomitant medicine intake between responders and non-responders, Lilly contends that this is unlikely to have any relevant impact on the total response rate of 33.3% and therefore to keep the proposed sentence “Eight (33.3 %) patients were baricitinib responders (7 bDMARD-IR and 1 MTX-IR), but results were not statistically significant” in the summary of product characteristics.

Assessment of the MAH’s response

Applicant has provided requested data regarding concomitant medication use in 7 bDMARD-IR baricitinib responders. As compared to bDMARD-IR baricitinib non-responders (n=12) the concomitant use was considerably lower in this group it can be concluded that the concomitant use has not impacted the response rate. The current suggested SmpC text is accepted. Issue solved.

Conclusion

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

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