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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Olumiant

baricitinib

Procedure no: EMEA/H/C/004085/P46/012.1

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]**
☐	Submission	09/11/2022	09/11/2022	☐
☐	Procedure start	28/11/2022	28/11/2022	☐
☐	CHMP Rapporteur Assessment Report	03/01/2023	24/12/2022	☐
☐	CHMP members comments	16/01/2023	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	19/01/2023	n/a	☐
☒	CHMP adoption of conclusions	26/01/2023	26/01/2023	☐

[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

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1. Introduction

On 2 March 2022, the MAH submitted a completed paediatric study for Olumiant, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended**.**

A Clinical Overview document has also been provided.

2. Scientific discussion

2.1. Information on the development program

The Applicant has submitted the clinical study report (CSR) of completed study I4V-MC-JAGA, which is a multi-center, open-label expanded access treatment program to provide baricitinib to patients with auto-inflammatory interferonopathies expected to benefit from JAK inhibition. The MAH stated that study I4V-MC-JAGA *'Treatment of Conditions Expected to Benefit from JAK 1/2 Inhibition: CANDLE, CANDLE-Related Conditions, SAVI, and Severe Juvenile Dermatomyositis'* is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

Baricitinib was provided as oral tablets of 1 mg, 2 mg or 4 mg. Tablets were not to be split for the purpose of dose adjustment without documented approval from the sponsor for each individual case. For patients who were not able to swallow intact tablets, tablets were to be added to a small amount of water, mixed until well dispersed, and administered to the patient immediately.

2.3. Clinical aspects

2.3.1. Introduction

Baricitinib is an orally administered selective JAK1 and JAK inhibitor that acts by blocking STAT1 phosphorylation downstream of JAK1 and JAK2 activation by interferon and upstream of interferon regulation gene (IRG) transcription. It has been approved for Rheumatoid Arthritis (RA) and Atopic Dermatitis (AD) in adults. In 2011, the MAH started an expanded treatment program in response to a clinical request to provide baricitinib to patients with CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature). During the course of the program the patient population was extended to other patient groups with auto-inflammatory interferonopathies. As auto-inflammatory interferonopathies are characterised by overexpression of the type I IRG signature, the use of baricitinib can be justified in these populations.

The submitted study **I4V-MC-JAGA** *'Treatment of Conditions Expected to Benefit from JAK 1/2 Inhibition: CANDLE, CANDLE-Related Conditions, SAVI, and Severe Juvenile Dermatomyositis'*, describes the results of this treatment programme.

2.3.2. Clinical study

Description

I4V-MC-JAGA is a multi-center, open-label expanded access treatment program to provide baricitinib to patients with auto-inflammatory interferonopathies expected to benefit from JAK inhibition; i.e. CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature), CANDLE-related conditions (CANDLE-RC), SAVI (Stimulator of interferon gene-Associated Vasculopathy with onset during Infancy), Juvenile DermatoMyositis (JDM), and Aicardi-Goutières syndrome (AGS).

Patients as from the age of 6 months with active disease, who inadequately responded to (corticosteroid) treatment, were included.

Methods

Study participants

Eligible patients were females and males who:

- Had a rare auto-inflammatory condition that could benefit from JAK inhibition, i.e. CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature), CANDLE-related conditions (CANDLE-RC), SAVI (Stimulator of interferon gene-Associated Vasculopathy with onset during Infancy), Juvenile Dermatomyositis (JDM), or Aicardi-Goutières syndrome (AGS);
- Were treated with high doses steroids to control disease activity, or failed an adequate course of steroid (this was not required for patients with AGS); and
- Weighed ≥ 8.5 kg and were ≥ 17.5 months of age (or ≥ 6 months in AGS); unless accepted otherwise by the sponsor.

Exclusion criteria were:

- Exposure to live vaccine within 12 weeks prior to entry;
- Cytopenia (except when part of underlying disease); and
- eGFR < 40mL/min/1.73 m2.

Standard medical treatment upon program entry was continued. Immunosuppressive biologicals / monoclonal antibodies were prohibited within 4 half-lives prior to entry and during the program.

CHMP comments

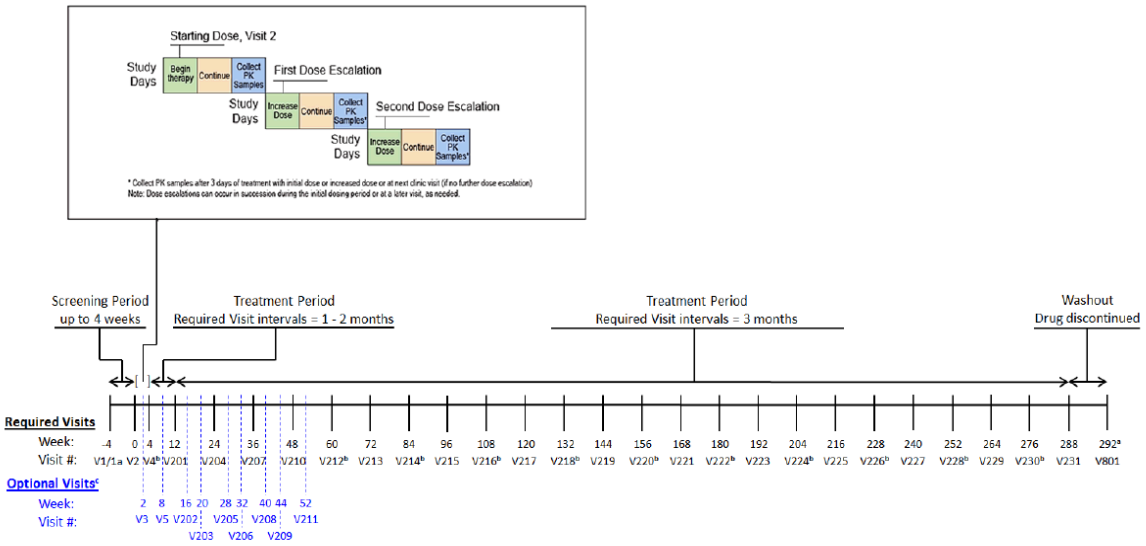
This extended access, 'compassionate use' treatment program (further on referred to as study) was clinically initiated to provide patients with CANDLE (Chronic Atypical Neutrophilic Dermatosis with Eipodystrophy and Elevated temperature) access to baricitinib treatment. It did not intend to provide clinical evidence on the efficacy of baricitinib in these diseases. During the course of the study the patient population was expanded to also include patients with CANDLE-RC, SAVI (Stimulator of interferon gene-Associated Vasculopathy with onset during Infancy), JDM (Juvenile Dermatomyositis), and AGS (Aicardi-Goutières Syndrome). The choice for this population can be justified given the phenotypic overlap between the diseases and their shared pathophysiological mechanisms, supported by early investigational trials supporting the concept of auto-inflammatory interferonopathies as a distinct group of immunological disorders that might benefit from JAK inhibition. Ultimately, patients were considered eligible when they had active disease despite treatment with corticosteroids (except for AGS), a minimum age of 6 months and / or a minimum weight of 8.5 kg. The study population is heterogeneous.

Although the expansion of the patient population can be understood, it resulted in multiple changes in the study protocol, especially with regard to in- and exclusion criteria, the addition of endpoints, and treatment duration. Validity of the disease-specific endpoints and cut-offs used also is unclear. This inherently affects the methodological quality of this study and interpretation of results. Given the purpose of the study, issues with methodological quality will not be pursued.

Study design and treatments

The design of this single-arm study is shown in Figure 1. Patients were hospitalised during the initiation of treatment and eventual subsequent dose escalation. After discharge, visits were planned every 1-2 months in the first 12 weeks after starting baricitinib, and every 3 months afterwards until the end of the treatment period at 288 weeks. Treatment duration was extended after 288 weeks during the course of the program. At the end of the study a wash out period of 4 weeks was planned.

Figure 1 Study design



Abbreviations: PK = pharmacokinetics; V = visit.

[a] V801 (optional) was to occur approximately 28 days after the last dose of study intervention.

[b] These required visits were to be performed at the investigative site or as a telephone visit. If a telephone visit was performed, laboratory samples should have been obtained and tested locally, and a copy of the laboratory report sent to the Principal Investigator.

[c] Optional visits may have been performed at the investigative site or as a telephone visit but were not considered a protocol violation if not performed. If a telephone visit was performed, laboratory samples should have been obtained and tested locally, and a copy of the laboratory report sent to the Principal Investigator.

Source: Figure 4.1 Article 46 Clinical Overview

Dose selection of oral baricitinib for individual patients was based on weight class (< 20 kg, 20-40 kg, and > 40 kg) and renal function (eGFR ≥ 120 ml/min/1.73 m2 or < 120 ml/min/1.73 m2) (Table 1). Diary scores were used to define whether patients responded adequately to the baricitinib dose. In case of an *inadequate response* (defined as an elevated disease activity score in the diary evaluated after 7-10 days on a stable dose) or ongoing clinical disease activity (defined as increased symptoms or elevated markers of inflammation evaluated after 7-10 days on a stable dose), the dose was escalated according to the schedule in Table 1. In case of an *adequate response*, baricitinib dose was continued and tapering of corticosteroids (if applicable) was initiated. Corticosteroids were also tapered when significant adverse events were observed.

Table 1 Dosing and dose escalation

Initial dose						
GFR ≥ 120 ml/min/1.73 m2				GFR 30 - 120 ml/min/1.73 m2		
Weight class	Total daily dose	Min/max dose (mg/kg)	Dosing frequency	Total daily dose	Min/max dose (mg/kg)	Dosing frequency
< 20 kg	6 mg	0.3 / NA	TID	4 mg	0.2 / NA	BID
20-40 kg	6 mg	0.15 / 0.3	BID	4 mg	0.1 / 0.2	BID
> 40 kg	8 mg	NA / 0.2	BID	4 mg	NA / 0.2	BID
First dose escalation						
				(only when GFR ≥ 60 ml/min/1.73 m2)		
< 20 kg	8 mg	0.4 / NA	QID	6 mg	0.3 / NA	TID
20-40 kg	8 mg	0.2 / 0.4	TID	6 mg	0.15 / 0.3	BID
> 40 kg	10 mg	NA / 0.25	BID	6 mg	NA / 0.15	BID
Second dose escalation						
> 40 kg	12 mg	NA / 0.3	BID	-	-	-

CHMP comments

This single arm study was performed with an anticipated duration of 288 weeks, which was prolonged during the course of the study based on emerging safety and efficacy data from other studies in the baricitinib development program. Dose selection of baricitinib was based on weight and kidney function. In case of inadequate response, a maximum of 2 dose escalations could be performed based on a predefined schedule, with a maximum dose of 12 mg daily. Of note, the posology for the adult indications Rheumatoid Arthritis (RA) and Atopic Dermatitis (AD) is 2 mg or 4 mg QD. The maximum total daily dose per mg/kg in the current study thus is considerably higher than to the dose in RA and AD. Although this can be understood given the severity of the diseases in the current study and the unmet treatment need in this patient population, it may induce safety issues and this is especially relevant in this vulnerable patient population. There were no data on tapering or treatment withdrawal.

Given the purpose of the study, these issues will not be pursued.

Objective(s) and endpoints

The primary intent of the study was to expand access to baricitinib to patients with conditions that might benefit from JAK inhibition. It was not intended to test hypotheses.

Efficacy

Several efficacy objectives were defined with corresponding endpoints (Table 2). Overall, the efficacy objective was to determine whether administration of baricitinib was followed by reductions in the patient's diary scores, and, in patients using corticosteroids, dose reduction of corticosteroids.

Table 2 Primary and secondary efficacy objectives and endpoints

Primary objective	**Endpoints**
To determine if the administration of baricitinib to patients with CANDLE, CANDLE-RC, SAVI, JDM, or AGS results in reduction in the patient's **mean daily diary scores**	- CANDLE (-RC): reduction in mean daily score to <0.5 - SAVI: reduction in mean daily score, exclusive of respiratory/breathing symptoms, to <1.0 and a respiratory/breathing symptoms score of <1.0 increase from baseline - JDM: reduction in mean score exclusive of fever and headache symptoms by ≥0.25 - AGS: reduction in mean daily score to <0.5
Secondary objectives	**Endpoints**
a. To determine, in patients receiving steroids at baseline, if administration of baricitinib to patients with CANDLE, CANDLE-related conditions, SAVI, or AGS results in a decrease in the **daily dose of corticosteroids**	Systemic corticosteroids <0.15 mg/kg/day oral prednisone or a decrease of at least 50% of the patient's daily dose at baseline
b. To determine, in patients receiving steroids at baseline, if the administration of baricitinib to patients with severe JDM results in a decrease in the **daily dose of corticosteroids**	Systemic corticosteroids <0.2 mg/kg/day oral prednisone or a decrease of at least 25% of the patient's daily dose at baseline
c. To determine if the administration of baricitinib to patients with severe JDM results in the reduction in the **patient's mean diary score**	JDM: reduction in mean diary score exclusive of fever and headache symptoms to <1.0
d. To determine if the administration of baricitinib to patients with AGS results in a reduction in the **patient's mean diary score** exclusive of neurological symptoms	AGS: reduction in mean diary score exclusive of neurological symptoms to <0.5
Abbreviations: AGS = Aicardi-Goutières Syndrome; CANDLE = chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; JDM = juvenile dermatomyositis; SAVI = STING-associated vasculopathy with onset during infancy; STING = stimulator of interferon genes	

The **dairy scores** were based on a maximum of 6 symptoms, and varied across the disease (see Table 3). Each symptom was scored on a Numeric Rating Scale (predominantly). The range of NRS scores varied, dependent on the symptom assessed. The diary scores had to be completed daily, at approximately the same time of the day, by the patient / caregiver during screening and study period. Daily diary scores since last visit were averaged for each symptom, then summed and finally divided by the number of assessments to calculate the average daily diary score for a patient. For SAVI, *respiratory / breathing* symptoms were excluded for calculation of the primary endpoint as these were not expected to improve from baricitinib. For JDM, *fever and headache* were excluded from calculation of the primary endpoint as these were not (clinically relevant) present. For AGS the secondary endpoint excluded *neurological symptoms* as these were considered static. Changes in diary scores were calculated between the last observation and baseline. A response was defined as < 0.5 (CANDLE, CANDLE-RC) and < 1.0 (SAVI) on the diary daily NRS assessments at last observation compared to baseline; these thresholds were based on previous investigator experience. For AGS a response was defined as < 0.5 on the diary daily NRS assessments; for JDM this threshold was ≥ 0.25.

Table 3 Symptoms assessed in the diary

Disease	Daily diary symptoms assessed
CANDLE and CANDLE-RC	Fever Rash Musculoskeletal pain Fatigue Headache
SAVI	Fever Rash Musculoskeletal pain Fatigue Respiratory/breathing problems Ulcers/ischemic lesions
jDM	Fever Rash Musculoskeletal pain Fatigue Headache Weakness
AGS	Crying Length of interrupted sleep Irritability Skin findings on body, hands, feet, ears Neurological disability

Daily dose of **corticosteroids** was noted in the diaries as well.

Safety

AEs, SAEs, deaths, AESIs, and other safety events were collected. Urine and blood samples were collected and analysed in local laboratories. BK tests were analysed in central laboratories.

Pharmacokinetics

Venous blood samples for measurement of baricitinib concentrations were collected from all patients at start of treatment and at each dose increase, after approximately 72 hours of treatment.

CHMP comments

Although the study was not developed for evaluating hypotheses, several objectives and endpoints were defined. **Efficacy endpoints** were based on diary scores on disease activity and corticosteroid use, specifically defined for each patient group. These endpoints incorporate fundamental problems, most importantly:

1) *Psychometric evaluation* is lacking; there was only anecdotal clinical experience with the diaries for CANDLE(-RC) and SAVI;
2) The diaries comprised symptoms to be scored on an NRS; most often the *NRS scale ranged* from 0-4, but for some symptoms the range appears different. This was not clearly presented by the MAH and a good understanding of the diary scores thus is hampered;
3) Endpoints are compared between 'last observation' and baseline. It is unclear when this 'last observation' was; if it is at the end of the study, which seems most likely, a lot of data is lost;
4) The feasibility of *daily completion of the diary* is questionable, especially given the multiple years of treatment duration.

It is acknowledged that there were neither research guidelines nor validated outcome measures for these rare diseases at initiation of the study, and that the study was not designed to test hypothesis.

Together with the methodological issues listed in this section, however, interpretation of the efficacy data is hardly possible.

Safety and **laboratory endpoints,** and **pharmacokinetics** can be agreed on.

Sample size

No minimum or maximum number of patients to be studied was defined.

CHMP comments

No sample size was calculated, which is understood given the purpose of this study.

Randomisation and blinding (masking)

JAGA was an open label study; there were no blinding measures.

CHMP comments

Being a single arm, open-label treatment program, randomisation and blinding were not applicable. This is accepted, given the purpose of this study.

Statistical Methods

No statistical analysis was initially planned. Average daily diary scores were calculated by summing the average scores of each symptom since last visit, dividing these by the number of assessed symptoms. These scores were then 1) classified as 'met' or 'not met' for each diagnosis separately, and 2) compared to baseline using ANOVA with disease as the factor. The difference of mean daily corticosteroid dose between baseline and last observation was also calculated, and handled analogous to the diary scores (see Table 2).

Data quality measures comprised delivery of instructional material, training sessions and meetings, periodic visits, the use of computer edits to detect errors in data collection, periodic checks, and audits by the MAH. A research physician of the MAH monitored safety data throughout the study and reviewed compliance with GCP. No quality audit assessments were performed.

CHMP comments

No statistical analysis was initially planned. Analyses were limited to calculating differences at 1) the daily diary scores and 2) average daily corticosteroid use, both at last observation compared to baseline. As noted above, the timing of this last observation remained unclear. Dichotomised scores into 'met' or 'not met' as well as absolute differences were analysed using ANOVA with disease as factor. There is no comparison group. Insight in, and information on handling missing data is not provided.

The issues listed here will not be pursued, given the purpose of this study.

Results

Participant flow

Seventy-eight patients entered the study from whom seven were considered screen failures. Ninety-one percent (n = 71) of the patients started treatment: Ten with CANDLE, nine with CANDLE-RC, five with JDM, eight with SAVI, and 39 with AGS. Eventually, 86% completed the treatment period and continued on commercial baricitinib; the remaining 14% (n = 10) discontinued treatment. No patient entered the washout period. Discontinuation was due to AE's (n = 2; 2.8%), death 4.2% (n = 3, all in AGS group), physician decision (n = 3, 4.2%), or withdrawal by patient / parent / guardian (n = 2; 2.8%). Discontinuation weas highest in the CANDLE-RC group (n = 6; 67%).

At time of data cut-off (Sept 10th, 2021), total patient-years of exposure was 251, varying from 11 in JDM, 20 in CANDLE-RC, 27 in SAVI, 64 in CANDLE, and 129 in AGS. Exposure ranged from 2 to 112 months; mean (SD) was 42 (24) months.

CHMP comments

Seventy-one patients entered the study. A substantial number of patients (n = 61; 86%) completed the treatment period and continued with commercial baricitinib. At what time point and under which conditions the switch to commercial baricitinib was made remained however unclear. No patients entered the wash-out period. Compliance was not evaluated.

The issues listed here will not be pursued, given the purpose of this study.

Recruitment

Data gathering starting in October 2011; last patient visit was September 2021. Date of data cut off was 4 October 2021. Participating centres were located in Azerbaijan, Canada, Chile, Germany, Israel, Poland, Spain, Turkey, United Arab Emirates, United Kingdom, and the United States.

Baseline data

Demographic and baseline characteristics by diagnosis are summarized in Table 4.

Table 4 Summary of demographic and baseline characteristics

Parameter	CANDLE(N = 10)	CANDLE-Related (N = 9)	SAVI (N = 8)	JDM (N = 5)	AGS (N = 39)	Total (N = 71)
Female sex, n (%)	3 (30.0)	4 (44.4)	3 (37.5)	3 (60.0)	15 (38.5)	28 (39.4)
Mean age in years ± SD (range)	11.5 ± 6.8 (2.34–19.71)	8.8 ± 7.1 (1.18–24.10)	12.0 ± 7.4 (2.25–23.71)	13.5 ± 5.9 (5.71–20.97)	5.9 ± 5.9 (0.19–21.79)	8.3 ± 6.8 (0.19–24.10)
Age categories, n (%)						
<2 years	0	2 (22.2)	0	0	11 (28.2)	13 (18.3)
2 – <12 years	5 (50.0)	5 (55.6)	4 (50.0)	2 (40.0)	20 (51.3)	36 (50.7)
12 – <18 years	2 (20.0)	1 (11.1)	2 (25.0)	2 (40.0)	6 (15.4)	13 (18.3)
(≥18 years	3 (30.0)	1 (11.1)	2 (25.0)	1 (20.0)	2 (5.1)	9 (12.7)
Race, n (%)						
White race	8 (80.0)	9 (100)	6 (75.0)	4 (80.0)	33 (84.6)	60 (84.5)
Ethnicity, n (%)						
Hispanic or Latino	4 (40.0)	2 (22.2)	1 (12.5)	1 (20.0)	2 (5.1)	10 (14.1)
Not Hispanic orLatino	6 (60.0)	7 (77.8)	6 (75.0)	4 (80.0)	37 (94.9)	60 (84.5)
Weight, kg						
Mean ± SD (range)	30.0 ± 17.8 (11.7–65.5)	27.0 ± 18.1 (9.2–50.3)	29.2 ± 22.7 (11.6–83.6)	58.7 ± 19.9 (28.5–80.3)	20.0 ± 14.9 (4.4–59.8)	26.1 ± 19.3 (4.4–83.6)
Height (cm)						
Mean ± SD (range)	118.8 ± 33.7 (75–164)	112. ± 30.5 (73–167)	121.8 ± 26.1 (84–171)	152.4 ± 24.3 (117–184)	98.5 ± 28.0 (52–150)	109.7 ± 31.8 (52–184)
Corticosteroid use, n	9	9	4	5	6	33
Mean dose in mg (SD)	16.3 (6.8)	9.2 (5.3)	10.4 (3.3)	11.2 (5.9)	16.0 (10.1)	12.9 (7.1)
Mean dose per mg/kg (SD)	0.81 (0.55)	0.44 (0.23)	0.58 (0.46)	0.24 (0.26)	0.78 (0.77)	0.60 (0.51)

Source: Adapted from Table 5.2 Clinical Overview

Concomitant drugs were listed in appendices, but not summarized nor discussed by the MAH. In short, all except one participant received at least 1 concomitant drug during the treatment program. Among the most frequently prescribed (groups of) drugs were corticosteroids, antibiotics, NSAIDs, and paracetamol.

CHMP comments

The study population consisted mainly of white (85%) males (61%), with a mean age of 8.3 (range 0.2 – 24.1) years. The numbers of patients across the diagnosis groups as well as several demographic characteristics were unbalanced across the group: The lowest numbers of patients with the highest mean age were found in the JDM group (n = 5; mean age 13.5 (5.9) years) and the highest numbers with the lowest mean age in the AGS group (n = 39; mean age 5.9 (5.9) years). Mean height and weight differed correspondingly. Mean overall dose of corticosteroids was 13 (7.1) mg/kg/day. As expected, the number of patients using corticosteroids was lowest in the AGS group (6 / 39). An overview of concomitant treatment was provided, but not discussed by the MAH.

The issues listed here will not be pursued, given the purpose of this study.

Numbers analysed

The *efficacy population* consisted of all enrolled patients who received at least one dose of baricitinib (n = 71); the *safety population* consisted of those who additionally did not discontinue the study for the reason 'Lost to Follow-up' at the first postbaseline visit (visit 3; n = 71).

CHMP comments

All patients who entered the treatment program were included in efficacy and safety analyses.

Efficacy results

The **primary endpoint** (a predefined reduction in mean daily diary score) was reached by the majority of patients with CANDLE (90%), SAVI (88%), JDM (60%), CANDLE-RC (56%), but not in patients with AGS (0%). For each diagnosis, mean daily diary scores were statistically significantly reduced compared to baseline (Table 5).

Considering the **secondary endpoints***,* a predefined reduction of corticosteroid daily use at last observation compared to baseline was reached by 83 – 100% of the patients, except for the JDM patients (20%, n = 1) (Table 6). Overall, the mean daily dose decreased from 13 mg (sd 7.1) at baseline to 5.6 mg (sd 8.3) at last observation; this difference was statistically significant for the CANDLE, JDM, and AGS groups (data not shown). The average (sd) dose corticosteroids per mg/kg was also reduced at last observation compared to baseline (0.6 mg/kg (0.5) versus 0.2 mg/kg (0.36)). Four out of the five patients (80%) with JDM reached the pre-defined reduction in the mean daily diary score < 1.0 at the last observation, exclusive of the fever and headache symptoms, and a total of 35 (90%) of the patients with AGS had a reduction in mean diary score <0.5 at the last observation versus baseline when neurological symptoms were excluded.

CHMP comments

The **primary endpoint**, decreased daily diary scores of disease activity, was met in 0% (AGS), 56% (CANDLE-RC), 60% (JDM), 88% (SAVI), and 90% (CANDLE) of the patients. The absolute difference was statistically significant for each diagnosis group. This was supported by the **secondary endpoints** (reduction in mean daily corticosteroid use, and reduced daily diary scores in AGS and JDM).

Although the results may seem supportive for the efficacy of baricitinib in patients with refractory, severe type I interferonopathies, methodological issues as described above severely hamper interpretation of these results and as a consequence no conclusion can be drawn on the efficacy of baricitinib in this population. Even if the data would be regarded as a systematic collection of case-series, it is difficult to draw conclusions to the efficacy findings.

The MAH proposes no adjustments of the SmPC. However, since there is an unmet need for treatment in these children with rare diseases, clinicians may consider off label prescription of baricitinib and available data on the efficacy in this population needs to be reported. The MAH is therefore asked to add to section 5.1 of the SmPC (subheading paediatric population): *'The efficacy of baricitinib up to 12 mg/day has been evaluated in 71 patients with CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature, n=10), CANDLE-related conditions (CANDLE-RC, n=9), SAVI (Stimulator of interferon gene-Associated Vasculopathy with onset during Infancy, n=8), Juvenile DermatoMyositis (JDM, n=5), and Aicardi-Goutières syndrome (AGS, n=39). Total patient-*

years of exposure (PYE) was 251. Due to methodological insufficiencies no definite conclusion could be drawn on the efficacy of baricitinib in these patients. Although safety patterns showed similarities with the adult indications, frequencies of adverse events were generally higher. Three deaths were observed, in the AGS population; it is unclear whether these deaths were related to treatment with baricitinib'. The wording of this addition is agreed.

Table 5 Summary of total daily diary scores

	CANDLE[a] (N = 10)	CANDLE-RC (N = 9)	SAVI[b] (N = 8)	SAVI[c] (N = 8)	JDM[d] (N = 5)	JDM[e] (N = 5)	AGS[a] (N = 39)	AGS[f] (N = 39)
Met the primaryobjective, n (%)	9 (90.0)	5 (55.6)	7 (87.5)	6 (75.0)	3 (60.0)	1 (20.0)	0	35 (89.7)
Mean daily diary scores								
Baseline	1.26	1.13	1.51	1.48	1.76	1.29	1.33	0.40
Last observation	0.12	0.50	0.60	0.63	0.49	0.37	1.17	0.21
Change from baseline								
LSM (SE)	-1.14 (0.14)	-0.63 (0.15)	-0.91 (0.16)	-0.84 (0.16)	-1.27 (0.20)	-192 (0.20)	-0.15 (0.07)	-0.19 (0.07)
p-Value(95% CI)	<0.01 (-1.41, -0.86)	<0.01 (-0.92, -0.34)	<0.01 (-1.21, -0.60)	<0.01 (-1.15, -0.54)	<0.01 (-1.66, -0.88)	<0.01 (-1.31, -0.53)	0.03 (-0.29, -0.01)	<0.01 (-0.33, -0.05)

Abbreviations: AGS = Aicardi-Goutières Syndrome; ANOVA = analysis of variance; CANDLE = chronic atypicalneutrophilic dermatosis with lipodystrophy and elevated temperature; CI = confidence interval; JDM = juvenile dermatomyositis; LSM = least-squares mean; n = number of patients; N = number of patients in the safety population within each disease subpopulation; SAVI = STING-associated vasculopathy with onset during infancy; SE = standard error; STING = stimulator of interferon genes.

[a] Patients using the CANDLE or AGS diaries were considered to have met the primary objective if their diaryscore was <0.5 at the last observation.

[b] Patients using the SAVI diary were considered to have met the primary objective if the mean daily diary score was <1.0 (exclusive of respiratory/breathing symptoms), with a <1.0 increase in respiratory/breathing symptomsfrom baseline at last observation.

[c] Daily diary score for patients using the SAVI diary that included respiratory and/breathing symptoms.

[d] Patients using the JDM diary were considered to have met the primary objective if their diary score (exclusive offever and headache symptoms) was reduced by ≥0.25 at the last observation.

[e] Daily diary score for patients using the JDM diary that included fever and headache symptoms.

[f] Daily diary score for patients using the AGS diary that excluded neurological symptoms. These AGS daily diaryscore data represent a secondary endpoint of the JAGA study.

Note: The mean diary score was calculated as the mean of all symptom scores, and p-values, LSM, SE, and 95% CIare from the ANOVA model, with disease diagnosis as the factor: Change = group for each indication.

Note: The p-values are presented for exploratory purposes only, as there was no comparator arm included.

Source: Table 5.3 Clinical Overview

Table 6 Summary of systemic corticosteroid reduction in patients with steroid use at baseline

	CANDLE (N = 10)	CANDLE-Related (N = 9)	SAVI (N = 8)	JDM (N = 5)	AGS (N = 39)
Patients with steroid use atbaseline	9	9	4	5	6
Patients with baseline steroiddose of ≥0.15 mg/kg or ≥0.2 mg/kg, n (%)[a]	9 (100.0)	9 (100.0)	4 (100.0)	1 (20.0)	5 (83.3)
Met the secondary objective atlast observation, n (%)	8 (88.9)	1 (11.1)	4 (100.0)	3 (60.0)	5 (83.3)
Number of patients with ≥100%reduction, n (%)	4 (44.4)	0	1 (25.0)	0	4 (66.7)
Mean corticosteroid dose at lastobservation (mg)	3.1 (4.2)	8.7 (7.9)	2.7 (2.2)	4.2 (3.0)	8.4 (16.1)
Change from baseline (mg)					
LSM (SE)	-13.24 (3.68)	-0.47 (3.90)	-7.69 (5.52)	-7.00 (4.93)	-7.62 (4.50)
p-Value (95% CI)	<0.01 (-20.79, -5.70)	0.91 (-8.47, 7.54)	--b	0.17 (-17.12, 3.12)	0.10 (-16.86, 1.63)

Abbreviations: -- = analysis not done; AGS = Aicardi-Goutières Syndrome; ANOVA = analysis of variance; CANDLE = chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; CI = confidence interval; JDM = juvenile dermatomyositis; LSM = least-squares mean; n = number of patients; N =number of patients in the safety population within each disease subpopulation; SAVI = STING-associated vasculopathy with onset during infancy; SE = standard error; STING = stimulator of interferon genes.

[a] Steroid dose of ≥0.15 mg/kg for CANDLE, CANDLE-related, SAVI, AGS. Steroid dose of ≥0.2 mg/kg for JDM.[b] p-Values and 95% CI only calculated if ≥5 patients were included in the sample.

Note: p-Values, LSM, SE, and 95% CI are from the ANOVA model, with disease diagnosis as the factor: Change =group for each indication.

Note: The p-values are presented for exploratory purposes only, as there was no comparator arm included.

Source: Table 5.4 Clinical Overview.

Safety results

Mean (range) duration of **exposure** was 42 (2 – 112) months, with a total of 251 patient years of exposure (PYE). PYE was 64 for CANDLE, 20 for CANDLE-RC, 11 for JDM, 27 for SAVI, and 129 for AGS.

Mean baricitinib dose at last observation was 6.8 mg in the total population (ranging from 6.0 mg in CANDLE-RC to 8.4 mg in JDM). Treatment compliance was assessed but not reported.

An overview of frequencies of TEAE's, death, SAE, and discontinuations due to AE's is presented in Table 7.

Table 7 Overview of Adverse Events

Incidence, n (%)	CANDLE (N = 10) n (%)	CANDLE-RC (N = 9) n (%)	SAVI (N = 8) n (%)	JDM (N = 5) n (%)	AGS (N = 39) n (%)	Total (N = 71)
TEAE[a]	10 (100.0)	9 (100.0)	8 (100.0)	5 (100.0)	39 (100.0)	71 (100.0)
Death	0	0	0	0	3 (7.7)	3 (4.2)
SAE	8 (80.0)	5 (55.6)	6 (75.0)	0	26 (66.7)	45 (63.4)
Discontinuation due to an AE	1 (10.0)	1 (11.1)	0	0	3 (7.7)	5 (7.0)

Source: Table 5.4.3 Clinical Overview

Most common **TEAE's** by SOCs were infections and infestations (90%, n = 64), investigations (79%, n = 56), gastro-intestinal disorders (70%, n = 50), respiratory, thoracic and mediastinal disorders (61%, n = 43), injury, poisoning and procedural complications (52%, n = 37), skin and subcutaneous tissue disorders (52%, n = 37), and blood and lymphatic system disorders (51%, n = 36). Most common TEAE's by PT were upper respiratory tract infection (70%, n = 50), BK polyomavirus test positive (48%, n = 34), cough (38%, n = 27), vomiting (34%, n = 24), BK virus infection (30%, n = 21), diarrhoea (28%, n = 20), pyrexia (25%, n = 18), urinary tract infection (24%, n = 17), anaemia (20%, n = 14), and pneumonia (20%, n = 14). Most TEAE's were moderate to severe.

A total of 21 *bone fractures* were reported in the total population; hand, foot, rib fractures (3 each), and rib, spinal compression, spinal, thoracic vertebral, tibia, ankle, lumbar vertebral, comminuted, facial bone, femur, radius, and ulna fractures (1 each). Another 13 bone-related TEAE's were observed, 9 in CANDLE(-RC), 3 in SAVI, and 1 in AGS, most concerned bone density problems.

Serious Adverse Events (SAE's) were reported in 63% (n = 45) of the participants; most of these resolved without discontinuation of baricitinib. Most frequent SAE's were BK virus infection (16%, n = 11), pneumonia (10%, n = 7), urinary tract infection and seizure (both in 7%, n = 5), and dehydration and pyrexia (both in 5.6%, n = 4). Of note, 7/11 BK infections were observed in patients with CANDLE; no other clear distribution across the diagnosis groups were observed (Table 8).

Table 8 Serious Adverse Events

Preferred Term	CANDLE (N = 10) n (%)	CANDLE-RC (N = 9) n (%)	SAVI (N = 8) n (%)	JDM (N = 5) n (%)	AGS (N = 39) n (%)	Total (N = 71) n (%)
Patients with ≥1 SAE	8 (80.0)	5 (55.6)	6 (75.0)	0	26 (66.7)	45 (63.4)
BK virus infection	7 (70.0)	1 (11.1)	3 (37.5)	0	0	11 (15.5)
Pneumonia	1 (10.0)	1 (11.1)	2 (25.0)	0	3 (7.7)	7 (9.9)
Urinary tract infection	1 (10.0)	1 (11.1)	0	0	3 (7.7)	5 (7.0)
Seizure	0	0	0	0	5 (12.8)	5 (7.0)
Dehydration	2 (20.0)	0	0	0	2 (5.1)	4 (5.6)
Pyrexia	1 (10.0)	0	0	0	3 (7.7)	4 (5.6)
Anaemia	1 (10.0)	0	0	0	2 (5.1)	3 (4.2)
Encephalopathy	0	0	0	0	3 (7.7)	3 (4.2)
Neutropenia	1 (10.0)	0	1 (12.5)	0	1 (2.6)	3 (4.2)
Muscle spasticity	0	0	0	0	3 (7.7)	3 (4.2)
Wound infection	0	0	3 (37.5)	0	0	3 (4.2)
Mental status changes	0	0	0	0	3 (7.7)	3 (4.2)
CANDLE syndrome	2 (20.0)	0	0	0	0	2 (2.8)
Cellulitis	0	0	2 (25.0)	0	0	2 (2.8)
Clostridium difficile infection	1 (10.0)	1 (11.1)	0	0	0	2 (2.8)
Device related infection	2 (20.0)	0	0	0	0	2 (2.8)
Dyskinesia	0	0	0	0	2 (5.1)	2 (2.8)
Gastroenteritis	0	0	0	0	2 (5.1)	2 (2.8)
Herpes zoster	2 (20.0)	0	0	0	0	2 (2.8)
Hospitalisation	0	2 (22.2)	0	0	0	2 (2.8)
Hyponatraemia	0	0	0	0	2 (5.1)	2 (2.8)
Hypoxia	0	0	1 (12.5)		1 (2.6)	2 (2.8)
Influenza	2 (20.0)	0	0	0	0	2 (2.8)
Joint dislocation	0	0	0	0	2 (5.1)	2 (2.8)
Lethargy	0	0	0	0	2 (5.1)	2 (2.8)
Mental disorder	0	0	0	0	2 (5.1)	2 (2.8)
Nephrolithiasis	1 (10.0)	1 (11.1)	0	0	0	2 (2.8)
Pneumonia aspiration	0	0	0	0	2 (5.1)	2 (2.8)
Pulmonary hypertension	1 (10.0)	0	0	0	1 (2.6)	2 (2.8)
Respiratory syncytialvirus infection	0	1 (11.1)	0	0	1 (2.6)	2 (2.8)
Staring	0	0	0	0	2 (5.1)	2 (2.8)
Thrombocytopenia	1 (10.0)	1 (11.1)	0	0	0	2 (2.8)
Urosepsis	0	1 (11.1)	0	0	1 (2.6)	2 (2.8)
Vasculitis	0	0	2 (25.0)	0	0	2 (2.8)
Viral infection	1 (10.0)	0	0	0	1 (2.6)	2 (2.8)
Vomiting	0	0	0	0	2 (5.1)	2 (2.8)

Source: Table 5.6 Clinical Overview

Treatment discontinuation due to AE's occurred in 7% (n = 5). TEAE's resulting in **temporary dose interruptions** were observed in three patients (with AGS); i.e. due to thrombocytosis, dysphagia, and catheter site infection. A total of 31 TEAE's resulted in **dose reductions**, primarily due to BK viruria (n = 8) / viremia (n = 6), anemia, thrombocytosis (both n = 3), and hepatic enzyme increase (n = 2).

A total of three **deaths** occurred during treatment with baricitinib, all in the AGS group. Causes of death were bilateral pulmonary embolus, Aspergillus fumigatus infection and multi-organ failure, and cardiopulmonary arrest. Another 2 deaths occurred 4 and 19 months after discontinuation of baricitinib, due to respiratory tract infection and ILD (CANDLE), and underlying liver- and kidney disease (CANDLE-RC).

Predefined **AESI's** were infections, myelosuppressive events, thrombocytosis, and hepatic laboratory elevations. TEAE's in the SOC Infections and infestations were observed in 90% (n = 64) of the subjects, with lowest numbers in the JDM group (60%) versus the other diagnosis groups (88-100%). Infections occurring in over 10% of the subjects were upper respiratory tract infections (71%), BK virus infection (30%), urinary tract infection (24%), pneumonia (20%), gastroenteritis (18%), ear infection and sinusitis (both 17%), viral gastroenteritis and viral infection (both 14%), influenza and streptococcal pharyngitis (both 13%), and cellulitis and viral upper respiratory tract infection (both 11%). Herpes zoster, herpes simplex, and oral herpes were reported as well, at lower frequencies (4.2%, 2.8%, and 1.4% respectively). There was no clear distribution across diagnosis groups, although CANDLE (100%) and AGS patients (95%) generally reported the largest proportions of patients with infections. At least one TEAE of myelosuppressive events and thrombocytosis were reported by a total of 58% (n = 41) of the participants (Table 9). Thrombocytosis and neutropenia were most often reported (36 and 24%), predominantly in SAVI and AGS.

Table 9 AESI's based on laboratory data reported during treatment

System Organ Class Preferred Term	CANDLE (N = 10) n (%)	CANDLE-Related (N = 9) n (%)	SAVI (N = 8) n (%)	JDM (N = 5) n (%)	AGS (N = 39) n (%)	Total (N = 71) n (%)
Patients with ≥1 treatment-emergent AESI	10 (20.0)	9 (44.4)	7 (87.5)	2 (40.0)	26 (66.7)	41 (57.7)
Thrombocytosis	0	1 (12.5)	4 (50.0)	1 (20.0)	19 (48.7)	25 (35.7)
Neutropenia	1 (10.0)	1 (11.1)	3 (37.5)	1 (20.0)	10 (28.6)	16 (23.9)
Lymphopenia	1 (16.7)	2 (25.0)	1 (14.3)	0	2 (5.1)	6 (9.4)
Thrombocytopenia	1 (11.1)	1 (11.1)	0	0	1 (2.6)	3 (4.3)
Leukopenia	0	1 (11.1)	0	0	1 (2.6)	2 (2.8)
Anemia	0	0	0	0	1 (2.6)	1 (1.4)

Abbreviations: AESI = adverse event of special interest; AGS = Aicardi-Goutières Syndrome; CANDLE = chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; JDM = juvenile dermatomyositis; n = number of patients; N = number of patients in the safety population within each disease subpopulation; SAVI = STING-associated vasculopathy with onset during infancy; STING = stimulator of interferon genes; TEAE =treatment-emergent adverse event.

Note: All percentages are based on the safety population. Adverse events were coded using the Medical Dictionaryfor Regulatory Activities, version 24.0.

Source: Table 5.8 Clin Overview

Hepatic laboratory elevations were reported in six (ALT ≥ 3xULN) and one (ALT ≥ 5xULN) patients. For AST these numbers were 2 and 1.

Among the **other findings**, increased CK (14%, n = 10) and hypercholesterolaemia (5.6%; n = 4)) were reported. Evaluation of vital signs and physical findings showed an increased Z-score for height with stable weight Z-scores in the CANDLE population. For the other groups no clear effects on growth and weight were observed.

CHMP comment

The safety of baricitinib in auto-inflammatory interferonopathies was evaluated over a total of 251 PY of exposure. Data on treatment compliance was not reported. Each subject (100%) reported at least 1 **TEAE**; most common were (≥ 60%) SOCs infections and infestations, investigations, gastro-intestinal disorders, and respiratory, thoracic and mediastinal disorders. In PT's, upper respiratory tract infections (70%) were most frequent; other common (≥ 20%) TEAE's in decreasing order of frequency were BK polyomavirus test positive / infection, cough, vomiting, diarrhoea, pyrexia, urinary tract infection, anaemia, and pneumonia. TEAE's were generally moderate to severe.

An remarkable finding concerns the high incidence of bone-related TEAE's (n = 13) and bone fractures (21 in total). Although the underlying disease, disease activity, as well as chronic corticosteroid use without a doubt contribute to this, non-clinical data obtained in the developmental program of baricitinib also suggest potential bone issues due to baricitinib use: Degeneration of sternal growth plate was observed in dogs, and an increased incidence of limb bone and rib abnormalities were seen in rats. To be able to judge whether this bone-related TEAE's concern a new safety signal requiring integration in section 4.8 of the SmPC, the MAH was asked to provide case descriptions of the patients with bone-related TEAE's and fractures, to discuss the potential relation with baricitinib use and dosing/exposure to baricitinib, and to discuss whether this finding requires adjustment of the SmPC. The point of view of the MAH that the data did not suggest a causal relation between (the dosing of) Olumiant and the occurrence of fractures could be agreed. Patients with fractures on average had higher doses of corticosteroids (>5 mg daily) than patients without fractures, and all patients with fractures had risk factors for fractures, more often than patients without fractures. There was no difference in average dose of baricitinib between patients with or without fractures. Fractures tended to cluster in patients, the onset of first fracture clustered around 6-24 months, follow-up fractures were spread over time. This pattern is in agreement with individual patients who have a high propensity for fractures. Consequently, it seems likely that corticosteroid use and other risk factors contributed to the occurrence of fractures in this population.

A total of 63% of the subjects reported **SAE's**, most often infectious in origin (BK virus infection, pneumonia, urinary tract infection); seizure, dehydration, and pyrexia also occurred in > 5% of the subjects. Treatment discontinuation due to AE's was, however, low (7%). Three **deaths** were reported, due to pulmonary embolism, opportunistic infection (Aspergillus), and cardiopulmonary arrest. Predefined **AESI's** were infections, myelosuppressive events and thrombocytosis, and hepatic laboratory elevations. Infections mainly concerned upper respiratory tract infections, BK virus infection, urinary tract infection, pneumonia, and gastroenteritis. Herpes infections were reported as well (up to 4.2%). Thrombocytosis was found in 36% and neutropenia in 24% of the subjects. ALT and AST elevations (≥ 5xULN) were found in 1 subject each. Given the current JAKi-referral (EMEA/H/A-20/1517), the AESI's MACE, malignancies, and VTE's require additional evaluation; these were however not separately discussed by the MAH. Thirteen (18.3%) subjects had treatment-emergent cardiac disorders; among which 1 with cardio-respiratory arrest in AGS. Malignancies were not observed in the current study. One fatal pulmonary embolism was reported, there were no DVT's.

Comparison of safety across the diagnosis groups is hampered by the small samples. Most remarkable findings were that the largest proportions of patients with infections were found in the CANDLE (100%) and AGS groups (95%), and that 7/11 of the BK infections were reported in the CANDLE group. All deaths occurred in the AGS group, which comprised the largest number of subjects but also likely the most severely affected population. Thrombocytosis and neutropenia were most often reported in the SAVI and AGS groups. Further, there was a high occurrence of bone-related TEAE's.

Comparison of the current safety data with the safety data from the adult indications (RA and AD) generally showed **higher frequencies of (TE)AE' and SAE's** in the current study compared to RA and AD. Major factors contributing to this are most likely the differences in underlying diseases, concomitant medication, the age of the study population, and the relatively higher dose of baricitinib mg/kg/day in the current study (see also above) compared to adults. No data on the relation between exposure and safety outcome was presented. **BK virus infections** were common in the current study but were only sporadically reported in patients with RA. This can be explained by the fact that BK typically is a pediatric infection, and that laboratory assessments for this virus were routinely performed during the study and not in the RA studies.

Pharmacokinetics

A total of 1817 baricitinib concentrations were obtained from the 71 subjects in the programme and used for the PopPK analysis. Total daily baricitinib dose varied from 0.1 mg to 17 mg daily in patients between 0.2 months and 29 years. According to the MAH, the PopPK model adequately described baricitinib disposition characteristics. Body weight and renal function were identified as relevant covariates of the volume and clearance terms respectively.

CHMP comments

PopPK analyses has been performed based on the current data. Details on the model development and results are described in a standalone PopPK report, which has not been provided by the MAH. It was considered that, at this stage, the data will not provide new information.

2.3.3. Discussion on clinical aspects

For this Article 46 procedure, the MAH submitted the final report for study **I4V-MC-JAGA,** a multi-centre, open-label expanded access treatment program to provide baricitinib to patients with auto-inflammatory interferonopathies expected to benefit from JAK inhibition; CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature), CANDLE-related conditions (CANDLE-RC), SAVI (Stimulator of interferon gene-Associated Vasculopathy with onset during Infancy), Juvenile DermatoMyositis (JDM), and Aicardi-Goutières syndrome (AGS).

Design of the study

The program consisted of a single-arm study, initiated by clinicians to provide patients with CANDLE access to baricitinib treatment. During the course of the study patients with CANDLE-RC, SAVI, Juvenile Dermatomyositis, and Aicardi-Goutières syndrome were included as well. This can be understood given the phenotypic overlap between these diseases and their (shared) pathophysiological mechanisms. Patients were at least 6 months old /weighed at least 8.5 kg, and had active disease despite (corticosteroid) treatment. They were treated with baricitinib orally in a dose based on weight

and kidney function. In case of inadequate response, two dose escalations could be performed with a maximum total daily dose of 6 mg BID, which is considerably higher than the posology for the adult indications Rheumatoid Arthritis (RA) and Atopic Dermatitis (AD) (2 mg or 4 mg QD). Study duration was anticipated to be 288 weeks and visits were planned every 1-3 months.

The study was not developed for evaluating hypotheses and sample size was not calculated. Primary efficacy endpoint was the reduction in diary scores of disease symptoms at an NRS scale at last observation compared to baseline, with a predefined cut-off for each patient group. Psychometric properties of the diary scores are not available and scoring of symptoms was not adequately described. Among the secondary endpoints was the reduction in corticosteroid use at last observation compared to baseline, again with a predefined cut-off for each patient group. For each of the endpoints, it remained unclear at what moment in time data were extracted for comparison with baseline. Safety and laboratory data were gathered during the entire study.

Data from the 71 patients were used for evaluation; 39 with AGS, 10 with CANDLE, 9 with CANDLE-RC, 8 with SAVI, and 5 with JDM. Average age was 8.3 (range 0.2 – 24.1) years. Demographic data were unbalanced between the groups.

Efficacy

The *primary endpoint* was met in 0% (AGS), 56% (CANDLE-RC), 60% (JDM), 88% (SAVI), and 90% (CANDLE) of the patients. Daily corticosteroid use was also reduced. Although these results might seem supportive for the efficacy of baricitinib in patients with auto-inflammatory interferonopathies, the poor methodological design and the lack of discussion of some essential aspects (e.g. NRS scoring, concomitant medication, last observation time points, etc.; see above) severely hampers interpretation of the results, including the lack of a control group. As a consequence no conclusion can be drawn on the efficacy of baricitinib in these patients.

The MAH proposes no adjustments of the SmPC. However, since there is an unmet need for treatment in these children with rare diseases, clinicians may consider off-label prescription of baricitinib and they should be informed that there are available data. The MAH was therefore asked to add to section 5.1 of the SmPC (subheading paediatric population): *'The efficacy of baricitinib has been evaluated in patients with CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature), CANDLE-related conditions (CANDLE-RC), SAVI (Stimulator of interferon gene-Associated Vasculopathy with onset during Infancy), Juvenile DermatoMyositis (JDM), and Aicardi-Goutières syndrome (AGS). Due to methodological limitations no definite conclusion could be drawn on the use of baricitinib in these patients.'*

Safety

Safety was studied during 251 PYE, without data on treatment compliance. Each subject (100%) reported at least 1 **TEAE**; most common (≥ 60%) were SOCs infections and infestations, investigations, gastro-intestinal disorders, and respiratory, thoracic and mediastinal disorders. Upper respiratory tract infections (70%) were most frequent TEAE's by PT. AE's were generally moderate to severe. There was a high rate of bone-related TEAE's (n = 13) and bone fractures (21 in total). Although the underlying disease, disease activity, as well as chronic corticosteroid use contribute to this, non-clinical data obtained in the developmental program of baricitinib also suggests possible bone issues in baricitinib use. Degeneration of sternal growth plate was observed in dogs, and an increased incidence of limb bone and rib abnormalities were seen in rats. To be able to judge whether this may concern a new safety signal requiring integration in section 4.8 of the SmPC, the MAH was asked to provide case descriptions of the patients with bone-related TEAE's and fractures, to discuss the potential relation with baricitinib and its dosing, and to discuss whether this finding requires adjustment of the SmPC. The findings of the study do not suggest that there is a causal association

between fractures and baricitinib or its dosing, and therefore, no changes in Section 4.8 of the SmPC are proposed. Fractures tended to cluster in patients, the onset of first fracture clustered around 6-24 months, follow-up fractures were spread over time. This pattern is in agreement with individual patients who have a high propensity for fractures. Patients with fractures on average had higher doses of corticosteroids (>5 mg daily) than patients without fractures, and that patients with fractures more often also had pre-existing conditions that are risk factors for fractures. There was no difference in average dose of baricitinib between patients with or without fractures.

A total of 63% of the subjects reported **SAE's**, most often infectious in origin (BK virus infection, pneumonia, urinary tract infection); seizure, dehydration, and pyrexia also occurred in > 5% of the subjects. Treatment discontinuation due to AE's was low (7%). Three **deaths** were reported due to pulmonary embolism, opportunistic infection (Aspergillus), and cardiopulmonary arrest. The deaths all occurred in the AGS group, the group with the largest number of patients, and are most likely related to the (severity of the) underlying disease. An association with baricitinib use cannot completely be ruled out, but as this cannot be unravelled and given the purpose of the current study, the issue will not be pursued. It remained unclear whether these deaths could be attributed to the underlying disease. As the AGS patients were the most severely affected, **AESI's** studied were infections, myelosuppressive events and thrombocytosis, and hepatic laboratory elevations. Most common were upper respiratory tract infections, BK virus infection, urinary tract infection, pneumonia, gastroenteritis, ear infection, sinusitis, viral gastroenteritis, and viral infections. Herpes infections were reported as well (in up to 4.2% of the participants). Myelosuppressive events (neutropenia in 24%) and thrombocytosis (36%) were common. Hepatic laboratory elevations were observed. Given the current JAKi-referral (EMEA/H/A-20/1517), AESI's MACE, malignancies, and VTE's require additional evaluation but these were not specifically discussed by the MAH. Thirteen (18.3%) subjects had treatment-emergent cardiac disorders; among which 1 with cardio-respiratory arrest in AGS. Malignancies were not observed in the current study. One fatal pulmonary embolism was reported, there were no DVT's.

Comparison of safety across the diagnosis groups is hampered by the small samples. The largest proportions of patients with infections were found in the CANDLE (100%) and AGS groups (95%), and 7/11 of the BK infections were reported in the CANDLE group. All deaths occurred in the AGS group. Thrombocytosis and neutropenia were most often reported in the SAVI and AGS groups. These differences may be explained by the underlying diseases.

Indirect comparison with data in adults with RA and AD, showed generally **higher frequencies of (TE)AE' and SAE's** in the current study, probably due to underlying diseases, disease severity, concomitant medication, age of the study population, and the relatively higher dose of baricitinib mg/kg/day in the current study (see also above) compared to adults. Unfortunately, no data on the relation between exposure and safety outcome was presented.

3. CHMP overall conclusion and recommendation

Study **I4V-MC-JAGA** provided data on the efficacy and safety data of baricitinib treatment in patients with auto-inflammatory interferonopathies (CANDLE, CANDLE-RC, SAVI, JDM, and AGS). No conclusions can be drawn on the efficacy due to poor methodological quality. There were no apparent new safety signals, except for bone adverse events that had occurred at a high frequency, which required further discussion by the MAH. There is insufficient evidence for a causal association of baricitinib with treatment-emergent adverse events of bone fracture in the sample of paediatric patients with CANDLE and several CANDLE-related conditions, and no change in the SmPC is warranted.

The following adjustments of the SmPC for section 5.1 are acceptable.

'*The efficacy of baricitinib up to 12 mg/day has been evaluated in 71 patients with CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature, n=10), CANDLE-related conditions (CANDLE-RC, n=9), SAVI (Stimulator of interferon gene-Associated Vasculopathy with onset during Infancy, n=8), Juvenile DermatoMyositis (JDM, n=5), and Aicardi-Goutières syndrome (AGS, n=39). Total patient-years of exposure (PYE) was 251. Due to methodological insufficiencies no definite conclusion could be drawn on the efficacy of baricitinib in these patients. Although safety patterns showed similarities with the adult indications, frequencies of adverse events were generally higher. Three deaths were observed, in the AGS population; it is unclear whether these deaths were related to treatment with baricitinib.*'

☒ **Fulfilled:**

No further action required, however further data are expected in the context of a variation prior any conclusion on product information amendments is made. The MAH should commit to submit this variation application no later than 60 days after the receipt of these conclusions.

4. Request for supplementary information (RSI)

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. The MAH proposes no adjustments of the SmPC. This is not agreed because since there is an unmet need for treatment in these children with rare diseases, clinicians may consider off-label prescription of baricitinib and they should be informed that there are available data. The MAH is therefore asked to add to section 5.1 of the SmPC (subheading paediatric population): *'The efficacy of baricitinib up to 12 mg/day has been evaluated in 71 patients with CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature, n=10), CANDLE-related conditions (CANDLE-RC, n=9), SAVI (Stimulator of interferon gene-Associated Vasculopathy with onset during Infancy, n=8), Juvenile DermatoMyositis (JDM, n=5), and Aicardi-Goutières syndrome (AGS, n=39). Total patient-years of exposure (PYE) was 251. Due to methodological insufficiencies no definite conclusion could be drawn on the efficacy of baricitinib in these patients. Although safety patterns showed similarities with the adult indications, frequencies of adverse events were generally higher. Three deaths were observed, in the AGS population; it is unclear whether these deaths were related to treatment with baricitinib'.* The definite wording of this addition is pending the response of the MAH to OC2 below **(OC)**.
2. There was a high rate of bone-related TEAE's bone fractures. To be able to judge whether this may concern a new safety signal requiring integration in section 4.8 of the SmPC, the MAH is asked 1) to provide case descriptions of the patients with bone-related TEAE's and fractures,2) to discuss the potential relation with baricitinib and its dosing, and 3) to discuss whether this finding requires adjustment of the SmPC (**OC**).

MAH responses to Request for supplementary information

1. Eli Lilly and Company (Lilly) accepts the request to adjust the summary of product characteristics (SmPC) within Section 5.1. However, Lilly proposes to make the following changes to the SmPC language that are marked in bold underline for additions and in strikethrough for deletions.

   "The efficacy of baricitinib up to 12 mg/day has been evaluated in 71 patients with CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature, n=10), CANDLE-related conditions (CANDLE-RC, n=9), SAVI (Stimulator of interferon gene-Associated Vasculopathy with onset during Infancy, n=8), Juvenile DermatoMyositis (JDM, n=5), and Aicardi-Goutières syndrome (AGS, n=39). Total patient-years of exposure (PYE) was 251. Due to methodological ~~insufficiencies~~ ***limitations,*** *no definite conclusion could be drawn on the efficacy of baricitinib in these patients,* ***but the results suggested that baricitinib is***

   associated with improvement in daily diary score (including assessment of fever, rash, pain, fatigue, headache, and additional disease specific symptoms as applicable) as well as reductions in corticosteroid dose. *Although safety patterns showed similarities with the adult indications, frequencies of adverse events were generally higher. Three deaths were observed, in the AGS population; it is unclear whether these deaths were related to treatment with baricitinib".*

   Lilly proposes to add limited information on the efficacy of baricitinib in patients with CANDLE, stimulator of interferon gene-associated vasculopathy with onset during infancy (SAVI), uvenile dermatomyositis (JDM), and Aicardi-Goutières syndrome (AGS) for a more balanced description. Lilly also proposes to change the term "insufficiencies" to "limitations".

   Lilly proposes to make this change as the word "insufficiencies" suggests that the methods used to investigate the efficacy were not effective. The primary measure of effectiveness for this programme was a decrease in the appropriate diary scores. The results of the diary scores for each disease type were as follows:

   - 9 (90.0%) patients with CANDLE met the primary objective
   - 5 (55.6%) patients with CANDLE-related conditions met the primary objective
   - 7 (87.5%) patients with SAVI met the primary objective
   - 3 (60.0%) patients with JDM met the primary objective, and
   - no patients with AGS met the primary objective.

   The majority of patients in the total study population who had corticosteroid use at baseline had a reduction in corticosteroid dose of at least 50% (CANDLE, CANDLE-related conditions, SAVI, and AGS) or 25% (JDM) from baseline at endpoint. These results reflect clinically meaningful reductions in corticosteroid use following treatment with baricitinib.

   CHMP comments

   The MAH proposal to change the proposed SmPC text: *'Due to methodological ~~insufficiencies~~ limitations,…'* is acceptable.

   The MAH proposal to add limited efficacy information is however not acceptable. The proposed text should be deleted: *~~'but the results suggested that baricitinib is associated with improvement in daily diary score … as well as reductions in corticosteroid dose.'~~* The reason is that the limitations of the study, as outlined in the AR above, do not allow for efficacy claims to be made in the SmPC.

The issue is **not solved**. It could be solved with adaptations of the text for the SmPC.

2. Lilly assessed the patients who experienced TEAEs of fracture when exposed to baricitinibduring Study JAGA. The findings of the assessment do not suggest that there is a causal association between fractures and baricitinib or its dosing, and therefore, no changes in Section 4.8 of the SmPC are proposed.

   Treatment-Emergent Adverse Events of Fracture: Case Descriptions

   The Injury, poisoning and procedural complications system organ class (SOC) and the Musculoskeletal and connective tissue disorders SOC were screened for TEAEs of fractures.

   Nine patients who received baricitinib in Study JAGA reported a total of 20 fractures. Case descriptions for the 9 patients are provided in Table 4.1. Of the 20 fractures, 2 were reported as serious adverse events (SAEs). Patient narratives for this study are provided in Appendix 1. Patients were reviewed to identify circumstances of the fracture and potential fracture risk factors reported in literature, including but not limited to pre-existing osteoporosis, previous fracture, and body mass index (BMI) <20 kg/m2 (De Laet et al. 2005; McCloskey et al. 2012).

   Medications reported to affect bone metabolism or mineralisation such as systemic corticosteroids prior to enrolment, proton-pump inhibitors (PPIs), and selective serotonin re-uptake inhibitors (SSRIs) (Richards et al. 2007, Samrao et al. 2013, Zhou et al. 2016) were also included in the analysis, as shown in Table 4.1.

   All patients who reported fracture had at least 1 pre-existing or concurrent risk factor for fracture, defined as a relevant comorbidity or had received treatment with a relevant medication in the 2 years prior to enrolment. Of the 9 patients (described in Table 4.1):

   - 6 patients (66.7%) had more than 1 fracture, and most fractures were upper extremities fractures (n=5) or lower extremities fractures (n=7)
   - 7 (77.8%) patients received prior systemic corticosteroids (mean dose = 16.7 mg or 0.88 mg/kg) for more than 3 consecutive months in the year prior to enrolment or corticosteroids for more than 1 year in the 2 years prior to enrolment. Five (55.6%) patients received PPIs during the study period
   - 8 (88.9%) patients had a pre-existing comorbidity or reported adverse events (AEs) that increase risk for fracture, such as
     - o osteoporosis: n=3
     - o osteopenia: n=2
     - o short stature: n=2
     - o feeding disorder: n=1
     - o neuromuscular scoliosis: n=1
     - o malnutrition: n=1, and
     - o quadriplegia: n=1, and
   - 3 (33.3%) patients had a low BMI (⩽20 kg/m2).

   There were 2 SAEs of fracture reported by patients during Study JAGA.

- Patient with AGS: medical history includes neuromuscular scoliosis, malnutrition, quadriplegia, and elevated thyroid-stimulating hormone (TSH). No systemic corticosteroid, PPI, or SSRI was used as prior or concomitant medication. The patient reported 2 fractures. The 1st fracture (closed fracture of left nasal bone) occurred on Day 333 of the study. The 2nd fracture (comminuted fracture of the left femur), reported as an SAE, was reported 104 weeks after initiating baricitinib treatment (Day 732). The patient was being transferred from a wheelchair when his left leg got caught in the railing. The family members heard a snap, and swelling on the left thigh was observed.
- Patient with AGS: medical history includes short stature. The patient reported a SAE of radius fracture (closed fracture of the head of right radius) meeting hospitalisation criteria on Day 299. The patient fell down the stairs due to a miss-step and was admitted in the emergency department. Computerised tomogram of the right elbow and X-ray showed evident fracture. On Day 300, the patient underwent a surgical repair, which was reported as an AE of open reduction of fracture (open reduction/internal fixation of olecranon fracture).

Table 4.1 Overview of Baricitinib -Treated Patients with Fractures

.1 **Overview of Baricitinib-Treated Patients with Fractures**

Patient Information (Gender)/ Age (years) at Study Entry)/ BMI (kg/m²) at Study Entry)	Disease	Preferred Term (Reported Term) (Time to Onset, Days) from Study Start/BARI Start)	Systemic Corticosteroids Prior to Enrolment	Steroid Dose at Time of First Fracture	Proton-Pump Inhibitors	Selective Serotonin Reuptake Inhibitors	Pre-Existing Comorbidity that Increases Risk for Fracture (Days prior to Treatment Start)
F/ 7.5/ 20.6	SAVI	Hand fracture (Finger fracture) (300) Stress fracture (Stress fractures - injury) (962) Lumbar vertebral fracture (Fracture L3 spine) (1139) Foot fracture (Fracture-right foot, first proximal phalanx) (1226)	10 mg (0.38 mg/kg) steroid use for 13 weeks prior to study enrolment	2.5 mg or 0.1 mg/kg	Lansoprazole since September 2009	No	Osteoporosis (-1736), Growth retardation (-1420)
M/ 7.4/ 17.4	CANDLE syndrome	Thoracic vertebral fracture (T6 vertebral fracture) (651) Spinal compression fracture (Vertebrae	30 mg (1.62 mg/kg) steroid use for 360 weeks prior to study enrolment	10 mg or 0.52 mg/kg	Omeprazole 01 Oct 2010 to 25 Nov 2018	No	Severe growth retardation (-1881), Osteoporosis (-1304)

Patient Information (Gender)/ Age (years) at Study Entry)/ BMI (kg/m^2) at Study Entry)	Disease	Preferred Term (Reported Term) (Time to Onset, Days) from Study Start/BARI Start)	Systemic Corticosteroids Prior to Enrolment	Steroid Dose at Time of First Fracture	Proton-Pump Inhibitors	Selective Serotonin Reuptake Inhibitors	Pre-Existing Comorbidity that Increases Risk for Fracture (Days prior to Treatment Start)
		compression Fraction (T4/T5)) (1293) Hand fracture (Finger fracture) (1442) Foot fracture (Fracture (right foot)) (2740) Rib fracture (Fracture (rib fracture)) (2872) Tibia fracture (Arthroscopy: knee: left for avulsion fracture of tibial spine) (3193)					
F/ 13.5/ 29.0	CANDLE syndrome	Hand Fracture (Fracture – Finger) (507) Ankle Fracture (Fracture – R Ankle) (507)	15 mg (0.30 mg/kg) steroid use for 373 weeks prior to study enrolment	7.5 mg or 0.15 mg/kg	No	No	No
M/	CANDLE	Spinal Fracture	15 mg (1.34 mg/kg)	14 mg or	Lansoprazole since	No	Short stature

Patient Information (Gender)/ Age (years) at Study Entry)/ BMI (kg/m^2) at Study Entry)	Disease	Preferred Term (Reported Term) (Time to Onset, Days) from Study Start/BARI Start)	Systemic Corticosteroids Prior to Enrolment	Steroid Dose at Time of First Fracture	Proton-Pump Inhibitors	Selective Serotonin Reuptake Inhibitors	Pre-Existing Comorbidity that Increases Risk for Fracture (Days prior to Treatment Start)
3.5/ 20.0	syndrome	(Vertebral Fracture) (204)	steroid use for 171 weeks prior to study enrolment	0.97 mg/kg	October 2012		(1531) and Feeding disorder (1531)
F/ 17.3/ 15.0	SAVI	Stress Fracture (Fracture L Foot (Stress)) (298)	No	N/A	No	No	Osteopenia (-254), Growth retardation (-254), Epiphysis delayed fusion (-254), and Myositis (-224)
F/ 5.7/ 20.7	JDM	Stress Fracture (Tibial Stress Fracture) (343) Foot Fracture (Right Foot Navicular Fracture) (886)	21 mg (0.70 mg/Kg) steroid use for 23 weeks prior to study enrolment	21 mg or 0.7 mg/Kg	Lansoprazole since April 2017	No	Osteoporosis (-22)
M/ 21.8/ 20.2	AGS	Facial bones fracture (Closed Fracture of Left Nasal Bone)	No	N/A	No	No	Neuromuscular scoliosis (-3023), Malnutrition

Patient Information (Gender)/ Age (years) at Study Entry)/ BMI (kg/m^2) at Study Entry)	Disease	Preferred Term (Reported Term) (Time to Onset, Days) from Study Start/BARI Start)	Systemic Corticosteroids Prior to Enrolment	Steroid Dose at Time of First Fracture	Proton-Pump Inhibitors	Selective Serotonin Reuptake Inhibitors	Pre-Existing Comorbidity that Increases Risk for Fracture (Days prior to Treatment Start)
		(333) Comminuted fracture (Comminuted Fracture of Left Femur) (732)					(-1232), Quadriplegia (-411), Elevated TSH (-357)
M/ 2.9/ 21.9	AGS	Femur Fracture (Fracture of Left Femur) (1445)	24 mg (1.76 mg/kg) steroid use for 21 weeks prior to study enrolment	NR	Lansoprazole since 04 Feb 2020	No	Developmental delay (-828) and Osteopenia (-518)
F/ 16.2/ 27.1	AGS	Ulna Fracture (Closed Fracture of Olecranon Process) (299), and Radius Fracture (Closed Fracture of Head of Right Radius) (299)	2 mg (0.03 mg/kg) steroid use for 134 weeks prior to study enrolment	2 mg or 0.03 mg/kg	No	No	Short stature (-1667)

Abbreviations: AGS = Aicardi-Goutières Syndrome; BARI = baricitinib; BMI = body mass index; CANDLE = chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; F = female; JDM = juvenile dermatomyositis; M = Male; N/A = not applicable; NR = none reported; SAVI = stimulator of interferon genes (STING)-associated vasculopathy with onset during infancy; TSH = thyroid-stimulating hormone.

Source: Appendix 1

Treatment-Emergent Adverse Events of Fracture and Baricitinib Dosing Relationship

From a total of 71 patients in Study JAGA, 9 (12.7%) patients reported TEAEs of fracture during the study. Time to onset of patient's first reported fracture ranged from 204 to 1445 days since initiation of baricitinib treatment. Patients who reported fractures received a maximum baricitinib total daily dose, before their first reported fracture, with an average dose of 7.0 mg (or 0.27 mg/kg). Patients who did not report a fracture received a similar maximum baricitinib total daily dose in the entire study, with an average dose of 7.37 mg (or 0.33 mg/kg). The use of corticosteroids has been associated with bone-related changes that increase the risk of fracture (Weldon 2009). Seven out of 9 (77.8%) patients who reported a TEAE of fracture were receiving systemic corticosteroids prior to study enrolment. The average total daily dose of corticosteroids during the study at the time of the first fracture was 9.50 mg, and the median was 8.75 mg. Data showing the cumulative doses of corticosteroids are not available. Of the 62 patients who did not report a fracture, only 23 (37.1%) patients were receiving systemic corticosteroids throughout the study. The average total daily dose of corticosteroids at the end of the study for those patients was 7.48 mg, and the median was 5.0 mg. These data suggest that the occurrence of fractures in this population is related to the amount and duration of systemic corticosteroid treatment before the fracture.

Eight out of 9 (88.9%) patients who reported a TEAE of fracture had a pre-existing comorbidity that increased the risk for fractures.

- Patient diagnosed with osteoporosis 1736 days before baricitinib treatment started. Patient was also diagnosed with growth retardation 1420 days before baricitinib treatment started.
- Patient diagnosed with osteoporosis 1304 days before baricitinib treatment started. Patient was also diagnosed with severe growth retardation 1881 days before baricitinib treatment started.
- Patient diagnosed with short stature 1531 days before baricitinib treatment started. Patient was also diagnosed with feeding disorder 1531 days before baricitinib treatment started.
- Patient diagnosed with osteopenia, growth retardation, and epiphysis 254 days before baricitinib treatment started. Patient was also diagnosed with myositis 224 days before baricitinib treatment started.
- Patient diagnosed with osteoporosis 22 days before baricitinib treatment started.
- Patient diagnosed with neuromuscular scoliosis, malnutrition, quadriplegia, and elevated TSH, 3023, 1232, 411, and 357 days before baricitinib treatment started, respectively.
- Patient diagnosed with developmental delay 828 days before baricitinib treatment started. Patient was also diagnosed with osteopenia 518 days before baricitinib treatment started.
- Patient diagnosed with short stature 1667 days before baricitinib treatment started.

Five out of 9 (55.6%) patients with fractures received PPIs throughout the study. The PPIs included omeprazole and lansoprazole. Literature reports that PPIs can lead to a decrease in bone mineral density and an increase in fracture risk (Lau and Ahmed 2012).

Data from a subset of 18 patients with an age range at study entry of 1.2 to 24.1 years with the severe autoinflammatory disorders of CANDLE and SAVI who were treated for a mean duration of 3.0 years with baricitinib have been published (Sanchez et al. 2018). Prior to baricitinib treatment, the patients' growth and physical maturation were delayed, with the mean bone age being lower by 3.49 ± 3.99 years relative to their chronological age. Of the patients receiving

baricitinib, 13 patients with growth potential improved their mean height Z-scores from – 4.03 ± 2.64 to –3.19 ± 2.33, with catch-up growth observed in 9 patients who were able to taper their corticosteroids to doses <0.16 mg/kg/day. Bone mineral density increased, with a mean Z-score change from –3.25 ± 1.97 to –2.20 ± 1.36 (p<.005; Sanchez et al. 2018).

The data and information provided show that all 9 patients with TEAE of fractures had at least 1 pre-existing or concurrent risk factor and the occurrence of fractures in the study population was associated with long-term treatment with high-dose corticosteroids. Higher baricitinib dose and longer exposure to baricitinib were not associated with fractures. The incidence of fracture did not increase with prolonged exposure, which would be expected if baricitinib impacted bone metabolism. Therefore, data do not suggest a causal association between fractures and baricitinib or its dosing.

Adjustment to the SmPC

Based on the evaluation of the available data, there is insufficient evidence for a causal association of baricitinib with TEAEs of fracture, and no change in Section 4.8 of the SmPC is warranted.

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CHMP comments

The MAH concludes that the findings of the assessment do not suggest that there is a causal association between fractures and baricitinib or its dosing, and therefore, no changes in Section 4.8 of the SmPC are proposed.

The claim that the data do not suggest a causal relation between, the dosing of, Olumiant and the occurrence of fractures can only partly be verified. So far, it can be agreed that patients with fractures on average had higher doses of corticosteroids (>5 mg daily) than patients without fractures, and that patients with fractures also had other risk factors for fractures.

The time of onset ranged between 204 and 1445 days since treatment start, the MAH claims that longer exposure to baricitinib was not associated with fracture risk, but this cannot be verified with the presented data (a survival plot or similar was not provided).

Most (7/9) of patient with fractures had received corticosteroids before study start, it is not clear how many of these patients received corticosteroids during the study; of the 62 patients without fractures, 37% were receiving corticosteroids. The average daily dose of corticosteroids at time of first fracture was in median 8.75 mg in patients with fractures, as compared to an average daily dose of median 5 mg at the end of study, for patients without fractures. It is acknowledged that providing cumulative dosages is not informative if follow-up time differs between patient groups.

Most (8/9) patients had pre-existing conditions that increase the risk for fractures, which may include sequels of CANDLE and SAVI (Sanchez et al. 2018; Gedik et al. 2021). However, it is not clear how the occurrences of pre-existing conditions differ from the patients without fractures. Of note, the relevance of 'short stature' as a risk factor is questionable: The underlying cause of a short stature (e.g. corticosteroid use, severe illness, etc.) is more likely a risk factor for fractures than 'short stature' itself.

The issue is **not solved**.

The MAH is kindly asked to provide data that can be used to verify whether: longer exposure to baricitinib was not associated with fracture risk; patients with fractures were more frequent corticosteroid users during the study than patients without fractures; that the specified pre-existing conditions were more frequent in the patient group without fractures (**OC**). Given the limitations of the sample size, it is not asked for a more sophisticated case-referent design with matched sampling of follow-up times.

5. 2nd Request for supplementary information (RSI)

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. The MAH proposal to add limited efficacy information is however not acceptable. The proposed text should be deleted: ~~*'but the results suggested that baricitinib is associated with improvement in daily diary score … as well as reductions in corticosteroid dose.'*~~ The reason is that the limitations of the study, as outlined in the AR above, do not allow for efficacy claims to be made in the SmPC.
2. The MAH is asked to provide data that can be used to verify whether:

a. longer exposure to baricitinib was not associated with fracture risk,

b. patients with fractures were more frequent corticosteroid users during the study than patients without fractures, and

c. specified pre-existing conditions were more frequent in the patients without fractures compared to the patients with fractures.

Accordingly, the MAH should provide an updated discussion on the potential relation of baricitinib and its dosing with the occurrence of fractures, and to discuss whether the findings requires adjustment of the SmPC.

MAH responses to the 2nd Request for supplementary information

1. The MAH proposal to add limited efficacy information is however not acceptable. The proposed text should be deleted: ~~*'but the results suggested that baricitinib is associated with improvement in daily diary score … as well as reductions in corticosteroid dose.'*~~ The reason is that the limitations of the study, as outlined in the AR above, do not allow for efficacy claims to be made in the SmPC.

Applicant's response:

The MAH accepts the request to delete the text regarding limited efficacy information from the Summary of Product Characteristics (SmPC).

CHMP comments

The text regarding efficacy results was deleted from the proposal for section 5.1, as was asked. The issue is **solved**.

2. The MAH is asked to provide data that can be used to verify whether:

a. longer exposure to baricitinib was not associated with fracture risk,

b. patients with fractures were more frequent corticosteroid users during the study than patients without fractures, and

c. specified pre-existing conditions were more frequent in the patients without fractures compared to the patients with fractures.

Accordingly, the MAH should provide an updated discussion on the potential relation of baricitinib and its dosing with the occurrence of fractures, and to discuss whether the findings requires adjustment of the SmPC.

Applicant's response:

Baricitinib Exposure and Fracture Risk

Longer exposure to baricitinib was not associated with fracture risk as shown in Table 4.1. The results indicate that fractures occurred at variable time after treatment onset, with no increased incidence with longer exposure.

Table 4.1. Occurrence of Fractures Relative to Baricitinib Exposure Intervals

	Patients with Fracture (Based on First Fracture) n (% of Patients Exposed during Period)	Number of Fractures	Total Patients Exposed during period
Total number of patients	9	9	71
Number of fractures	9	20	
Exposure in subset of months			
0-6	0	0	71
6-12	5 (7.4%)	5	68
12-18	1 (1.6%)	1	63
18-24	2 (3.2%)	3	62
24-30	0	1	59
30-36	0	2	54
36-42	0	1	39
42-48	0	2	27
48-54	1 (4.5%)	2	22
54-60	0	0	15
>60[a]	0	3	11

Abbreviation: n = number of patients in specified group.
Source: Appendix 1.
[a] This exposure subset is from Month 60 up to Month 112 indicating there were 3 fractures within 52 months.

Frequency of Corticosteroid Use

Patients with fractures were more frequent corticosteroid users during the study than patients without fractures as shown in Table 4.2. A total of 52 patients received corticosteroids throughout the study. Of these, 7 patients (13.5%) experienced a bone fracture. Of the19 patients not treated with corticosteroids, 2 patients (10.5%) experienced a bone fracture. At the time of the first fracture and at the end of the study, the average daily dose for patients receiving corticosteroids was higher for patients who experienced a bone fracture at 9.5 mg and 9.8 mg (0.41 mg/kg and 0.36 mg/kg), respectively, compared to 7.48 mg (0.27 mg/kg) at the end of the study for patients who did not experience a bone fracture. All 7 patients who were receiving corticosteroids and experienced a bone fracture were on corticosteroid treatment prior to starting treatment with baricitinib.

Table 4.2. Subset of Patients who Received Corticosteroids

Subset of Patients who Received Corticosteroids

Reported Fracture	Week Number of First Recorded Steroid Dose	Week Number of Last Recorded Steroid Dose	Daily Dose of Steroid at Last Recorded Steroid Dose, mg (mg/kg)
Yes	-360	456	5.0 (0.13)
No	-12	110	3.5 (0.11)
No	-3	407	3.0 (0.07)
No	-1	75	0.3 (0.00)
No	-82	107	3.0 (0.04)
No	-166	240	2.5 (0.12)
Yes	-171	116	13.0 (0.82)
No	-701	378	4.3 (0.17)
No	-861	51	2.5 (0.05)
No	83	89	2.5 (0.05)
No	-1	34	27.0 (0.50)
No	-24	292	12.0 (0.72)
No	-3	NR	7.5 (0.15)
Yes	-373	226	4.5 (0.08)
No	-1	8	5.0 (0.17)
No	-10	30	3.0 (0.17)
No	-7	122	7.0 (0.38)
No	-130	82	6.3 (0.35)
No	-64	8	5.0 (0.47)
No	-22	113	2.5 (0.04)
Yes	-23	145	1.0 (0.02)
No	-31	117	4.0 (0.04)
No	-120	73	4.5 (0.07)
No	-71	29	9.0 (0.13)
Yes	-295	216	7.5 (0.22)
No	200	204	5.0 (0.15)
No	-399	133	3.8 (0.11)
No	-9	74	2.0 (0.08)
No	-5	35	5.0 (0.35)
Yes	-21	48	12.5 (0.89)
No	-304	193	40.3 (1.79)
No	6	38	37.5 (1.91)
No	3	3	37.5 (2.95)
No	95	95	17.5 (0.97)
No	179	200	15.0 (1.09)
No	134	179	12.5 (0.53)
No	8	164	12.5 (0.56)
No	27	166	725.0 (30.85)
No	-12	153	30.0 (0.67)
No	54	54	50.0 (0.79)
No	9	94	23.0 (2.02)

Reported Fracture	Week Number of First Recorded Steroid Dose	Week Number of Last Recorded Steroid Dose	Daily Dose of Steroid at Last Recorded Steroid Dose, mg (mg/kg)
No	74	74	12.5 (1.44)
No	62	62	15.6 (0.91)
No	125	125	50.0 (2.79)
No	58	145	15.0 (0.99)
No	62	96	0.3 (0.02)
Yes	-134	125	25.0 (0.38)
No	0	9	0.2 (0.01)
No	4	126	37.5 (2.48)
No	115	115	62.5 (2.92)
No	30	69	60.0 (0.89)
No	-205	27	10.0 (0.17)

ıt recorded.

Pre-existing Conditions for Patients with and without Bone Fracture

Twelve of 62 (19.4%) patients who did not experience a bone fracture compared to 7 of 9 (77.8%) patients who experienced a bone fracture had a pre-existing comorbidity or reported adverse events that increased risk of fracture (Table 4.3). For patients who did not experience a bone fracture, pre-existing conditions of neuromuscular scoliosis or quadriplegia were not reported, which occurred for some patients who experienced a bone fracture. Overall, specified pre-existing conditions were more frequent in patients with fractures (77.8%) compared to patients without fractures (19.4%).

Note: As recommended in the request, short stature was not considered as a pre-existing risk for bone fractures.

Table 4.3. Pre-existing Conditions Reported in Patients with and without a Bone Fracture

Pre-existing Conditions	Number of Patients with a Reported Bone Fracture (n = 9)	Number of Patients without Reported Bone Fracture (n = 62)
Osteoporosis	3	2
Osteopenia	2	5
Feeding disorder	1	3
Malnutrition	1	3
Neuromuscular scoliosis	1	0
Quadriplegia	1	0

Abbreviation: n = total number of patients in subgroup.

Treatment-Emergent Adverse Events of Fracture and Baricitinib Dosing Relationship

Patients who reported fractures received an average maximum baricitinib total daily dose, before their first reported fracture, of 7.0 mg (or 0.27 mg/kg). Patients who did not report a fracture received a similar average maximum baricitinib total daily dose in the entire study of 7.4 mg (or 0.33 mg/kg).

As presented in Section 4.2.1.2, the data for corticosteroid use suggest that the occurrence of fractures in this population is related to the amount and duration of systemic corticosteroid treatment before the fracture.

Conclusion

Exposure to baricitinib was not associated with an increased risk of bone fracture. The results demonstrated that fractures occurred at variable time after treatment onset, with no increased incidence with longer exposure. Patients who experienced a bone fracture were more frequent corticosteroid users and received higher daily doses than those without a bone fracture. Preexisting conditions that can increase the risk of fracture were also more common in patients who experienced a bone fracture. Higher baricitinib dose and longer exposure to baricitinib were not associated with fractures. Overall, the data presented in this response support that there is no relationship between baricitinib use and bone fractures.

Adjustment to the SmPC

Based on the evaluation of the available data, there is insufficient evidence for a causal association of baricitinib with treatment-emergent adverse events of bone fracture, and no change in the SmPC is warranted.

CHMP comments

The MAH concludes that there is insufficient evidence for a causal association of baricitinib with treatment-emergent adverse events of bone fracture in the sample of paediatric patients with CANDLE and several CANDLE-related conditions, and no change in the SmPC is warranted. This is agreed.

Fractures tended to cluster in patients, the onset of first fracture clustered around 6-24 months, follow-up fractures were spread over time. This pattern is in agreement with individual patients who have a high propensity for fractures. Patients with fractures on average had higher doses of corticosteroids (>5 mg daily) than patients without fractures, and that patients with fractures more often also had pre-existing conditions that are risk factors for fractures. There was no difference in average dose of baricitinib between patients with or without fractures.

Consequently, it seems likely that corticosteroid use and other risk factors contributed to the occurrence of fractures in this population, there is no evidence pointing to an influence of baricitinib in causing fractures. No changes to the SmPC are necessary.

The issue is **solved**.