CLINICAL PRIORITIES ADVISORY GROUP
10 May 2021

Agenda Item No	2.1
National Programme	Blood and Infection
Clinical Reference Group	Immunology and Allergy
URN	1930

Title
Baricitinib for use in monogenic interferonopathies (adults and children 2 years and over)

Actions Requested	1. Support the adoption of the policy proposition.
	2. Recommend its approval as an IYSD.

Proposition
Routinely commissioned This is a clinical commissioning policy proposition that recommends the routine commissioning of baricitinib as a treatment option for adults and children aged 2 years and over with monogenic interferonopathies. Children 2 years and over should also meet all of the criteria set out in the NHS England Commissioning Medicines for Children in Specialised Services policy (NHS England 2017). Monogenic interferonopathies can lead to poor quality of life, the requirement for frequent hospital admissions and can eventually be fatal. There is currently no available effective treatment option; treatment is currently based on symptom management, of which the current first line treatment is corticosteroids.

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Engagement Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

In patients with monogenic interferonopathies, what is the clinical effectiveness and safety of baricitinib?

Outcome	Evidence statement
Clinical effectiveness	
Critical outcomes	
Change from baseline in quality of life scores **Certainty of evidence:** very low	Improvement in quality of life is a marker of successful treatment. People with monogenic interferonopathies often have poor quality of life so this outcome is relevant to them. One uncontrolled prospective cohort study (Sanchez et al. 2018) provided evidence relating to quality of life for a median duration of treatment of 2.8 years. In this study, median quality of life measurements (Pediatric Quality of Life Inventory [PedsQL]) improved numerically from baseline in 18 people with chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperatures syndrome (CANDLE), stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI) and other interferonopathies who were taking baricitinib. However, the improvements were not statistically significant (p value not reported, results reported graphically). (**VERY LOW**).

	This study provides very low certainty evidence that baricitinib increases quality of life in people with CANDLE, SAVI and other interferonopathies by a small, nonsignificant amount after 2.8 years of treatment.
Change from baseline in clinical severity of symptoms **Certainty of evidence:** very low	Clinical severity of symptoms is relevant to people with monogenic interferonopathies because symptoms can be severe and disabling and affect their function, activities of daily living and quality of life. Improvement in symptoms is a marker of treatment success. One uncontrolled prospective cohort study (Sanchez et al. 2018) provided evidence relating to clinical severity of symptoms for a median duration of treatment of 2.8 years. This study mainly included people with CANDLE and SAVI. A prospective case series (Zimmermann et al. 2019) provided evidence relating to clinical severity of symptoms over 3 months in people with familial chilblain lupus (FCL). In the cohort study (n=18), after a median 2.8 years, disease-specific daily symptom (DDS) scores improved from baseline by an amount considered to be clinically meaningful in 12/18 (67%) participants treated with baricitinib (8/10 [80%] with CANDLE, 3/4 [75%] with SAVI and 1/4 [25%] with other interferonopathies, no statistical analyses). Overall, the median DDS score decreased by 1.05 (from 1.3 at baseline to 0.25, p<0.0001, statistically significant). In this study, 5/10 (50%) people with CANDLE experienced remission with no disease symptoms (DDS<0.15, no statistical analysis). No people with SAVI or other interferonopathies experienced remission. (**VERY LOW**). In the case series (n=3), after 3 months' treatment, a statistically significant improvement was seen in the area and severity of cutaneous lesions (mean Revised Cutaneous Lupus Area and Severity Index [RCLASI] score reported graphically, p=0.01). One patient had complete remission of skin and joint pain. In the other 2 patients, pain was partially reduced (individual visual analogue scale [VAS] scores reported graphically, all p<0.001). (**VERY LOW**). **These studies provide very low certainty evidence that baricitinib improves symptoms in people with CANDLE, SAVI, FCL and other interferonopathies. It is not known if the improvements seen are all clinically meaningful, but symptoms resolved completely in some people.**
Physician and patient global assessment of wellbeing	People with monogenic interferonopathies often have poor quality of life and debilitating symptoms that affect their wellbeing so this outcome is relevant to them. Global assessment is a holistic measure of treatment effect,

Certainty of evidence: very low	subjectively assessed by the patient and clinician, which may not be captured by individual measures. One uncontrolled prospective cohort study (Sanchez et al. 2018) provided evidence relating to global assessment of wellbeing for a median duration of treatment of 2.8 years. In this study (n=18), during treatment with baricitinib, the median score for physicians' global assessment improved by a statistically significant 87.5 mm (from 90 mm at baseline to 2.5 mm at a median 2.8 years, p<0.001). Over the same period, the median score for patient or carers' global assessment improved by 22 mm (from 48 mm to 26 mm). However, the improvement was not statistically significant. (**VERY LOW**). **This study provides very low certainty evidence that treatment with baricitinib for 2.8 years improves wellbeing in people with CANDLE, SAVI and other interferonopathies. The improvement in physicians' global assessment is likely to be clinically meaningful.**
Important outcomes	
Direct measurement of interferon (IFN) **Certainty of evidence: very low**	This outcome is relevant to people with monogenic interferonopathies because these blood tests are a way of measuring whether their condition is responding to treatment or not. A reduction suggests improvement and normal levels can indicate remission. One uncontrolled prospective cohort study (Sanchez et al. 2018) provided evidence relating to IFN levels for a median duration of treatment of 2.8 years. This study mainly included people with CANDLE and SAVI. A prospective case series (Zimmermann et al. 2019) provided evidence relating to IFN levels over 3 months in people with FCL. In the cohort study (n=18), serum levels of the chemokine IP-10 and a 25-gene IFN response gene score (measures of IFN) decreased by a statistically significant amount during treatment with baricitinib. Median serum IP-10 reduced from 9196.7 at baseline to 1857.6 at a median 2.8 years, p<0.005. Median 25-gene IFN reduced from 417.5 at baseline to 113.3 at a median 2.8 years, p<0.01. The IFN score normalised in 5 people with CANDLE who experienced remission**. (VERY LOW).** In the case series (n=3), a statistically significant reduction was seen in the interferon-stimulated genes (ISG) score (a measure of IFN) after 3 months' treatment with baricitinib (mean reported graphically, p=0.01). **(VERY LOW).** **These studies provide very low certainty evidence that baricitinib improves IFN levels in people with CANDLE,**

	SAVI, FCL and other interferonopathies. The clinical significance of the improvement is unclear, except perhaps for people with CANDLE.
Reduction in corticosteroid use **Certainty of evidence:** very low	This outcome is relevant to people with monogenic interferonopathies because corticosteroids have serious adverse effects (such as diabetes, osteoporosis and psychiatric reactions), especially when they are taken long-term at high doses. Reducing the dose reduces the risk of adverse effects. One uncontrolled prospective cohort study (Sanchez et al. 2018) provided evidence relating to reducing corticosteroid use over a median duration of treatment of 2.8 years. Of the 14 people on corticosteroids at baseline, 10 (71%) successfully reduced their dose and fulfilled the corticosteroid improvement criteria while taking baricitinib (no statistical analysis). Median corticosteroid dose reduced by a statistically significant 0.33 mg/kg/day (from a prednisone equivalent dose of 0.44 mg/kg/day at baseline to 0.11 mg/kg/day at a median 2.8 years, p<0.005). (**VERY LOW**). **This study provides very low certainty evidence that treatment with baricitinib for 2.8 years enables people with CANDLE, SAVI and other interferonopathies to reduce their dose of corticosteroid.**
Growth improvement in children **Certainty of evidence:** very low	People with monogenic interferonopathies often have chronic inflammation, which reduces their rate of growth. Improved growth is a marker of controlled inflammation in children and is a relevant outcome to them. One uncontrolled prospective cohort study (Sanchez et al. 2018) provided evidence relating to growth improvement in children over a median duration of treatment of 2.8 years. At baseline in this study, growth and physical maturation were delayed, with mean bone age 3.5 years lower than chronological age. In 13 children with growth potential who took baricitinib, mean height Z-scores improved from −4.03 to −3.19 (statistically significant, p=0.015). The authors report that this is clinically significant. 'Catch up growth' was seen in 9 children who were able to reduce their corticosteroid dose below 0.16 mg/kg/day. Mean height percentile increased from the 1.4th percentile to the 7.2nd percentile. (**VERY LOW**). **This study provides very low certainty evidence that growth improves in children with CANDLE, SAVI and other interferonopathies treated with baricitinib for 2.8 years.**
Change in inflammatory markers (C-	This outcome is relevant to people with monogenic interferonopathies because these blood tests are measures of treatment response. They are markers of inflammation and, if

reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) **Certainty of evidence:** very low	they are raised at baseline, they are a way of assessing improvement in inflammation. One uncontrolled prospective cohort study (Sanchez et al. 2018) provided evidence relating to inflammatory markers over a median duration of treatment of 2.8 years. In this study (n=18), CRP and ESR decreased during baricitinib treatment. However, the differences from baseline were not statistically significant. Median CRP reduced from 15.9 mg/L at baseline to 2.9 mg/L and median ESR reduced from 53 mm/hour at baseline to 37 mm/hour after a median 2.8 years. (**VERY LOW**). **This study provides very low certainty evidence that treatment with baricitinib for 2.8 years does not significantly improve inflammatory markers in people with CANDLE, SAVI and other interferonopathies.**
Safety	
Withdrawal from treatment due to adverse events **Certainty of evidence:** very low	This outcome is important to people because it is an indicator of serious adverse effects or lack of efficacy of the treatment and could affect the person's decision to take baricitinib. One uncontrolled prospective cohort study (Sanchez et al. 2018) provided evidence relating to withdrawal from treatment over a median duration of treatment of 2.8 years. In the cohort study (n=18), 1 person without a genetic diagnosis stopped baricitinib because of osteonecrosis and an unsatisfactory treatment response. 1 person with CANDLE developed BK viremia and azotemia and stopped treatment because of acute kidney injury. These people later died due to worsening disease. (**VERY LOW**). **This study provides very low certainty evidence that some people with CANDLE, SAVI and other interferonopathies may need to stop taking baricitinib because of adverse effects or because the treatment is ineffective.**
Serious adverse events **Certainty of evidence:** very low	This outcome is important to people because serious adverse effects can be life threatening or require hospitalisation or intervention to prevent permanent impairment or damage. They may also result in persistent or significant disability or incapacity. Serious adverse events may or may not be directly related to treatment. One uncontrolled prospective cohort study (Sanchez et al. 2018) provided evidence relating to serious adverse events over a median duration of treatment of 2.8 years. This study mainly included people with CANDLE and SAVI. A prospective case

	series (Zimmermann et al. 2019) provided evidence relating to serious adverse events over 3 months in people with FCL. In this cohort study (n=18), 15 participants (83%) had at least 1 serious adverse event. In most instances, these resolved without interrupting baricitinib treatment. No deaths were reported during the study. (**VERY LOW**). In the case series (n=3), baricitinib was reportedly well-tolerated and no serious adverse effects occurred. (**VERY LOW**). **The cohort study provides very low certainty evidence that serious adverse events are common in people with CANDLE, SAVI and other interferonopathies taking baricitinib for 2.8 years. However, the treatment is unlikely to need stopping because of these serious adverse events. The case series was likely to have been too small and too short to detect serious or rare adverse events in people with FCL taking baricitinib for 3 months.**
Treatment-related adverse events **Certainty of evidence:** very low	Treatment-related adverse events are side effects that were new or worsened after starting baricitinib treatment. They are relevant to people with monogenic interferonopathies because they can affect their decision to start treatment with baricitinib. One uncontrolled prospective cohort study (Sanchez et al. 2018) provided evidence relating to treatment-related adverse events over a median duration of treatment of 2.8 years. In the cohort study (n=18), 16 people (89%) experienced treatment-related infections (most commonly upper respiratory tract infections [see below]). 2 people developed herpes zoster. Transient cytopenias developed in the context of infections and intermittent disease exacerbations. Viral reactivation with BK virus (BK viremia and viruria, n=9 and n=15 respectively) was also seen. Other non-infection treatment-related adverse events were also common. (**VERY LOW**). **The study provides very low certainty evidence that treatment-related adverse events (particularly infections) are common in people with CANDLE, SAVI and other interferonopathies taking baricitinib for 2.8 years. The adverse events seen in the study were generally consistent with those listed in the summary of product characteristics for baricitinib, except for viral reactivation with BK virus, which was considered unique to the study population compared with people with rheumatoid arthritis (the licensed indication). Note that, although these adverse events were new or worsened after starting baricitinib**

	treatment, they may not be solely caused by baricitinib and may be related to the disease or concomitant treatment.
Upper respiratory tract infections **Certainty of evidence:** very low	This outcome is relevant because it is one of the most common adverse effects of baricitinib and can sometimes be serious, requiring hospitalisation. One uncontrolled prospective cohort study (Sanchez et al. 2018) provided evidence relating to upper respiratory tract infections over a median duration of treatment of 2.8 years. This study mainly included people with CANDLE and SAVI. A prospective case series (Zimmermann et al. 2019) provided evidence relating to upper respiratory tract infections over 3 months in people with FCL. In the cohort study (n=18), 15 people (83%) experienced upper respiratory tract infections. (**VERY LOW**). In the case series (n=3), 2 people experienced repeated mild upper respiratory tract infections. (**VERY LOW**). **These studies provide very low certainty evidence that baricitinib is associated with upper respiratory tract infections in two thirds of people with CANDLE, SAVI, FCL and other interferonopathies.**
Raised liver transaminases **Certainty of evidence:** very low	This outcome is relevant because raised liver transaminases are a marker of liver damage and, if treatment-induced liver injury is suspected, baricitinib may need to be stopped temporarily. One uncontrolled prospective cohort study (Sanchez et al. 2018) provided evidence relating to raised liver transaminases over a median duration of treatment of 2.8 years. In the cohort study (n=18), liver transaminases were raised in 9 people (50%). (**VERY LOW**). **This study provides very low certainty evidence that baricitinib is associated with raised liver transaminases in people with CANDLE, SAVI and other interferonopathies.**

Abbreviations: CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperatures syndrome; CRP, C-reactive protein; DDS, disease-specific daily symptom; ESR, erythrocyte sedimentation rate; FCL, familial chilblain lupus; IFN, interferon; ISG, interferon-stimulated genes; RCLASI, Revised Cutaneous Lupus Area and Severity Index; SAVI, stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy; VAS, visual analogue scale

In patients with monogenic interferonopathies, what is the cost-effectiveness of baricitinib?

Outcome	Evidence statement
Cost-effectiveness	No evidence was found to assess the cost-effectiveness of baricitinib for patients with monogenic interferonopathies.

From the evidence selected, are there any subgroups of patients that may benefit from baricitinib more than the wider population of interest?

Outcome	Evidence statement
Patient Subgroups **Certainty of evidence: Very low**	Neither of the included studies performed statistical analyses in subgroups of people with monogenic interferonopathies. However, the uncontrolled prospective cohort study (Sanchez et al. 2018) reported some outcomes numerically in subgroups of people with CANDLE, SAVI and other interferonopathies. For example, in this study, after a median 2.8 years' treatment with baricitinib, 5/10 (50%) people with CANDLE experienced remission with no disease symptoms (DDS<0.15, no statistical analysis). No people with SAVI (n=4) or other interferonopathies (n=4) experienced remission. Sanchez et al. (2018) reported that half of the patients with CANDLE could permanently discontinue corticosteroid therapy (without return of disease symptoms), their inflammatory markers normalised and they achieved durable inflammatory remission on baricitinib. In patients with SAVI, baricitinib treatment improved flares of vasculitis, and prevented the progression of spontaneous amputations and the development of gangrene. However, inflammatory markers did not normalise in any of the patients with SAVI, and although IFN scores decreased, the absolute levels remained elevated.

Abbreviations: CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperatures syndrome; DDS, disease-specific daily symptom; IFN, interferon; SAVI, stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy

From the evidence selected, what are the criteria used by the research studies to confirm a diagnosis of monogenic interferonopathy?

Outcome	Evidence statement
Patient selection criteria	The study by Sanchez et al. (2018), included people with genetically confirmed CANDLE or SAVI, or a suspected undifferentiated interferonopathy who were referred to an expanded access programme. Details of the criteria used to confirm a genetic diagnosis of monogenic interferonopathy (such as CANDLE or SAVI) are not reported. For people for whom a genetic diagnosis of a monogenic interferonopathy had not been made, inclusion criteria included no response to at least 1 biologic therapy and treatment with or no response to corticosteroids. All participants had to have at least 2 of the following systemic signs and symptoms of inflammation: rash, fever, musculoskeletal pain, headache, fatigue, weakness, respiratory or breathing symptoms, and ulcers or ischaemic lesions. It is not reported how FCL was diagnosed in the study by Zimmermann et al. (2019), but the included cases were diagnosed with early onset in childhood.

Patient Impact Summary
The condition has the following impacts on the patient's everyday life: • **Mobility:** Patients have severe problems in walking about or are unable to walk about. • **Ability to provide self-care:** Patients have severe problems in washing or dressing or are unable to wash or dress. • **Undertaking usual activities:** Patients have severe problems in doing their usual activities or are unable to do their daily activities. • **Experience of pain/discomfort:** Patients have moderate, occasionally severe pain or discomfort. • **Experience of anxiety/depression:** Patients are moderately anxious or depressed.
Further details of impact upon patients: There are frequent digestive problems associated with this condition, as food and drink are not absorbed well. Low muscle tone also affects swallowing. There is associated pain, which means eating and drinking can be challenging and sometimes requires extra nasogastric feeding. Even with this, weight gain can be poor. The low muscle tone also causes reflux, which can also cause vomiting and limits oral intake even more. This can also contribute to feeling very low in energy and increased sleep. Patients also experience poor temperature regulation with hyperthermic episodes. All of this affects usual activities, and often requires carers to help with all self-care. These symptoms can frequently lead to anxiety and depression.

Further details of impact upon carers:
Carers find it very distressing to see their child in pain and as a result seek alternatives such as therapies, equipment and medication as well as using massage and baths to compensate. Sleep can be very disturbed, waking nightly at irregular times for varied time periods in pain. This often requires the carers to stay up late, get up early and be intermittently awake during the night. It is difficult for the carers to see the patients in pain and be able to offer very little comfort.

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
This clinical commissioning policy proposition recommends baricitinib as a treatment option for adults and children 2 years and over with monogenic interferonopathies within the criteria set out in this document. This is an off-label use of baricitinib both for the indication and use in children 2-17. It is excluded from tariff.

Considerations from review by National Programme of Care
1) The proposal received the full support of the Blood and Infection Programme of Care on the 16 February 2021.