CLINICAL PRIORITIES ADVISORY GROUP
10 07 2023

Agenda Item No	
National Programme	Cancer
Clinical Reference Group	Chemotherapy
URN	2124

Title
Siltuximab for idiopathic multicentric Castleman disease (adults)

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its relative prioritisation

Proposition
The policy proposition recommends that siltuximab is made available as a routine commissioning treatment option for idiopathic multicentric Castleman disease (iMCD) within the criteria set out in the Proposition. iMCD is a rare disorder of uncontrolled growth of cells in lymph nodes at multiple sites. Severe cases can lead to multiorgan failure and death. Whilst the underlying cause of iMCD remains unknown, it is driven by a chemical called IL-6. In 2018 the responsible commissioner for Castleman's Disease transferred from Clinical Commissioning Groups (CCGs) to NHS England Specialised Commissioning. As the CCGs did not have an overarching clinical commissioning policy for the treatment of Castleman's disease with siltuximab, decisions were therefore made locally by individual CCGs. Consequently, there is no nationally commissioned treatment for a debilitating and potentially life-threatening disease. Siltuximab is a monoclonal antibody that blocks the action of IL-6 and received European Marketing Authorisation for the treatment of iMCD in 2014. Siltuximab is currently the only licensed therapy for iMCD. The aim of treatment is to reduce severity of disease, limiting risk of end-organ damage or death. Whilst the exact incidence and prevalence of iMCD in the UK is unknown, clinical consensus gives an estimated incidence of 116-157 patients with severe iMCD requiring treatment. iMCD is typically diagnosed later in life in the 50-60s. Siltuximab is an intravenous infusion that can be given via chemotherapy delivery units. Chemotherapy can be prescribed and delivered at any provider commissioned by NHS England; this includes Cancer Centres,

Teaching Hospitals and District General Hospitals in line with the service specification.

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

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Cancer Programme 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 iMCD, what is the clinical effectiveness and safety of siltuximab and best supportive care compared to best supportive care alone or with standard care?

Outcome	**Evidence statement**
Clinical effectiveness	
Critical outcomes	
Overall response **Certainty of evidence:** Moderate to very low	Overall response is important for patients because it provides a global indicator of the response to treatment/ treatment effect. In total, one RCT and one retrospective cohort study provided evidence relating to overall response rate in patients with iMCD. Results comparing siltuximab plus best supportive care (BSC) to placebo plus BSC were available from the RCT. Results comparing siltuximab to rituximab and to chemotherapy or

	corticosteroids[1] were available from the retrospective cohort study. **At approximately 14 months:** *Siltuximab plus BSC vs placebo plus BSC* • One RCT (van Rhee et al 2014) reported that a *statistically significantly higher* proportion of patients had an overall response[2] with siltuximab (27/53, 50.9%) vs placebo (0/26, 0%). Difference between groups: 50.9% (95%CI 29.2 to 70.1), p<0.0001. Of the 27 siltuximab responders, three had a complete response and 24 a partial response. Median (range) follow-up: 422 days (5 to 1,051). **(MODERATE)** **At an unknown timeframe:** *Siltuximab vs rituximab* • One retrospective cohort study (Yu et al 2017) reported an overall response[3] in 16 of 21 (76.2%) patients receiving siltuximab and 17 of 25 (68.0%) patients receiving rituximab. No statistical test comparing the treatments was reported. Of the 16 siltuximab responders, nine had a complete response and seven a partial response. Of the 17 rituximab responders, five had a complete response and 12 a partial response. Median follow-up was not reported. **(VERY LOW)** *Siltuximab vs chemotherapy or corticosteroids* • One retrospective cohort study (Yu et al 2017) reported that a *statistically significantly higher* proportion of patients had an overall response with siltuximab (16/21, 76.2%) vs chemotherapy or corticosteroids (12/29, 63.2%), p=0.034. Of the 16 siltuximab responders, nine had a complete response and seven a partial response. Of the 12 chemotherapy or corticosteroids responders, two had a complete response and ten a partial response. Median follow-up was not reported. **(VERY LOW)** **One RCT provided moderate certainty evidence that a statistically significantly higher proportion of patients had an overall response with siltuximab plus BSC vs placebo plus BSC at a median of approximately 14 months follow-up. One retrospective cohort study provided very low certainty evidence that a higher proportion of patients had an overall response with siltuximab vs rituximab or vs**

	chemotherapy or corticosteroids (timeframe not stated). This was statistically significant vs chemotherapy or corticosteroids but siltuximab and rituximab were not statistically compared[4]
Durability of response **Certainty of evidence:** High to very low	Durability of response is important for patients because it gives an indicator of how long any response to treatment may last. In total, one RCT and one retrospective cohort study provided evidence relating to durability of response rate in patients with iMCD. Results comparing siltuximab plus BSC to placebo plus BSC were available from the RCT. Results comparing siltuximab to rituximab and to chemotherapy or corticosteroids were available from the retrospective cohort study. Durability of response was assessed by durable tumour and symptomatic response[5], durable symptomatic response[6], durable complete symptomatic response, time to treatment failure, time to next treatment and progression free survival. **At approximately 14 months:** *Siltuximab plus BSC vs placebo plus BSC* • One RCT (van Rhee et al 2014) reported that a *statistically significantly higher* proportion of patients had a durable tumour and symptomatic response with siltuximab (18/53, 34.0%) vs placebo (0/26, 0%). Difference between groups: 34.0% (95%CI 11.1 to 54.8), p=0.0012. Of the 18 siltuximab responders, one had a complete response and 17 a partial response. Median (range) duration of durable tumour and symptomatic response for siltuximab: 383 days (232 to 676). Median (range) follow-up: 422 days (5 to 1,051). **(MODERATE)** • van Rhee et al (2014) also reported that a *statistically significantly higher* proportion of patients had a durable symptomatic response with siltuximab (30/53, 56.6%) vs placebo (5/26, 19.2%). Difference between groups: 37.4% (95%CI 14.9 to 58.2), p=0.0018. Median (range) follow-up: 422 days (5 to 1,051). **(HIGH)** • van Rhee et al (2014) also reported that a *statistically significantly higher* proportion of patients had a durable complete symptomatic response with siltuximab (13/53, 24.5%) vs placebo (0/26, 0%). Difference between groups: 24.5% (95%CI 1.4 to 46.2), p=0.0037. Median (range) follow-up: 422 days (5 to 1,051). **(MODERATE)**

	• van Rhee et al (2014) also reported a *statistically significantly longer* time to treatment failure for siltuximab vs placebo (HR 0.418 (95%CI 0.214 to 0.815), p=0.0084). The median time to treatment failure (days) was not reached for siltuximab (95%CI 378 to not estimable). For placebo this was 134 (95%CI 85 to not estimable). **(MODERATE)** • van Rhee et al (2014) also reported a *statistically significantly longer* time to next treatment for siltuximab vs placebo (HR 0.298 (95%CI 0.137 to 0.652), p=0.0013). The median time to next treatment (days) was not reached for siltuximab (95%CI not estimable). For placebo this was 280 (95%CI 161 to not estimable). **(HIGH)** **At an unknown timeframe:** *Siltuximab vs rituximab* • One retrospective cohort study (Yu et al 2017) reported *no statistically significant difference* in the proportion of patients with progression free survival between siltuximab (n=21) and rituximab (n=25) (p=0.059). Progression free survival percentage was only presented graphically. Median follow-up was not reported. **(VERY LOW)** *Siltuximab vs chemotherapy or corticosteroids* • One *retrospective* cohort study (Yu et al 2017) reported *no statistically significant difference* in the proportion of patients with progression free survival between siltuximab (n=21) and chemotherapy or corticosteroids (n=25) (p=0.335). Progression free survival percentage was only presented graphically. Median follow-up was not reported. **(VERY LOW)** **One RCT provided high to moderate certainty evidence that a statistically significantly higher proportion of patients had durable tumour and symptomatic responses with siltuximab plus BSC vs placebo plus BSC at a median of approximately 14 months follow-up. The same RCT also provided high to moderate certainty evidence that time to treatment failure and time to next treatment were statistically significantly longer with siltuximab. One retrospective cohort study provided very low certainty evidence of no statistically significant difference in the proportion of patients with progression free survival between siltuximab and rituximab, or between siltuximab**

	and chemotherapy or corticosteroids. The follow-up timeframe was not clear.
Survival **Certainty of evidence:** Moderate	Survival is important for patients because it reflects how long people live after treatment, although it does not provide information about their health and wellbeing during that time. In total, one RCT comparing siltuximab plus BSC to placebo plus BSC provided evidence relating to survival in adults with iMCD. No evidence was identified relating to survival for siltuximab vs rituximab, vs chemotherapy or vs corticosteroids. **At one year:** *Siltuximab plus BSC vs placebo plus BSC* • One RCT (van Rhee et al 2014) reported overall survival at one year for siltuximab (100% (95%CI 100 to 100)) and placebo (92% (95%CI 72 to 98)). The groups were not statistically compared. **(MODERATE)** **One RCT provided moderate certainty evidence of higher overall survival at one year with siltuximab plus BSC than placebo plus BSC. The groups were not statistically compared.**
Important outcomes	
Quality of life **Certainty of evidence:** High to moderate	Quality of life is important to patients because it provides a holistic evaluation and indication of the patient's general health and their perceived well-being and their ability to participate in activities of daily living. In total, one RCT comparing siltuximab plus BSC to placebo plus BSC provided evidence relating to quality of life in adults with iMCD. Quality of life was assessed using the SF-36[7] which includes a physical component score (PCS) and a mental component score (MCS). No evidence was identified relating to quality of life for siltuximab vs rituximab, vs chemotherapy or vs corticosteroids. **At approximately 12 months[8]:** *Siltuximab plus BSC vs placebo plus BSC* • One RCT (van Rhee et al 2015) reported an improvement of at least five points on the SF-36 PCS for 24 of 50 (48%) siltuximab patients and eight of 26 (31%) placebo patients during the blinded treatment period. The median (range) masked treatment duration was 375 days (1 to 1,031) for siltuximab and 152 days (23 to 666) for placebo. The groups were not statistically compared. **(MODERATE)** • van Rhee et al (2015) also found that a *statistically significantly higher* proportion of patients receiving

	siltuximab reported an improvement of at least five points on the SF-36 MCS during the blinded treatment period. Siltuximab: 34/50, 68% vs placebo: 9/26, 35% (p=0.0074). The median (range) masked treatment duration was 375 days (1 to 1,031) for siltuximab and 152 days (23 to 666) for placebo. **(HIGH)** • Mean (SD) PCS and MCS scores were only reported at baseline. For the PCS these were 42.9 (9.9) for siltuximab and 41.6 (11.1) for placebo. For the MCS these were 39.7 (10.8) for siltuximab and 43.3 (12.3) for placebo. **One RCT provided moderate to high certainty evidence that a higher proportion of siltuximab plus BSC patients reported an improvement in quality of life than placebo plus BSC patients at a median of approximately 12 months. This difference was statistically significant for the mental component of the quality of life measure used but the groups were not statistically compared for the physical component.**
Symptom alleviation **Certainty of evidence:** High to moderate	Symptom alleviation is important to patients because reduction of symptoms directly improves the patient's quality of life. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment. In total, one RCT comparing siltuximab plus BSC to placebo plus BSC provided evidence relating to symptom alleviation in adults with iMCD. Symptom alleviation was assessed by the MCD-Symptom Scale (MCD-SS)[9] and the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale[10]. No evidence was identified relating to symptom alleviation for siltuximab vs rituximab, vs chemotherapy or vs corticosteroids. **At approximately 12 months:** *Siltuximab plus BSC vs placebo plus BSC* • One RCT (van Rhee et al 2015) reported an improvement of at least one point[11] on the MCD-SS total score for 32 of 51 (63%) siltuximab patients and 13 of 26 (50%) placebo patients during the blinded treatment period. The median (range) masked treatment duration was 375 days (1 to 1,031) for siltuximab and 152 days (23 to 666) for placebo. The groups were not statistically compared. **(MODERATE)** • Mean (SD) MCD-SS total score was only reported at baseline. This was 2.9 (2.1) for siltuximab and 2.3 (1.2) for placebo.

	• van Rhee et al (2015) also reported a *statistically significant improvement* in the MCD-SS fatigue domain score for siltuximab vs placebo (p=0.02). The mean (SD) baseline scores were 4.1 (2.4) for siltuximab (n=52) and 4.5 (3.3) for placebo (n=26). The mean score at approximately one year (cycle 18 day 1) follow-up was 2.6 for siltuximab and 5.7 for placebo (SD not reported). **(HIGH)** • van Rhee et al (2015) also reported a *statistically significant improvement* in the FACIT-Fatigue scale for siltuximab vs placebo (p=0.0364). The mean (SD) baseline scores were 32.4 (11.0) for siltuximab (n=52) and 31.0 (14.6) for placebo (n=26). The mean score at approximately one year (cycle 18 day 1) follow-up was 38.6 for siltuximab and 26.9 for placebo (SD not reported). **(HIGH)** ***At ≥120 days*** • van Rhee et al (2015) also reported that a *statistically significantly higher* proportion of patients with a FACIT-Fatigue baseline score of <44[12] achieved an improved score of ≥44 with durability for ≥120 days with siltuximab (35%) vs placebo (11%) (p=0.0475). The number of patients with a fatigue score of <44 at baseline was 43/52 (83%) for siltuximab and 19/26 (73%) for placebo. **(HIGH)** **One RCT provided high certainty evidence of statistically significantly higher improvements with siltuximab plus BSC vs placebo plus BSC on two measures of fatigue at up to approximately 12 months. The proportion of patients achieving a result that the study authors considered meaningful was higher with siltuximab on one measure of fatigue and one broader measure of symptoms. The difference was statistically significantly different for the measure of fatigue but the groups were not statistically compared for the broader measure.**
Tumour response **Certainty of evidence:** High	Tumour response is important to patients because it is a key indicator of the effectiveness of treatment. In total, one RCT comparing siltuximab plus BSC to placebo plus BSC provided evidence relating to tumour response rate[13] in adults with iMCD. No evidence was identified relating to tumour response for siltuximab vs rituximab, vs chemotherapy or vs corticosteroids. **At approximately 14 months:** *Siltuximab plus BSC vs placebo plus BSC* • One RCT (van Rhee et al 2014) reported that a *statistically significantly higher* proportion of patients had

	a tumour response with siltuximab (20/53, 37.7%) vs placebo (1/26, 3.8%). Difference between groups: 33.9% (95%CI 11.1 to 54.8), p=0.0022. Median (range) follow-up: 422 days (5 to 1,051). **(HIGH)** **One RCT provided high certainty evidence that a statistically significantly higher proportion of patients had a tumour response with siltuximab plus BSC vs placebo plus BSC at a median of approximately 14 months follow-up.**
Haematological markers **Certainty of evidence:** Moderate	Haematological markers are important for patients as they provide a secondary indicator as to the efficacy of treatment. In total, one RCT comparing siltuximab plus BSC to placebo plus BSC provided evidence relating to haematological markers in adults with iMCD. Haematological markers were assessed as the number of patients with anaemia at baseline who had a ≥15g/L increase in haemoglobin concentration between baseline and week 13. No evidence was identified relating to haematological response for siltuximab vs rituximab, vs chemotherapy or vs corticosteroids. **At week 13:** *Siltuximab plus BSC vs placebo plus BSC* • One RCT (van Rhee et al 2014) reported that a *statistically significantly higher* proportion of patients had an increase in haemoglobin concentration between baseline and week 13 with siltuximab (19/31, 61.3%) vs placebo (0/11, 0%). Difference between groups: 61.3% (95%CI 28.3 to 85.1), p=0.0002. **(MODERATE)** **One RCT provided moderate certainty evidence that a statistically significantly higher proportion of patients had an increase in haemoglobin concentration between baseline and week 13 with siltuximab plus BSC vs placebo plus BSC.**
Safety	
Adverse events **Certainty of evidence:** Moderate	Safety is important to patients as it reflects the risks involved in taking siltuximab and allows a risk to benefit assessment to be undertaken. In total, one RCT comparing siltuximab plus BSC to placebo plus BSC provided evidence relating to safety in adults with iMCD. No evidence was identified relating to safety for siltuximab vs rituximab, vs chemotherapy or vs corticosteroids. **At approximately 14 months:** *Siltuximab plus BSC vs placebo plus BSC* • One RCT (van Rhee et al 2014) reported serious adverse events (not further defined) for 12 of 53 (23%) siltuximab

	patients and five of 26 (19%) placebo patients. The groups were not statistically compared. Three siltuximab patients had serious adverse events judged to be related to siltuximab (lower respiratory tract infection, anaphylactic reaction and sepsis). The authors also stated that no Grade 4 or higher haematological or chemistry abnormalities occurred with siltuximab. Median (range) follow-up: 422 days (5 to 1,051). **(MODERATE)** • van Rhee et al (2014) also reported the number of patients with at least one Grade ≥3[14] adverse event. This was 25 of 53 (47%) for siltuximab patients and 14 of 26 (54%) for placebo patients. The groups were not statistically compared. The most common (>5% of patients) Grade ≥3 adverse events with siltuximab were fatigue (9%) and night sweats (8%). The most common (>5% of patients) Grade ≥3 adverse event with placebo was anaemia (12%). Median (range) follow-up: 422 days (5 to 1,051). **(MODERATE)** • van Rhee et al (2014) also reported the number of patients with at least one adverse event (all grades). This was 53 of 53 (100%) for siltuximab patients and 25 of 26 (96%) for placebo patients. The groups were not statistically compared. The most common (≥25% of patients) adverse events with siltuximab were pruritus (42%), upper respiratory tract infection (36%), fatigue (34%), maculopapular rash (34%), peripheral oedema (32%), malaise (28%), dyspnoea (25%) and peripheral sensory neuropathy (25%). The most common (≥25% of patients) adverse events with placebo were fatigue (38%) and dyspnoea (35%). Median (range) follow-up 422 days (5 to 1,051). **(MODERATE)** **One RCT provided moderate certainty evidence of similar proportions of serious adverse events, Grade ≥3 adverse events and adverse events (all grades) with siltuximab plus BSC and placebo plus BSC. The groups were not statistically compared.**
Abbreviations BSC: Best supportive care; CI: Confidence intervals; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue scale; g: grams; HR: Hazard ratio; iMCD: Idiopathic multicentric Castleman disease; L: Litre; MCD-SS: Multicentric Castleman Disease-Symptom Scale; MCS: Mental component score; PCS: Physical component score; RCT: Randomised controlled trial; SD: Standard deviation; SF: Short-Form	

In patients with iMCD, what is the cost effectiveness of siltuximab and best supportive care compared to best supportive care alone or with standard care?

Outcome	Evidence statement

Cost effectiveness	No evidence was identified for cost effectiveness.

From the evidence selected, are there any subgroups that may benefit from siltuximab and best supportive care more than the wider population of interest?

Outcome	Evidence statement
Subgroups	Subgroup results for newly diagnosed and previously treated patients were reported from one RCT for the critical outcomes of overall response and durability of response and for the important outcomes of tumour response and haematological markers. Subgroup analysis was pre-planned in the RCT and results were primarily reported as siltuximab plus BSC vs placebo plus BSC for the different patient subgroups. Only one outcome (time to treatment failure) included a comparison between newly diagnosed and previously treated patients. **Overall response** • One RCT (van Rhee et al 2021) reported a *statistically significantly higher* overall response rate[15] for siltuximab vs placebo for both newly diagnosed patients (11/24, 46% vs 0/9, 0%, p=0.022) and previously treated patients (16/29, 55% vs 0/17, 0%, p=0.0003). The proportion of patients showing a complete or partial response was not reported. Median (range) follow-up: 422 days (5 to 1,051). **Durability of response** • One RCT (van Rhee et al 2021) reported *no statistically significant difference* in durable tumour and symptomatic response rate[16] between siltuximab (8/24, 33%) and placebo (0/9, 0%) for newly diagnosed patients (p=0.09). Of the eight siltuximab responders, one had a complete response and seven a partial response. The proportion of non-responders with stable disease was 16/24 (67%) for siltuximab and 7/9 (78%) with placebo and the proportion with progressive disease was 0/24 (0%) with siltuximab and 2/9 (22%) with placebo. Median (range) follow-up: 422 days (5 to 1,051). • van Rhee et al (2021) reported a *statistically significantly higher* durable tumour and symptomatic response rate for siltuximab (10/29, 34%) vs placebo (0/17, 0%) for previously treated patients (p=0.013). All ten siltuximab responders had a partial response. The proportion of non-responders with stable disease was 15/29 (52%) for siltuximab and 15/17 (88%) with placebo and the proportion with progressive disease was 4/29 (14%) with siltuximab and 2/17 (12%) with placebo. Median (range) follow-up: 422 days (5 to 1,051).

	• One RCT (van Rhee et al 2021) reported a *statistically significantly higher* durable symptomatic response rate for siltuximab (17/24, 71%) vs placebo (1/9, 11%) for newly diagnosed patients (p=0.0040). For previously treated patients, the difference between siltuximab (13/29, 45%) and placebo (4/17, 24%) was *not statistically significant* (p=0.1478). Median (range) follow-up: 422 days (5 to 1,051). • van Rhee et al (2021) reported *no statistically significant difference* in durable complete symptomatic response rate between siltuximab and placebo for either newly diagnosed patients (8/24, 33% vs 0/9, 0%, p=0.0891) or previously treated patients (5/29, 17% vs 0/17, 0%, p=0.1290). Median (range) follow-up: 422 days (5 to 1,051). • van Rhee et al (2021) also reported *no statistically significant difference* in time to treatment failure between newly diagnosed and previously treated patients (p=0.11). Time to treatment failure was *statistically significantly longer* for siltuximab vs placebo (HR 0.19 (95%CI 0.06 to 0.61), p=0.005) for newly diagnosed patients but there was *no statistically significant difference* for previously treated patients (HR 0.60 (95%CI 0.26 to 1.38), p=0.23). The median time to treatment failure (days) was not reached for siltuximab for either subgroup and was 106 and 184 for newly diagnosed and previously treated placebo patients respectively. **Tumour response** • One RCT (van Rhee et al 2021) reported *no statistically significant difference* in tumour response rate[17] between siltuximab (10/24, 42%) and placebo (1/9, 11%) for newly diagnosed patients (p=0.1941). For previously treated patients, there was a *statistically significantly higher* tumour response rate for siltuximab (10/29, 34%) vs placebo (0/17, 0%) (p=0.0208). The proportion of patients showing a complete or partial response was not reported. Median (range) follow-up: 422 days (5 to 1,051). **Haematological markers** • One RCT (van Rhee et al 2021) reported a *statistically significantly higher* haemoglobin response rate[18] for siltuximab vs placebo for both newly diagnosed patients (9/14, 64% vs 0/4, 0%, p=0.0373) and previously treated patients (10/17, 59% vs 0/7, 0%, p=0.0160). Median (range) follow-up: 422 days (5 to 1,051). **One RCT compared time to treatment failure between newly diagnosed and previously treated patients and reported no**

	statistically significant difference between the subgroups. For other outcomes, results for the two subgroups of patients were separately reported. These suggested a mixed pattern of results for the different outcomes reported with no clear advantage for one subgroup over the other.
Abbreviations: BSC: Best supportive care; HR: Hazard ratio; RCT: Randomised controlled trial		

From the evidence selected, what are the criteria used by the research studies to define iMCD?

Outcome	Evidence statement
Criteria to define iMCD	In the RCT by van Rhee et al (2014), the diagnosis of iMCD was based on: • A detailed patient history, physical examination, assessment of laboratory abnormalities, pathological diagnosis, and radiological imaging • A histologically confirmed diagnosis using pre-specified criteria[19] by a central pathology laboratory from an excisional lymph node biopsy sample Additional inclusion criteria for the RCT were that patients had measurable disease not limited to cutaneous lesions, grade I or greater disease symptoms according to the NCICTC for Adverse Events and an ECOG-PS score of 0 to 2. Patients were excluded if they were HIV-seropositive, had evidence of HHV8 infection or had other clinically significant infections including hepatitis B or C or had a history of concurrent lymphoma. In the retrospective cohort study by Yu et al (2017), the diagnosis of Castleman disease was based on clinical, laboratory and pathological findings. MCD was defined by the involvement of ≥2 lymph nodes in at least two separate regions. Patients with concomitant malignancies, HIV infection, HHV8 or POEMS syndrome were excluded.
Abbreviations: ECOG-PS: Eastern Cooperative Oncology Group Performance Status; HHV8: Human herpesvirus-8; HIV: Human immunodeficiency virus; iMCD: Idiopathic multicentric Castleman disease; NCICTC: National Cancer Institute Common Terminology Criteria; POEMS: Polyneuropathy, organomegaly, endocrinopathy, M-protein and skin pigmentation; RCT: randomised controlled trial	

From the evidence selected, what dosage (size/ frequency/ duration) of siltuximab was used?

Outcome	Evidence statement
Dosage of siltuximab	In the RCT by van Rhee et al (2014), the siltuximab dose was 11mg/kg as a single intravenous infusion every three weeks. Patients had to meet retreatment criteria[20] before each dose. Dose reductions were not permitted. Siltuximab patients

	discontinued study treatment at treatment failure[21]. The median (range) duration of masked treatment for siltuximab was 375 days (1 to 1,031). In the retrospective cohort study by Yu et al (2017), the siltuximab dose was 11mg/kg as a single intravenous infusion every three weeks or every six weeks at the investigator's discretion. Median duration of treatment not reported.
Abbreviations: kg: Kilograms; mg: Milligrams; RCT: randomised controlled trial	

Patient Impact Summary
The condition has the following impacts on the patient's everyday life: • **mobility:** patients with acute disease are often hospitalised for weeks to months at a time, with many being admitted to critical care. This can have profound impact on their mobility and physicality after a prolonged hospital stay. • **ability to provide self-care:** patients with severe forms of iMCD may become entirely dependent on others for all forms of personal care, including washing and dressing, due to fatigue and pain associated with the disease, as well as loss of muscle mass from prolonged hospital admissions. • **undertaking usual activities:** patients that have not achieved stable disease activity can have severe problems in carrying out their usual activities, including working, due to extreme fatigue and pain associated with the disease and immunosuppressive therapy. • **experience of pain/discomfort:** patients with iMCD can experience debilitating pain or discomfort including severe headaches, muscle and joint aches and severe levels of fatigue. • **experience of anxiety/depression:** patients with iMCD can be severely anxious or depressed. Given the rarity of the disease, a diagnosis comes with a lot of uncertainty about the course of the disease and constant worries and fears of relapses.
Further details of impact upon patients: The effects of active Castleman disease on patients can range from mild symptoms with minimal impact through to severe symptoms leading to significant problems in all the measures above requiring hospital admission for care. Most patients who require treatment will have moderate or severe impact on the above measures. Fatigue and pain are the most commonly reported symptoms, alongside lymph node enlargement, with fatigue being one of the most debilitating symptoms for patients to live with. A recent survey of patients with iMCD by Mukherjee et al found that most patients experienced a range of constitutional (82%), gastrointestinal, neuropsychiatric (68%), dermatologic, respiratory and haematological symptoms in the week prior to completing the survey. When rating

their most impacted aspects of daily life due to symptoms, majority reported pain and discomfort, as well as personal relationships and sexual functioning (www.EHA.org).

Many patients with iMCD have to give up work due to fatigue from the disease itself and from the immunosuppressant drugs they are on. Many patients reschedule their entire lives around their treatment schedule.

The disease follows a responding and relapsing pattern and living with the unpredictability of relapse, which can come at any time with any degree of severity, takes an understandable toll on people's mental health. This causes a lot of patients with iMCD to experience anxiety and depression alongside the symptoms of the disease (www.cdcn.org).

Further details of impact upon carers:

Those living with and caring for people with iMCD might be providing help with medication, hospital appointments, or emergency attendances and hospitalisations, and this requires a lot of organisation and time whilst trying to balance other responsibilities such as employment or childcare. Carers of people with severe iMCD often reduce their working hours or give up work to provide care.

The unpredictability of the disease relapsing can mean that planning life is challenging. There are often mixed emotions associated with this including guilt, bitterness and sadness. This affects carers' mental health and the relationship between carers and people living with iMCD. These challenges are only more substantial for carers of people with severe disease and limited treatment options, who live with more uncertainty and morbidity.

Considerations from review by Rare Disease Advisory Group
RDAG were supportive of the proposition.

Pharmaceutical considerations
The policy proposition supports the use of siltuximab as a treatment option in idiopathic multicentric castleman disease (iMCD) in line with its marketing authorisation. Post pubescent children will be able to access siltuximab under the Commissioning Medicines for Children Policy. Siltuximab is an excluded high cost drug.

Considerations from review by National Programme of Care
1) The proposal received the full support of the Cancer PoC on the 24 March 2023