NHS England Evidence Review:

Sirolimus (also known as Rapamycin) for patients with extracranial slow-flow vascular malformations refractory to standard therapies

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Prepared by Solutions for Public Health (SPH) on behalf of NHS England Specialised Commissioning

Contents

1. Introduction

This review examines the clinical effectiveness, safety and cost effectiveness of sirolimus compared with no sirolimus in people with extracranial slow-flow vascular malformations that are refractory to standard therapies.

Sirolimus (also known as rapamycin) is a drug available in topical and oral forms; this review is looking at oral sirolimus only. Sirolimus inhibits or blocks a protein known as the mammalian target of rapamycin (mTOR). This protein is involved in pathways which regulate several cell functions including growth, proliferation and metabolism. Sirolimus inhibits the mTOR pathway which is overactive in patients with certain slow-flow vascular malformations.

Slow-flow vascular malformations are inborn errors in the formation of blood vessels caused by genetic mutations. The types of blood vessels affected in slow-flow vascular malformations include veins, lymphatics and capillaries. Extracranial slow-flow vascular malformations have been estimated to affect about 1-1.5% of the population and although often present at birth can develop at any age.

Slow-flow vascular malformations can affect any organ system; this review focuses on patients with slow-flow vascular malformations outside skull / cranium. Patients with extracranial slow-flow vascular malformations may suffer with debilitating symptoms and complications including pain, swelling, ulceration, bleeding, blood clots, infection, disfiguration, organ failure, limb loss, and death. Patients with extracranial slow-flow vascular malformations also demonstrate significantly poorer quality-of-life and mental health when compared to the general population.

Treatment of symptomatic extracranial slow-flow vascular malformations is limited to supportive and medical measures (compression hosiery, pain control, antibiotics) and invasive procedures (excision or debulking surgery, sclerotherapy and cryotherapy). Invasive procedures are ineffective in managing severe symptoms and complications in a small subset of patients, particularly those with lesions that are large and diffuse or located within challenging anatomy or vital organs, major blood vessels and nerves.

For patients with extracranial slow-flow vascular malformations refractory to standard care there is no licenced treatment available.

The review scope included the identification of possible subgroups of patients within the included studies who might benefit from sirolimus more than the wider population of interest.

2. Executive summary of the review

This review examines the clinical effectiveness, safety and cost effectiveness of sirolimus compared with no sirolimus in people with extracranial slow-flow vascular malformations that are refractory to standard therapies. The searches for evidence published since January 2013 were conducted on 4 July 2023 and identified 462 references. These were screened using their titles and abstracts and 58 references potentially relating to the use of sirolimus in people with extracranial slow-flow vascular malformations were obtained in full text and assessed for relevance.

Five studies were identified and included in this review: one randomised trial; three open-label, single arm clinical trials; and one prospective case series. No comparator evidence was identified.

The randomised trial (Maruani et al 2021) was a single-arm clinical trial in which paediatric patients with extracranial slow-flow vascular malformations from 11 tertiary hospitals in France were randomised to their sirolimus start date. All patients had a four month observation period and were randomised to start sirolimus at month 4, 5, 6, 7 or 8 out of the 12 month trial period.

Three single arm, open-label phase II clinical trials reported non-comparator evidence. Adams et al (2016) included children and young adults with complicated extracranial vascular anomalies in two hospitals in the United States, Ji et al (2021) included only children with complicated extracranial vascular anomalies from five hospitals in China and Harbers, Zwerink et al (2023) recruited adults and children in the Netherlands. This latter study was the only one to specify a diagnosis of extracranial slow-flow vascular malformations that were also refractory to standard care.

One prospective case series (Tian et al 2020) recruited children with extracranial lymphatic malformations from a single hospital in China.

No cost effectiveness evidence was identified.

In terms of clinical effectiveness:

- **Disease response (critical outcome)**
  - One single-arm trial provided very low certainty evidence that following six months and 12 months of sirolimus treatment, a statistically significant higher proportion of patients were classed as having a partial disease response compared to progressive disease or stable disease. One randomised trial found very low certainty evidence of no statistically significant disease response following oral sirolimus treatment in children with extracranial slow-flow vascular malformations. Two single-arm trials provided very low certainty evidence that following six months and 24 months of sirolimus treatment, a higher proportion of patients were classed as having a disease response compared to those having no response; the data were not statistically compared. One prospective case series found very low certainty evidence that in children with extracranial lymphatic malformations, disease response was statistically significantly higher following 13 to 24 months of sirolimus treatment when compared to those that received one to six months of sirolimus treatment. All results were compared to baseline data.
- **Overall survival (critical outcome)**

- One single-arm trial provided very low certainty evidence of a low mortality rate in children with extracranial vascular malformations treated with sirolimus during three years of follow-up.

- **Symptom alleviation (critical outcome)**
  - One single-arm trial provided very low certainty evidence of a statistically significant improvement in pain scores for patients with extracranial slow-flow vascular malformations following sirolimus therapy. A randomised trial provided very low certainty evidence that pain and bleeding / oozing decreased for all children following sirolimus therapy; the before and after effects were not compared statistically. Finally, another single-arm trial provided very low certainty evidence of a statistically significant decrease in functional disability in children following 12 months of sirolimus treatment. All results were compared to baseline.
- **Radiographic changes (important outcome)**
  - One single-arm trial provided very low certainty evidence that following six months of sirolimus therapy a higher proportion of patients had no change to the volume of their extracranial vascular malformation on MRI measurements compared to either an increased or decreased volume; the data were not statistically compared. A second single-arm trial provided very low certainty evidence of no statistically significant change in the volume of the vascular malformation on MRI following six and 12 courses[1] of oral sirolimus treatment; following 12 courses of sirolimus treatment all patients had either no increase or a reduction in the volume of their vascular malformation (not statistically significant). A randomised trial provided very low certainty evidence of a small decrease in the volume of the extracranial vascular malformation following 12 months sirolimus treatment; the data were not statistically compared. All results were compared to baseline.
- **Organ specific disease response (important outcome)**
  - One single-arm trial provided very low certainty evidence that following six and 12 courses of sirolimus therapy, patients were statistically significantly more likely to report an organ response than no organ response. One randomised trial provided very low certainty evidence of a statistically significant improvement in skin and subcutaneous disease resolution using a physician, patient and parent visual analogue scale in children treated with sirolimus. All results were compared to baseline.
- **Quality of life (important outcome)**
  - One single-arm trial provided very low certainty evidence of a statistically significant increase in the quality of life scores for both children and adults following six months of oral sirolimus treatment. For adults, before sirolimus treatment, the quality of life scores for all domains except mental health were statistically significantly worse in the study population compared to the general Dutch population; whereas after six months of sirolimus treatment, the quality of life scores for the domains of social functioning, role limitations – emotional, mental health and energy levels/vitality were not statistically significantly different in the study population compared to the general Dutch population. One single-arm trial reported very low certainty evidence of an increase in quality of life scores following six and 12 courses of sirolimus treatment. One randomised trial and one single-arm trial provided very low certainty evidence of improvements in quality of life scores following sirolimus treatment at 12 months follow-up. All results were compared to baseline.

[1] A course of treatment was equal to 28 days. Courses were taken consecutively with no break, thus six courses represented 168 days; 12 courses 336 days / 48 weeks of sirolimus treatment.

- **Activities of daily living (important outcome)**
  - No evidence was identified for activities of daily living.

In terms of safety:

- **Adverse events**
  - All five included studies provide very low certainty evidence that many patients with extracranial slow-flow vascular malformations reported adverse events during sirolimus treatment; however, most were not severe. The most common adverse events reported across the included studies were infections, particularly respiratory, and mucositis.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness.

In terms of subgroups:

- One randomised trial reported subgroup results by slow-flow malformation type (venous, lymphatic and venolymphatic) for the critical outcomes, disease response and symptom alleviation, and for the important outcomes, radiographic changes, organ specific disease response and quality of life.
- One randomised trial reported outcomes for patients treated with sirolimus by extracranial slow-flow vascular malformation type: venous malformations, lymphatic malformations and venolymphatic malformations; all results were compared to baseline. The authors reported a statistically significant decrease in the volume of the lymphatic malformations following sirolimus treatment but no statistically significant effect of sirolimus on venous or venolymphatic malformations. Pain symptoms were alleviated across all three malformation types, though the score decreases were most pronounced in those with lymphatic malformations. Bleeding and oozing were decreased in those with lymphatic and venolymphatic malformations and slightly increased in those with venous malformations. MRI changes were noted for each of the malformation types following sirolimus treatment; increasing volume for venous malformations and decreasing volume for lymphatic and venolymphatic malformations. Quality of life and skin disease activity were reported to improve across all disease malformation types.
- One single-arm trial reported subgroup results by age group (children and adults) for the critical outcomes, disease response and symptom alleviation, and the important outcomes, radiographic changes, organ specific disease response, quality of life and safety.
- One single-arm trial reported outcomes for patients with extracranial slow-flow vascular malformations treated with six months of sirolimus by age group: children and adults; all results were compared to baseline. The authors reported a better disease response in children compared with adults; however, the groups were not statistically compared. Pain symptoms were statistically significantly lower for adults following sirolimus treatment, but no statistically significant difference was seen for children. Symptoms other than pain were alleviated for both children and adults, though the decreases were most pronounced in children. The changes were not statistically compared. The majority of both children and adults had either no change in the volume or a decreasing volume of their extracranial slow-flow vascular malformations on MRI; no statistical analysis was

performed. Liver function and quality of life were both reported to improve for children and adults. More adverse events were reported in the adult population but there were fewer severe adverse events in this population.

In terms of sirolimus dose:

- Evidence about sirolimus doses came from one randomised trial, three single-arm trials and one prospective case series.
- One randomised trial, three single-arm trials and one prospective case series started every paediatric patient with vascular malformations on an initial sirolimus dose of 0.8 mg/m^2, twice daily. Dose adjustments were made until the desired plasma levels were reached; in two single-arm trials and the prospective case series this was between 10 and 15 ng/mL, in one randomised trial it was between 4 and 10 ng/mL, and in one single-arm trial it was between 4 and 12 ng/mL. One single-arm trial started adults on a twice daily 0.8 mg/m^2 sirolimus dose and increased until plasma concentrations reached 10 to 15 ng/mL, whilst another single-arm trial began all >18 years on a 1 mg sirolimus dose, twice daily, with increases until plasma concentrations reached between 4 and 10 ng/mL.

Please see the results table (section 5) in the review for further details of outcomes and definitions

Limitations

All of the outcomes reported were classed as very low certainty evidence and results were compared only with baseline data for the patients. Two of the included studies (Maruani et al 2021 and Ji et al 2021) reported the outcomes as intention-to-treat; the other included studies presented observed results only which increases selection bias and Type I errors.

Limitations reducing certainty for the outcomes in the single-arm trials (Adams et al 2016 and Ji et al 2021) and the prospective case series (Tian et al 2020) included uncertainty about whether the inclusion of participants was complete or consecutive and uncertainty about the direct relevance of the population selected, particularly uncertainty if the included participants were all refractory to standard care. Some single-arm trials and the prospective case series did not present statistical analyses or summary statistics for some or all outcomes; a lack of comparator was also a limitation across all three of the single-arm trials and the prospective case series.

Limitations due to the lack of comparator, lack of blinding and potential residual confounding due to lack of adjustment for the stepped-wedge study design reduced certainty for the randomised trial (Maruani et al 2021).

Conclusion

This evidence review includes three single arm clinical trials, one randomised trial and one prospective case series. The single-arm trials were analysed as case series due to the lack of comparator. Two studies included children and adults (single-arm trials); the remaining three included paediatric patients only. One study only included children with lymphatic malformations (prospective case series).

All of the studies provided non-comparator data and the evidence for all the outcomes of interest was of very low certainty.

All of the included studies provided evidence for sirolimus use in children with extra-cranial, slow-flow vascular malformations for all the critical outcomes of interest. There was evidence of a partial response following sirolimus treatment in children and adults; this finding was statistically significant in some studies. There was evidence of a low mortality rate in children treated with sirolimus; there was no evidence of statistical significance and no data for populations >18 years. There was evidence that adults had a statistically significant improvement in their pain scores and children had an improvement in their functional disability following sirolimus treatment. There was also evidence of no statistically significant improvement in children's pain scores following sirolimus treatment.

Data were available for the important outcomes of radiographic changes, organ specific disease response, quality of life and safety. There was evidence of no statistically significant difference in the volume of the vascular malformation on MRI following sirolimus treatment for both children and adults; this may be an indication of clinically significant stable disease. There was evidence of statistically significantly improved organ specific disease function in those receiving sirolimus therapy; both adults and children reported a statistically significant improvement in organ response and children, their physicians and parents reported a statistically significant improvement on the skin Visual Analogue Score (VAS scale). Single-arm trials and prospective case series data provided evidence of a statistically significant improvement in quality of life for both children and adults.

Safety outcomes, in the form of adverse events, were reported for those receiving sirolimus therapy. Adverse events were common in both adults and children; however, most were not severe. The most common adverse events reported across all the studies were infection related.

There was very low certainty evidence of a difference in sirolimus response in children with extracranial lymphatic malformations compared with children with extracranial venous malformations. When examined separately in one randomised trial, children with extracranial venous malformations had no statistically significant response to sirolimus when compared to baseline, whilst those with extracranial lymphatic malformations had a statistically significant improvement in disease state across several domains. One single-arm trial provided very low certainty evidence of a better disease response in children when compared to adults. Despite children having a better disease response, adults had statistically significantly lower pain scores following sirolimus treatment whereas children's pain scores did not show a statistically significant improvement. These subgroup results should be interpreted with caution as the subgroups were very small; however, they did reach statistical significance.

No evidence on cost effectiveness was identified.

Although all the studies provided very low certainty evidence of the outcomes, there was congruence in the results reported. The studies identified in this review provide evidence, for a range of pre-specified critical and important outcomes, suggesting that sirolimus may be an effective treatment for children and adults with extracranial slow-flow vascular malformations that are refractory to standard therapies.

3. Methodology

Review questions

The review question(s) for this evidence review are:

1. In people with extracranial slow-flow vascular malformations that are refractory to standard therapies, what is the clinical effectiveness of sirolimus compared with no sirolimus?
2. In people with extracranial slow-flow vascular malformations that are refractory to standard therapies, what is the safety of sirolimus compared with no sirolimus?
3. In people with extracranial slow-flow vascular malformations that are refractory to standard therapies, what is the cost effectiveness of sirolimus compared with no sirolimus?
4. From the evidence selected, are there any subgroups of patients that may benefit from sirolimus more than the wider population of interest?
5. From the evidence selected what were the ongoing schedules/doses used for sirolimus?

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 4 July 2023.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text of potentially relevant studies were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE profiles.

4. Summary of included studies

Five studies were identified and included in this review: three single-arm clinical trials (Adams et al 2016; Harbers, Zwerink et al 2023; Harbers, Bouwman et al 2023 & Ji et al 2021), one randomised trial (Maruani et al 2021)[2] and one prospective case series (Tian et al 2020). Two studies included children and adults, whilst three studies focused on paediatric patients. No comparator evidence was identified.

Table 1 provides a summary of the included studies and full details are given in Appendix E.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported

Adams et al 2016
 	
Single-arm trial
 	
US
	n=61
	
	Children and young adults with complicated vascular anomalies and at least one complication
	
	No subgroups reported
		Intervention
		
		Oral sirolimus
		
		Comparison
		
		No comparator
			Treatment duration: 12 courses; course equivalent to 28 days[3]
			
			Critical outcome
			
			• Disease response
			  • Overall response at course six and 12
			  • Efficacy by 2014 ISSVA classification at course six and 12
			
			Important Outcomes
			
			• Radiographic changes at course six and 12
			• Organ specific disease response at course six and 12
			• Quality of life at course six and 12
			• Safety
			  • Adverse events
			  • Grade 2 or higher AEs attributability to sirolimus
			  • Grade 3 or 4 AE

Harbers, Zwerink et al 2023
 	
Harbers, Bouwman et al 2023 reports detailed QoL results
 	
Single-arm trial
 	
The Netherlands
	n=74
	
	Children and adults with a diagnosis of a slow-flow vascular malformation that was refractory to standard care
	
	Subgroups
	
	• age group: children and adults
		Intervention
		
		Oral sirolimus
		
		Comparison
		
		No comparator
			Results are following the challenge phase of the trial (six months of sirolimus therapy)
			
			Critical outcome
			
			• Disease response at six months
			  • Overall response
			  • Responder / non-responder
			• Symptom alleviation
			  • Change in pain symptoms
			  • Pain score
			  • Change of symptoms to the vascular malformation (excluding pain)

[2] This was a single-arm clinical trial in which patients were randomised to their sirolimus start date. All patients had a 4 month observation period and were randomised to start sirolimus at month 4, 5, 6, 7 or 8 out of the 12 month trial period.
[3] A course of treatment was equal to 28 days. Courses were taken consecutively with no break, thus six courses represented 168 days; 12 courses 336 days / 48 weeks.

Study	Population	Intervention and comparison	Outcomes reported

			Important Outcomes
			• Radiographic changes at six months
			  • Change in size of the vascular malformation (2D MRI)
			• Organ specific disease response at six months
			  • Hepatic (live) disease activity: D-dimer level
			• Quality of Life at baseline and six months
			  • Change in HRQoL
			  • Magnitude of HRQoL change
			  • Comparison of HRQoL to Dutch population
			• Safety at six months
			  • Adverse events
			  • Specific AEs by grade and attributable to sirolimus
			  • Grade 3 or 4 AEs

Ji et al 2021
Single-arm trial
China
	n=126
	Children with complicated vascular anomalies and at least one complication
	No subgroups reported
		Intervention
		Oral sirolimus
		Comparison
		No comparator
			All the patients received ≥12 months of treatment. The mean length of follow-up was 3.0 years (range 0.4 to 4.5 years).
			Critical outcome
			• Disease response at six and 12 months
			  • Overall response
			  • Total responses / no response
			  • Total responses by VA diagnosis
			• Overall survival at 12 months
			• Symptom alleviation
			  • Mean severity score at baseline, six and 12 months
			  • Improvement in severity score by VA diagnosis at 12 months
			Important Outcomes
			• Radiographic changes
			  • see disease response (six and 12 months)
			• Quality of Life at baseline and 12 months
			  • Change in HRQoL
			  • Improvement in HRQoL by VA diagnosis

Study	Population	Intervention and comparison	Outcomes reported

			• Safety at 12 months
			  • Adverse events
			  • Specific AEs by grade, possibly related to sirolimus

Maruani et al 2021
 	
Randomised trial
 	
France
	n=63
	
	Children with slow-flow vascular malformation
	
	Subgroups
	
	• type of vascular malformation: venous malformation (VM), lymphatic malformation (LM), combined malformations (combined)
		Intervention
		
		Oral sirolimus
		
		Comparison
		
		No comparator
		
		[Patients acted as their own comparator and were randomised to length of observation period. All patients had a 4 month observation period and were randomised to start sirolimus at month 4, 5, 6, 7 or 8.]
			All the patients were followed for 12 months; 59 patients were included in the analysis.
			
			Critical outcome
			
			• Disease response at baseline and 12 months
			  • Difference in malformation on MRI volume
			  • Difference in malformation volume on MRI by type of malformation
			• Symptom alleviation at baseline, transition to sirolimus and 12 months
			  • Pain
			  • Pain by type of malformation
			  • Oozing and bleeding
			  • Oozing and bleeding by type of malformation
			
			Important Outcomes
			
			• Radiographic changes at baseline, transition to sirolimus and 12 months
			  • volume of vascular malformations
			  • volume of vascular malformations by type of malformation
			• Organ specific disease response at one month after sirolimus introduction, three months after sirolimus and 12 months
			  • skin and subcutaneous disease activity: global assessment of efficacy by physician, patient and parent
			  • skin and subcutaneous disease activity: global assessment of efficacy by physician, patient and parent by type of malformation
			• Quality of Life at baseline, introduction of sirolimus and 12 months

Study	Population	Intervention and comparison	Outcomes reported

			• Proportion of children with a HRQoL score indicating malformation has “no effect on their life”
			• Proportion of children with a HRQoL score indicating malformation has “no effect on their life” by type of malformation
			• Safety at 12 months
			  • Nonserious AEs
			  • AEs possibly related to sirolimus
			  • AEs probably related to sirolimus

Tian et al 2020
 	
Prospective case series
 	
China
	n=56
	
	Children with complex lymphatic malformations treated with sirolimus
	
	No subgroups reported
		Intervention
		
		Oral sirolimus
		
		Comparison
		
		No comparator
			Patients were divided into three groups based on treatment length: Group 1 = 1-6 months (n=15); Group 2 = 7-12 months (16); Groups 3 = 13-24 months (n=25).
			
			Critical outcome
			
			• Disease response at 24 months
			  • Overall response
			  • Effective/ineffective responses by treatment group
			
			Important Outcomes
			
			• Safety at 24 months
			  • Adverse events
			  • Specific AEs by grade

Abbreviations
2D: two dimensional; AE: adverse event; HRQoL: health related quality of life; ISSVA: International Society for the Study of Vascular Anomalies; LM: lymphatic malformation; MRI: magnetic resonance imaging; n: number; QoL: quality of life; US: United States; VA: vascular anomalies; VM: venous malformation

a. International Society for the Study of Vascular Anomalies (ISSVA) Classification: earliest version developed in Rome in 1996. Ji et al used the 2018 revised classification.

5. Results

In people with extracranial slow-flow vascular malformations that are refractory to standard therapies, what is the clinical effectiveness and safety of sirolimus compared with no sirolimus?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Disease response **Certainty of evidence:** Very low	This outcome is important to patients because it can reflect the benefits the treatment may have for a patient. This can be important to control the symptomatic burden of the disease and/or reflect subgroups who may configure additional response benefits, allowing the treatment protocol to be individualised. In total, one randomised trial, three single-arm trials and one prospective case series provided evidence relating to disease response in patients with extracranial slow-flow vascular malformations. Overall response was measured using a composite measure and presented as complete response (CR), [good response (GR)][4], partial response (PR), stable disease (SD) and progressive disease (PD). Treatment efficacy was indicated by a CR/GR/PR. The outcomes used to create this composite measure varied between studies. All results were compared to baseline. At six months: • One single-arm trial (Adams et al 2016, n=57) reported disease response following six courses[5] of treatment (168 days). No patients had a complete disease response, but 47 patients (83%, 95%CI 70% to 95%) reported a partial response to sirolimus treatment.[6] This result was *statistically significant*, demonstrating a benefit of sirolimus treatment. **(VERY LOW)** • One single-arm trial (Harbers, Zwerink et al 2023, n=67) reported that 79.1% of patients had a response to sirolimus (n=53) at six months[7]. No patients were categorised as having a complete response and no statistical comparisons were reported. **(VERY LOW)** • One single-arm trial (Ji et al 2021, n=126) reported that 72.2% of patients had a response to sirolimus (n=91).[8] No patients were reported to have a complete response; 4.0% had a good response and 68.3% had a partial response. No statistical comparisons were reported. **(VERY LOW)** At 12 months: • One single-arm trial (Adams et al 2016, n=57) reported disease response following 12 courses[9] of treatment (336 days). No patients had a complete response, but 45 patients (85%, 95%CI 73% to 97%) had a partial response to sirolimus treatment. This result was *statistically significant*, demonstrating a benefit of sirolimus treatment. **(VERY LOW)**

[4] not presented in all studies
[5] A course of treatment was equal to 28 days. Courses were taken consecutively with no break, thus six courses represented 168 days; 12 courses 336 days / 48 weeks.
[6] This composite measure was established by noting changes in at least 1 parameter: response by radiologic imaging, health quality-of-life questionnaire [Pediatric Quality of Live Inventory 4.0 (3-18 years) and Infant Scales (≤2 years) or the Functional Assessment of Chronic Illness System (>18 years)] or using defined clinical criteria in a functional impairment score (measures of organ function).
[7] The composite measure was established by noting a change in at least 1 parameter: response to pain symptoms, health related quality of life (Paediatric Quality of Life Inventory / SF-36 / Physical Component Summary), clinical symptoms related to the vascular malformation – excluding pain, response to imaging (MRI)
[8] The response measure was based solely on changes in the volumetric measurements of VA lesions on MRI. CR = complete resolution of measured VAs at 12 months; GR = decrease of ≥75% but <100%; PR = decrease of ≥20% but <75%; SD = Increase of <20% but decrease of <20% in volumes of VA lesions; PD = Increase of ≥20% in volume of index LMs compared with baseline volume
[9] A course of treatment was equal to 28 days. Courses were taken consecutively with no break, thus six courses represented 168 days; 12 courses 336 days / 48 weeks of sirolimus treatment.

Outcome	Evidence statement
	• One randomised trial (Maruani et al 2021, n=59) reported *no statistically significant change* in the volume of the vascular malformation following sirolimus treatment (-0.002mm^3; 95%CI -0.004mm^3 to 0.001mm^3; p=0.24) in children with complex slow-flow vascular malformations.[10] **(VERY LOW)** At 24 months: • One single-arm trial (Ji et al 2021, n=126) reported that 78.6% of patients had a response to sirolimus treatment (n=99). No patients had a complete response but 22.2% had a good response and 56.3% a partial response to sirolimus treatment. No statistical comparisons were reported. **(VERY LOW)** • One prospective case series (Tian et al 2020, n=56) reported that 30 children with lymphatic malformations had a complete or partial response to sirolimus therapy (n=2 CR; n=28 PR; 89%)[11]. Disease response was higher in those that had longer courses of sirolimus therapy; 1 to 6 months of sirolimus: 73.3% complete or partial response, 7 to 12 months: 93.8% complete or partial response, 13 to 24 months: 96% complete or partial response. These results were statistically significant when compared to those with stable disease or progressive disease. **(VERY LOW)** **One single-arm trial provided very low certainty evidence that following six months and 12 months of sirolimus treatment, a statistically significant higher proportion of patients were classed as having a partial disease response compared to progressive disease or stable disease. One randomised trial found very low certainty evidence of no statistically significant disease response following oral sirolimus treatment in children with extracranial slow-flow vascular malformations. Two single-arm trials provided very low certainty evidence that following six months and 24 months of sirolimus treatment, a higher proportion of patients were classed as having a disease response compared to those having no response; the data were not statistically compared. One prospective case series found very low certainty evidence that in children with extracranial lymphatic malformations, disease response was statistically significantly higher following 13 to 24 months of sirolimus treatment when compared to those that received one to six months of sirolimus treatment. All results were compared to baseline data.**
Overall survival **Certainty of evidence:** Very low	Overall survival is important to patients as individuals with extracranial slow-flow vascular malformations which have failed standard therapy as it can have life-threatening complications. Improved survival is an important marker of effective treatment. One single-arm trial provided narrative evidence relating to overall survival in children with extracranial slow-flow vascular malformations. Narrative data was provided from one paediatric single-arm trial. • One single-arm trial (Ji et al 2021, n=126) reported that two children died due to disease progression during follow-up (mean length of follow-up 3.0 years; range 0.4 to 4.5 years). **(VERY LOW)** **One single-arm trial provided very low certainty evidence of a low mortality rate in children with extracranial vascular malformations treated with sirolimus during three years of follow-up.**
Symptom alleviation	This outcome 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

[10] difference in the volume of the vascular malformation between the observational period and the interventional period

[11] The composite measure was determined based on changes in the volumetric measurements of VA lesions on MRI, clinical changes in the lesion and/or changes in symptoms. CR = complete disappearance of either the lesion (clinical and/or radiological), and the symptoms; PR = reduction of >20% in size of the lesion (clinical and/or radiological) and improvement in symptoms; PD = enlargement of >20% in size of the lesion (clinical and/or radiological) or as new lesions appearing; SD = none of the above

Outcome	Evidence statement
Certainty of evidence: Very low	effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment. In total, one randomised trial and two single-arm trials provided evidence relating to symptom alleviation in patients with extracranial slow-flow vascular malformations. All results were compared to baseline. At six months: • One single-arm trial (Harbers, Zwerink et al 2023, n=67) reported that 37 (55.2%) patients had an improvement in their pain scores following six months of sirolimus therapy[12]. Following treatment with sirolimus, pain scores were *statistically significantly decreased* by a mean score of -1.8 (95%CI -2.8 to -0.8; p<0.001). **(VERY LOW)** At 12 months: • One single-arm trial (Ji et al 2021, n=126) reported a *statistically significant decrease* in functional disability[13] following six months (baseline: 2.6, six months: 2.0; p<0.001) and 12 months (six months: 2.0, 12 months: 1.3; p<0.001) of sirolimus treatment. **(VERY LOW)** • One randomised trial (Maruani et al 2021, n=59) reported that pain[14] decreased for all children following sirolimus treatment (mean±SD – start of sirolimus treatment: 3.49±3.23 to end of trial: 1.76±2.29). No statistical comparisons were reported. **(VERY LOW)** • The same trial (Maruani et al 2021, n=59) also reported a decrease in the overall number of children oozing or bleeding from their malformations following sirolimus therapy (start of sirolimus therapy: 33.9%, 12 months: 13.6%). No statistical comparisons were reported. **(VERY LOW)** **One single-arm trial provided very low certainty evidence of a statistically significant improvement in pain scores for patients with extracranial slow-flow vascular malformations following sirolimus therapy. A randomised trial provided very low certainty evidence that pain and bleeding / oozing decreased for all children following sirolimus therapy; the before and after effects were not compared statistically. Finally, another single-arm trial provided very low certainty evidence of a statistically significant decrease in functional disability in children following 12 months of sirolimus treatment. All results were compared to baseline.**
Important outcomes	
Radiographic changes **Certainty of evidence:** **Very low**	Changes to the appearance of scans or the location of malformations are important to patients as they are used to help determine treatment success and requirement for further treatment. Imaging results might not be expected to return to normal, however, stabilisation may indicate treatment has successfully limited disease progression and may be associated with improvement in clinical features. One randomised trial and two single-arm trials provided evidence relating to radiographic changes in patients with extracranial slow-flow vascular malformations. All results were compared to baseline. At six months: • One single-arm trial (Harbers, Zwerink et al 2023, n=62) reported that 39 (62.9%) patients had no change in the volume, 22 (35.5%) had decreased volume and one patient (1.6%) had an increased volume in their extracranial vascular anomaly following six months of sirolimus therapy. The differences were not statistically compared. **(VERY LOW)**

[12] Pain was recorded using the Children and Infants Postoperative Pain Scale for children aged 0–3 years, visual analogue scale (VAS) clinical pictures for children aged 4–7 years, VAS for patients aged 8–17 years and numeric pain rating scale (NRS) for adults

[13] Disease severity was recorded using a scale of 0 to 5 with higher values representing more profound symptoms and/or functional disability

[14] Pain was self-assessed using a visual analogue scale 0 – 10, where 0 means no pain and 10 signifies the worst pain imaginable

Outcome	Evidence statement
	• One single-arm trial (Adams et al 2016, n=57) reported that following six courses of sirolimus treatment (168 days) there was *no statistically significant* MRI response to treatment; 20 (35%) children and adults had partial response on MRI (95%CI 20% to 51%) and 36 (63%) reported stable disease (95%CI 47% to 79%). **(VERY LOW)** At 12 months: • One single-arm trial (Adams et al 2016, n=53) reported that following 12 courses of sirolimus treatment (336 days) there continued to be *no statistically significant difference* in the MRI response to treatment; 28 (52%) of children and adults had partial response on MRI (95%CI 36% to 69%) and 25 (48%) reported stable disease (95%CI 31% to 64%). No patients reported complete resolution or disease progression at this timepoint **(VERY LOW)** • One randomised trial (Maruani et al 2021, n=59) reported a small decrease in the median volume of the extracranial vascular malformation following sirolimus treatment (start of sirolimus treatment: 158mm^3 (IQR 48 to 510); end of trial: 151mm^3 (IQR 31 to 420)). No statistical comparisons were reported. **(VERY LOW)** **One single-arm trial provided very low certainty evidence that following six months of sirolimus therapy a higher proportion of patients had no change to the volume of their extracranial vascular malformation on MRI measurements compared to either an increased or decreased volume; the data were not statistically compared. A second single-arm trial provided very low certainty evidence of no statistically significant change in the volume of the vascular malformation on MRI following six and 12 courses of oral sirolimus treatment; following 12 courses of sirolimus treatment all patients had either no increase or a reduction in the volume of their vascular malformation (not statistically significant). A randomised trial provided very low certainty evidence of a small decrease in the volume of the extracranial vascular malformation following 12 months sirolimus treatment; the data were not statistically compared. All results were compared to baseline.**
Organ specific disease response **Certainty of evidence:** **Very low**	This outcome is important to patients as objective measures of functioning of affected organs. Disease activity results might not be expected to return to normal following treatment; however, stabilisation may indicate treatment has successfully limited disease progression. In total, one randomised trial and one single-arm trial provided evidence relating to organ specific disease response in patients with extracranial slow-flow vascular malformations. All results were compared to baseline. *Functional impairment score*[15] • One single-arm trial (Adams et al 2016, n=57) piloted a new functional impairment score which measured improvements in target organ dysfunction using previously validated instruments. The authors reported that adults and children were *statistically significantly more likely* to report an organ response than no organ response following both six courses and 12 courses of sirolimus therapy (n (%, 95%CI)), at six months: PR 40 (71%, 95%CI 56% to 85%); SD: 17 (29%, 95%CI 15% to 44%); at 12 months: PR 42 (80%, 95%CI 67% to 94%); SD n=11 (16%, 95%CI 4% to 28%).[16] **(VERY LOW)**

[15] The functional impairment score was adopted from the measures of organ function that have been validated in the quantification of adverse event results from medical therapies and procedures. The instrument was piloted in the present study. Changes were defined as - CR: no evidence of organ dysfunction due to disease; PR: improvement in target organ dysfunction by at least 1 grade; PD: worsening in target organ dysfunction by at least 1 grade; SD: no change in target organ dysfunction

[16] Each sirolimus course lasted 28 days.

Outcome	Evidence statement
	Skin and subcutaneous disease activity: Global assessment by physician, patient and parent • One randomised trial (Maruani et al 2021, n=59) used the global assessment of efficacy[17] as a marker of skin disease activity. Skin malformations were assessed using the VAS scale by physician, patient and parent at one month following sirolimus initiation, three months post-sirolimus initiation and at the final 12 month visit (visit three to visit 12 months, physician assessment: 2.64±2.56 to 4.85±2.58; patient assessment: 4.04±3.52 to 5.95±3.18; parent assessment: 3.24±2.81 to 5.32±2.77. All assessors found a *statistically significant increase* in skin and subcutaneous disease resolution following the introduction of sirolimus (p<0.001). **(VERY LOW)** **One single-arm trial provided very low certainty evidence that following six and 12 courses of sirolimus therapy, patients were statistically significantly more likely to report an organ response than no organ response. One randomised trial provided very low certainty evidence of a statistically significant improvement in skin and subcutaneous disease resolution using a physician, patient and parent visual analogue scale in children treated with sirolimus. All results were compared to baseline.**
Quality of life **Certainty of evidence:** **Very low**	Quality of life is important to patients as it provides an indication of an individual's general health, their self-perceived well-being and their ability to participate in activities of daily living. Measurement of quality of life can help inform patient-centred decision making. One randomised trial and three single-arm trials provided evidence relating to quality of life in patients with extracranial slow-flow vascular malformations. All results were compared to baseline. At six months: • One single-arm trial (Harbers, Zwerink et al 2023, n=44) reported that 65.9% (n=29) patients had an improved quality of life following six months of sirolimus therapy. No statistical comparisons were reported. **(VERY LOW)** • One single arm trial (Harbers, Bouwman et al 2023, n=44) reported participants' health related quality of life[18] before and after six months of sirolimus treatment. The HRQoL scores in the trial were compared to that of the general Dutch population, For adults, the authors reported that the quality of life scores for all domains except mental health were statistically significantly worse in patients with an extracranial slow-flow vascular malformation compared to the general Dutch population, whereas after six months of sirolimus treatment, there was no statistically significant difference in the quality of life scores between adults with an extracranial slow-flow vascular malformation diagnosis and the general Dutch population in the domains of social functioning, role limitations – emotional, mental health and energy levels/vitality. For the domains of physical functioning, role limitations – physical, pain and general health perception the study population continued to have *statistically significantly worse* HRQoL scores than the general Dutch population. **(VERY LOW)** • One single-arm trial (Adams et al 2016, n=57) reported that following six courses of sirolimus treatment (168 days) there was an increase in quality of life of the children and adults included in the trial;[19] 18 (32%) children

[17] Score was assessed using a visual analogue scale at each visit (0=no efficacy; 10=complete resolution) by the physician, parent and patient.
[18] HRQoL was assessed by Research and Development-36 (SF-36) for adults, the parents' version of the Paediatric Quality of Life Inventory 4.0 Generic Core Scales for the parents of children aged 2–17 years and the children's PedsQL version for children aged 5–17 years. For all HRQoL measures a higher score indicates a better QoL.
[19] Quality-of-Life (QoL) changes were measured as CR: normalisation of QoL criteria; PR: improvement of self-report PedsQL by >4.4 or proxy-report PedsQL by >4.5 or FACT-G by >3.99 compared with baseline; PD:

Outcome	Evidence statement
	and adults had complete response (95%CI 17% to 47%), 30 (52%) had a partial response (95%CI 36% to 68%) and nine (16%) reported stable disease (95%CI 4% to 28%). No statistical comparisons were reported. **(VERY LOW)** At 12 months: • One single-arm trial (Adams et al 2016, n=53) reported that following 12 courses of sirolimus treatment (366 days) there was an increase in quality of life of the children and adults included in the trial; 21 (39%) children and adults had complete response (95%CI 22% to 55%), 26 (50%) had a partial response (95%CI 34% to 67%), five (9%) reported stable disease (95%CI 0% to 19%) and one patient (2%) reported progressive disease (95%CIs not reported). No statistical comparisons were reported. **(VERY LOW)** • One single-arm trial (Ji et al 2021, n=126) reported that the majority of children (n=100, 79.4%) had an improvement in their quality of life scores from baseline following 12 months of sirolimus treatment; 18 children reported a worsening in their HRQoL from baseline (14.3%). No statistical comparisons were reported. **(VERY LOW)** • One randomised trial (Maruani et al 2021, n=59) reported that the number of children reporting that their vascular malformation had "no effect on their life" increased from 16 patients (27.1%) at start of sirolimus treatment to 32 (54.2%) following sirolimus treatment. No statistical comparisons were reported. **(VERY LOW)** **One single-arm trial provided very low certainty evidence of a statistically significant increase in the quality of life scores for both children and adults following six months of oral sirolimus treatment. For adults, before sirolimus treatment, the quality of life scores for all domains except mental health were statistically significantly worse in the study population compared to the general Dutch population; whereas after six months of sirolimus treatment, the quality of life scores for the domains of social functioning, role limitations – emotional, mental health and energy levels/vitality were not statistically significantly different in the study population compared to the general Dutch population. One single-arm trial reported very low certainty evidence of an increase in quality of life scores following six and 12 courses of sirolimus treatment. One randomised trial and one single-arm trial provided very low certainty evidence of improvements in quality of life scores following sirolimus treatment at 12 months follow-up. All results were compared to baseline.**
Activities of daily living (ADLs) **Certainty of evidence:** **N/A**	ADLs are important outcomes to patients as they facilitate enablement and independence, allowing individuals to function in education, work, home, and recreational settings. They encompass patients' individual needs and facilitate inclusion and participation. The complications of slow-flow vascular malformations can lead to progressively worsening physical symptoms and altered ability to complete ADLs without assistance. **No evidence was identified for activities of daily living.**
Safety	
Adverse events **Certainty of evidence:** Very low	Safety of sirolimus is important to patients as it allows comparison of interventional approaches. One randomised trial, three single-arm trials and one prospective case series provided evidence relating to adverse events in patients with extracranial slow-flow vascular malformations. *Number of adverse events (AEs)*

worsening of self-report PedsQL by >4.4 or proxy-report PedsQL by >4.5 or FACT-G by >3.99 compared with baseline; SD: ≤4.4 change in self-report of PedsQL or ≤4.5 change in proxy-report PedsQL or ≤3.99 change in FACT-G compared with baseline

Outcome	Evidence statement
	• One single-arm trial (Harbers, Zwerink et al 2023) reported a total of 276 adverse events in 67 patients over a six month period; seven AEs were categorised as serious AEs of which three were deemed attributable to sirolimus. **(VERY LOW)** • One single-arm trial (Adams et al 2016) reported two AEs leading to a sirolimus dose reduction and two AEs leading to drug discontinuation out of 60 patients. **(VERY LOW)** • One single-arm trial (Ji et al 2021) reported a total of 290 AEs in 126 patients during 12 months of sirolimus treatment. Patients were reported to have 23 Grade 3 AEs and 4 Grade 4 AEs. Twelve adverse events led to temporary sirolimus discontinuation, and seven AEs led to a reduction in the target serum level. **(VERY LOW)** • One randomised trial (Maruani et al 2021) reported 43 of 59 patients experiencing one of 101 nonserious adverse events possibly related to sirolimus (73%). Patients experiencing nonserious adverse events had a median age of 14 (IQR 11 to 17). The authors reported 5 of 59 patients experienced a serious AE possibly related to sirolimus (5%; 5 events; median age 15, IQR 10 to 19). The authors further reported AEs probably related to sirolimus, including 35 patients reporting 89 nonserious AE events with no serious AEs (median age 12, IQR 8 to 14). **(VERY LOW)** • One prospective case series (Tian et al 2020) reported a total of 37 AEs in their cohort of 56 children, three of which were serious AEs. **(VERY LOW)** *Specific AEs* • One single-arm trial (Harbers, Zwerink et al 2023, n=67) reported the most common AEs possibly, probably or definitely related to sirolimus were infection (n=13), neurologic toxicity (n=11), gastrointestinal toxicity (n=10), general symptoms (n=7) and metabolic toxicity (n=10). One Grade 4 AE was noted, Infection, and rated as being “possibly” related to sirolimus treatment. **(VERY LOW)** • One single-arm trial (Adams et al 2016, n=60) reported the most common AEs to be blood/bone marrow (n=30), gastrointestinal (n=33), metabolic/laboratory (n=12) and pain (n=11). Grade 3/4 AEs were most likely to be blood/bone marrow (n=30), gastrointestinal (n=10), infection (n=22), metabolic/laboratory (n=11) and pulmonary/upper respiratory (n=7). **(VERY LOW)** • One single-arm trial (Ji et al 2021, n=126) reported the most common AEs to be mucositis (n=47), upper respiratory infection (n=33), nausea/vomiting (n=27), increased liver enzyme levels(n=25) and thrombocytosis (n=25). Grade 3/4 AEs were most likely to be upper respiratory infections (n=8) and increased liver enzyme levels (n=6). **(VERY LOW)** • One prospective case series (Tian et al 2020, n=56) reported the most common AEs in their paediatric population with lymphatic malformations to be oral mucositis (n=17), upper respiratory infection (n=6), pneumonia (n=4), cystic haemorrhage (n=4) and rash (n=3). Severe AEs were reported for oral mucositis (n=1) and pneumonia (n=2); the two children with pneumonia were treated in ITU and required temporary sirolimus discontinuation. **(VERY LOW)** **All five included studies provide very low certainty evidence that many patients with extracranial slow-flow vascular malformations reported adverse events during sirolimus treatment; however, most were not severe. The most common adverse events reported across the included studies were infections, particularly respiratory, and mucositis.**

Abbreviations
AE: adverse event; C-DLQI: Children-Dermatological Life Quality Index; CI: confidence interval; CR: complete response; FACT-G: Functional Assessment of Cancer Therapy – General; GR: good response; HRQoL: health related quality of life; IQR: interquartile range; ISSVA: International Society for the Study of Vascular Anomalies; ITU: intensive therapy unit; LM: lymphatic malformation; MCS: mental component summary; mL: millilitres; MRI: magnetic resonance imaging; n: number; ng: nanograms; NRS: numeric rating scale; PCS: physical component summary; PD: progressive disease; PedsQL: Paediatric Quality of Life Inventory; PR: partial response; QoL:

Outcome	Evidence statement
quality of life; RAND-36: Research and Development-36; SD: stable disease; SD: standard deviation; SF-36: Short Form 36; TNO-AZL: Nederlandse Organisatie voor toegepast-natuurwetenschappelijk onderzoek van het Academisch Ziekenhuis in Leiden Preschool Children; VA: vascular anomalies; VAS: visual analogue scale; VM: venous malformation	

In people with extracranial slow-flow vascular malformations that are refractory to standard therapies, what is the cost effectiveness of sirolimus compared with no sirolimus?

Outcome	Evidence statement
Cost effectiveness	**No evidence was identified for cost effectiveness.**

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

Subgroup	Evidence statement
Slow-flow malformation type (venous, lymphatic and venolymphatic)	One randomised trial reported subgroup results by slow-flow malformation type (venous, lymphatic and venolymphatic) for the critical outcomes, disease response and symptom alleviation, and for the important outcomes, radiographic changes, organ specific disease response and quality of life. All results were compared to baseline. **Critical Outcomes** **Disease response** • One randomised trial (Maruani et al 2021; venous: n=22, lymphatic: n=18, venolymphatic: n=19) reported a *statistically significant decrease* in the volume of the extracranial lymphatic malformations following sirolimus treatment (LM, n=17, -0.004; 95%CI -0.006 to -0.002; p<0.001). The authors reported, however, *no statistically significant change* in the volume of extracranial venous malformations or extracranial venolymphatic malformations following sirolimus treatment (VM: p=0.24; combined: p=0.70). **Symptom alleviation** • One randomised trial (Maruani et al 2021) reported lower pain scores following sirolimus treatment across all extracranial vascular malformation types; this was most pronounced in those with lymphatic malformations (mean±SD – start of sirolimus treatment to end of trial; venous malformations: 3.24±3.03 to 2.40±2.39; lymphatic malformations: 2.21±2.98 to 0.58±1.25; venolymphatic malformations: 5.08±3.18 to 2.14±2.61; total: 3.49±3.23 to 1.76±2.29). No statistical comparisons were reported. • One randomised trial (Maruani et al 2021) reported less bleeding and oozing for those with extracranial lymphatic and extracranial venolymphatic malformations following sirolimus treatment; there was a small increase in the number of patients with bleeding and/oozing in those with extracranial venous malformations (venous malformations: baseline: 0%, 12 months: 9.1%; lymphatic malformations: baseline: 44.4%, 12 months: 22.2%; venolymphatic malformations: baseline: 52.6%, 12 months: 10.5%). No statistical comparisons were reported. **Important Outcomes** **Radiographic changes** • One randomised trial (Maruani et al 2021) reported a decreasing volume of extracranial lymphatic and extracranial venolymphatic malformations following sirolimus treatment but an increasing volume of extracranial venous malformations (venous malformations: baseline: 128, IQR 24 to 276, 12 months: 135, IQR 23 to 311; lymphatic malformations: baseline: 173, IQR 47 to 343, 12 months: 145, IQR 17 to 373; venolymphatic malformations: baseline: 189, IQR 79 to 832, 12 months: 151, IQR 49 to 800;). No statistical comparisons were reported.

Subgroup	Evidence statement
	Organ specific disease response *Skin and subcutaneous disease activity* • One randomised trial (Maruani et al 2021) used the global assessment of efficacy[20] as a marker of skin disease activity. Skin malformations were assessed using the VAS scale by physician, patient and parent at one month following sirolimus initiation, three months post-sirolimus initiation and at the final 12 month visit (Physician assessment, visit three to 12 months; venous malformations: 1.77±2.05 to 4.60±2.16; lymphatic malformations: 3.64±2.82 to 5.08±2.75; venolymphatic malformations: 2.94±2.70 to 5.00±3.14). A *statistically significant increase* in the VAS score was noted by the physician, patient and parent for extracranial venous malformations, extracranial lymphatic malformations and extracranial venolymphatic malformations following sirolimus treatment (p<0.001). **Quality of Life (QoL)** • One randomised trial (Maruani et al 2021) reported that the number of children reporting that their vascular malformation had "no effect on their life" increased for each vascular malformation type following sirolimus treatment (venous malformations: baseline: 18.2%, 12 months: 45.5%; lymphatic malformations: baseline: 55.6%, 12 months: 77.8%; venolymphatic malformations: baseline: 10.5%, 12 months: 42.1%); no statistical comparisons were reported. **One randomised trial reported outcomes for patients treated with sirolimus by extracranial slow-flow vascular malformation type: venous malformations, lymphatic malformations and venolymphatic malformations; all results were compared to baseline**. **The authors reported a statistically significant decrease in the volume of the lymphatic malformations following sirolimus treatment but no statistically significant effect of sirolimus on venous or venolymphatic malformations. Pain symptoms were alleviated across all three malformation types, though the score decreases were most pronounced in those with lymphatic malformations. Bleeding and oozing were decreased in those with lymphatic and venolymphatic malformations and slightly increased in those with venous malformations. MRI changes were noted for each of the malformation types following sirolimus treatment; increasing volume for venous malformations and decreasing volume for lymphatic and venolymphatic malformations. Quality of life and skin disease activity were reported to improve across all disease malformation types.**
Age Group (Children and Adults)	One single-arm trial reported subgroup results by age group (children and adults) for the critical outcomes, disease response and symptom alleviation, and the important outcomes, radiographic changes, organ specific disease response, quality of life and safety. All results were compared to baseline. **Critical Outcomes** **Disease response** • One single-arm trial (Harbers, Zwerink et al 2023) reported 30/32 children with extracranial slow-flow vascular malformations (93.8%) had a partial response and 2/32 (6.3%) reported stable disease following six months of sirolimus treatment. No children reported a complete response or progressive disease. The adults in the study had a lower disease response rate with 23/35 (65.7%) reporting partial response, 9/35 (25.7%) stable disease and 3/35 (8.6%) progressive disease. No adults had a complete response. The groups were not statistically compared. **Symptom alleviation** • One single-arm trial (Harbers, Zwerink et al 2023) reported *statistically significantly lower* pain scores for adults with extracranial slow-flow vascular

[20] Score was assessed using a visual analogue scale at each visit (0=no efficacy; 10=complete resolution) by the physician, parent and patient

Subgroup	Evidence statement
	anomalies following sirolimus treatment (EMM[21] difference: -1.9, 95%CI -3.2 to -0.5, p<0.001); when examining children separately, *no statistically significant difference* on pain scores before and after sirolimus treatment was found (EMM difference: -1.5, 95%CI -3.1 to 0.08, p>0.05).[22] When reporting symptoms other than pain, 22/35 (62.9%) of adults and 28/32 (87.5%) of children reported an improvement in symptoms following six months of sirolimus treatment. No statistical comparisons were reported for this measure. **Important Outcomes** **Radiographic changes** • One single-arm trial (Harbers, Zwerink et al 2023; n=31 children, n=31 adults) reported that the majority of both children and adults had either no change in the volume or a decreasing volume of their extracranial slow-flow vascular malformations following six months of sirolimus treatment (n, %; children: no change – 19, 61.3%, decreased volume – 12, 38.7%, increased volume – 0, 0%; adults: no change – 20, 64.5%, decreased volume – 10, 32.3%, increased volume – 1, 3.2%). The groups were not statistically compared. **Organ specific disease response** *Hepatic (liver) disease activity: D-dimer level* • One single-arm trial (Harbers, Zwerink et al 2023, children: n=32; adults: n=35) reported a decrease in D-dimer levels following six months of sirolimus therapy in both adults and children (children - baseline: 1345 ng/mL (95% CI 620 to 2770); six months: 1070 ng/mL (95%CI 860 to 2580); adults - baseline: 1315 ng/mL (95%CI 820 to 2300); six months: 1030 ng/mL (95%CI 600 to 2280). The results were *not statistically significant*. **Quality of Life (QoL)** • One single-arm trial (Harbers, Zwerink et al 2023) reported that a large majority of (15/18, 83.3%) children had improved quality of life following six months of sirolimus treatment; 3/18 (16.7%) had no change in their quality of life and no children reported a worsening in their quality of life. In adults, 14/26 (53.3%) reported improved quality of life, 8/26 (30.8%) reported no change and 4/26 (15.4%) reported worsening quality of life. The results were not statistically compared. • One single arm trial (Harbers, Bouwman et al 2023) detailed participants' health related quality of life before and after six months of sirolimus treatment. Both children (n=18) and adults (n=26) had a statistically significant increase in their quality of life following sirolimus treatment (child reported: +9.9, p<0.05; parent reported: +10.9, p<0.05; adult MCS score: +3.6, p<0.005; adult PCS score: +6.2, p<0.005). **Safety** • One single-arm trial (Harbers, Zwerink et al 2023, children: n=32; adults: n=35) reported all adverse events in both children and adults. The adults had proportionally more adverse events than the children (64.1% vs 35.9%) but the distribution of the adverse events between the AE Grades was similar between the two age groups (children – Grade 1: 72.7%, Grade 2: 22.2%, Grade 3: 4.0%, Grade 4: 1.0%; adults – Grade 1: 73.4%, Grade 2: 25.4%, Grade 3: 1.1%, Grade 4: 0%). • One single-arm trial (Harbers, Zwerink et al 2023, children: n=32; adults: n=35) reported serious adverse events that were suspected to be related to sirolimus. No adults reported serious adverse events, whilst three serious adverse events were reported in children.

[21] EMM: estimated marginal mean

[22] Pain was recorded using the Children and Infants Postoperative Pain Scale for children aged 0–3 years, visual analogue scale (VAS) clinical pictures for children aged 4–7 years, VAS for patients aged 8–17 years and numeric pain rating scale (NRS) for adults.

Subgroup	Evidence statement
	One single-arm trial reported outcomes for patients with extracranial slow-flow vascular malformations treated with six months of sirolimus by age group: children and adults; all results were compared to baseline. The authors reported a better disease response in children compared with adults; however, the groups were not statistically compared. Pain symptoms were statistically significantly lower for adults following sirolimus treatment, but no statistically significant difference was seen for children. Symptoms other than pain were alleviated for both children and adults, though the decreases were most pronounced in children. The changes were not statistically compared. The majority of both children and adults had either no change in the volume or a decreasing volume of their extracranial slow-flow vascular malformations on MRI; no statistical analysis was performed. Liver function and quality of life were both reported to improve for children and adults. More adverse events were reported in the adult population but there were fewer severe adverse events in this population.
Abbreviations EMM: estimated marginal mean; IQR: interquartile range; LM: lymphatic malformation; mL: millilitres; MRI: magnetic resonance imaging; n: number; ng: nanograms; NRS: numeric rating scale; QoL: quality of life; VA: vascular anomalies; VAS: visual analogue scale; VM: venous malformation	

From the evidence selected what were the ongoing schedules/doses used for sirolimus?

Outcome	Evidence statement
Sirolimus dose	Evidence about sirolimus doses came from one randomised trial, three single-arm trials and one prospective case series. • Two single-arm trials (Adams et al 2016 and Ji et al 2016) and one prospective case series (Tian et al 2020) used pharmacokinetically guided dosing when treating children with complicated vascular anomalies. A starting sirolimus dose of 0.8 mg/m^2, twice daily, was used and increased until plasma levels reached between 10 and 15 ng/mL. • One single-arm trial (Adams et al 2016) used the same protocol for treating young adults with complicated vascular anomalies; starting dose of 0.8 mg/m^2, twice daily, and increased until plasma levels reached between 10 and 15 ng/mL. • One single-arm trial (Harbers, Zwerink et al 2023) also began with a paediatric sirolimus dose of 0.8 mg/m^2, twice daily, and an adult dose of 1mg, twice daily. Dose adjustments were made until plasma levels reached between 4 and 10 ng/mL. • Maruani et al 2021 began their paediatric patients with slow-flow vascular malformations on a starting sirolimus dose of 0.08 mg/kg/d dose, twice daily and increased until plasma levels reached between 4 and 12 ng/mL at day 15. **One randomised trial, three single-arm trials and one prospective case series started every paediatric patient with vascular malformations on an initial sirolimus dose of 0.8 mg/m^2, twice daily. Dose adjustments were made until the desired plasma levels were reached; in two single-arm trials and the prospective case series this was between 10 and 15 ng/mL, in one randomised trial it was between 4 and 10 ng/mL, and in one single-arm trial it was between 4 and 12 ng/mL. One single-arm trial started adults on a twice daily 0.8 mg/m^2 sirolimus dose and increased until plasma concentrations reached 10 to 15 ng/mL, whilst another single-arm trial began all >18 years on a 1 mg sirolimus dose, twice daily, with increases until plasma concentrations reached between 4 and 10 ng/mL.**
Abbreviations kg: kilogram; m: metres; mg: milligrams; mL: millilitres; ng: nanogram	

6. Discussion

This evidence review considered the clinical effectiveness and safety of oral sirolimus compared to no oral sirolimus in people with extracranial slow-flow vascular malformations that are refractory to standard therapies. The critical outcomes of interest were disease response, overall survival and symptom alleviation. Important outcomes were radiographic changes, organ specific disease response, quality of life, activities of daily living and safety. Evidence on cost effectiveness was also sought.

Five studies were identified and included in this review: one randomised trial (Maruani et al 2021); three open-label, single arm clinical trials (Adams et al 2021, Harbers, Zwerink et al 2023, Harbers, Bouwman et al 2023 and Ji et al 2021); and one prospective case series (Tian et al 2020).

The randomised trial (Maruani et al 2021) was a single-arm clinical trial in which patients were randomised to their sirolimus start date. All patients had a four month observation period and were randomised to start sirolimus at month 4, 5, 6, 7 or 8 out of the 12 month trial period. It included paediatric patients (n=59) with extracranial slow-flow vascular malformations from 11 tertiary hospitals in France.

The first single-arm trial, Adams et al (2016), included children and young adults with complicated extracranial vascular anomalies in two hospitals in the United States (n=57); another (Ji et al 2021, n=126) included only children across five hospitals in China. Only one single-arm trial specified a diagnosis of extracranial slow-flow vascular malformations that were also refractory to standard care; two papers from this trial in the Netherlands were included in the review (Harbers, Zwerink et al 2023 and Harbers, Bouwman et al 2023, n=67). The trial included adults and children. The three open-label, phase II clinical trials were analysed as prospective case series as they did not present comparator evidence.

The prospective case series (Tian et al 2020, n=56) recruited children with extracranial lymphatic malformations from a single hospital in China.

Baseline characteristics of all patients are included in Appendix E. None of the studies were conducted in the United Kingdom and it is not clear from the data presented if the patients in the studies reflect the range of patients seen in clinical practice in England.

No comparator evidence nor cost effectiveness evidence was identified.

Duration of sirolimus treatment and length of follow-up varied considerably within the included studies. Sirolimus treatment was offered for six months in the single-arm trial conducted in the Netherlands (Harbers, Zwerink et al 2023 and Harbers, Bouwman et al 2023) and for approximately 12 months in the single-arm trials conducted by Adams et al (2016) and Ji et al (2021). Maruani et al (2021) randomised patients to the commencement of treatment and sirolimus treatment ranged from four to six months. The prospective case series presented by Tian et al (2020) divided patients by treatment sirolimus treatment time, which ranged from one to 24 months. Only one study reported following patients beyond the end of the treatment period, Ji et al (2021).

Evidence was identified for all the critical outcomes of interest for this review; however, evidence was not identified for the important outcome ‘activities of daily living.’ It is possible that there is some overlap between some of the quality of life domains or categories of symptom alleviation which may affect ability to perform activities of daily living (ADLs), but it is not possible to infer from these outcomes, the extent to which ADL functions might be impaired.

The disease response outcome was comprised of a composite variable for most studies, using the terms complete response, good response[23], partial response, stable disease and disease progression; however, the variables used to compile this composite variable varied between studies making direct comparison difficult. The outcomes reported were primarily objective or assessed using standardised assessment tools; however, only narrative text was available for the outcome 'overall survival.' Additionally, some detail in the safety outcomes was also reported as narrative description. The use of standardised outcome measures allows some interpretation of the level of function associated with specific scores; however, it was not clear how clinically significant the changes observed were. No specific detail about what the minimal clinically important thresholds or differences might be was reported for the outcomes considered.

All of the outcomes reported were classed as very low certainty evidence. Two of the included studies (Maruani et al 2021 and Ji et al 2021) reported the outcomes as intention-to-treat; the other included studies presented observed results only which increases selection bias and Type I errors. Limitations reducing certainty for the outcomes in the single-arm trials (Adams et al 2016 and Ji et al 2021) and the prospective case series (Tian et al 2020) included uncertainty about whether the inclusion of participants was complete or consecutive and uncertainty about the direct relevance of the population selected, particularly uncertainty if the included participants were all refractory to standard care. Some single-arm trials and the prospective case series did not present statistical analyses or summary statistics for some or all outcomes; a lack of comparator was also a limitation across all three of the single-arm trials and the prospective case series. Limitations due to the lack of comparator, lack of blinding and potential residual confounding due to lack of adjustment for the stepped-wedge study design reduced certainty for the randomised trial (Maruani et al 2021).

One randomised trial presented subgroup results by extracranial slow-flow malformation type (venous, lymphatic and venolymphatic). The critical outcomes, disease response and symptom alleviation, and the important outcomes, radiographic changes, organ specific disease response and quality of life were presented by each of the venous malformation types; sirolimus was found to have little to no effect in venous malformations but a statistically significant effect in lymphatic malformations.

A single-arm trial presented further subgroup results by age group (adults and children). The critical outcomes, disease response and symptom alleviation, and the important outcomes, radiographic changes, organ specific disease response, quality of life and safety were presented by each of the age groups; sirolimus was found to have a better response in children than adults.

No evidence on cost effectiveness was identified.

[23] not presented in all studies

7. Conclusion

This evidence review includes three single arm clinical trials, one randomised trial and one prospective case series. The single-arm trials were analysed as case series due to the lack of comparator. Two studies included children and adults (single-arm trials); the remaining three included paediatric patients only. One study only included children with lymphatic malformations (prospective case series).

All of the studies provided non-comparator data and the evidence for all the outcomes of interest was of very low certainty.

All of the included studies provided evidence for sirolimus use in children with extra-cranial, slow-flow vascular malformations for all the critical outcomes of interest. There was evidence of a partial response following sirolimus treatment in children and adults; this finding was statistically significant in some studies. There was evidence of a low mortality rate in children treated with sirolimus; there was no evidence of statistical significance and no data for populations >18 years. There was evidence that adults had a statistically significant improvement in their pain scores and children had an improvement in their functional disability following sirolimus treatment. There was also evidence of no statistically significant improvement in children's pain scores following sirolimus treatment.

Data were available for the important outcomes of radiographic changes, organ specific disease response, quality of life and safety. There was evidence of no statistically significant difference in the volume of the vascular malformation on MRI following sirolimus treatment for both children and adults; this may be an indication of clinically significant stable disease. There was evidence of statistically significantly improved organ specific disease function in those receiving sirolimus therapy; both adults and children reported a statistically significant improvement in organ response and children, their physicians and parents reported a statistically significant improvement on the skin Visual Analogue Score (VAS scale). Single-arm trials and prospective case series data provided evidence of a statistically significant improvement in quality of life for both children and adults.

Safety outcomes, in the form of adverse events, were reported for those receiving sirolimus therapy. Adverse events were common in both adults and children; however, most were not severe. The most common adverse events reported across all the studies were infection related.

There was very low certainty evidence of a difference in sirolimus response in children with extracranial lymphatic malformations compared with children with extracranial venous malformations. When examined separately in one randomised trial, children with extracranial venous malformations had no statistically significant response to sirolimus when compared to baseline, whilst those with extracranial lymphatic malformations had a statistically significant improvement in disease state across several domains. One single-arm trial provided very low certainty evidence of a better disease response in children when compared to adults. Despite children having a better disease response, adults had statistically significantly lower pain scores following sirolimus treatment whereas children's pain scores did not show a statistically significant improvement. These subgroup results should be interpreted with caution as the subgroups were very small; however, they did reach statistical significance.

All of the outcomes reported were classed as very low certainty evidence and results were compared only with baseline data for the patients. Two of the included studies (Maruani et al 2021 and Ji et al 2021) reported the outcomes as intention-to-treat; the other included studies presented observed results only which increases selection bias and Type I errors. Limitations

reducing certainty for the outcomes in the single-arm trials (Adams et al 2016 and Ji et al 2021) and the prospective case series (Tian et al 2020) included uncertainty about whether the inclusion of participants was complete or consecutive and uncertainty about the direct relevance of the population selected, particularly uncertainty if the included participants were all refractory to standard care. Some single-arm trials and the prospective case series did not present statistical analyses or summary statistics for some or all outcomes; a lack of comparator was also a limitation across all three of the single-arm trials and the prospective case series. Limitations due to the lack of comparator, lack of blinding and potential residual confounding due to lack of adjustment for the stepped-wedge study design reduced certainty for the randomised trial (Maruani et al 2021).

No evidence on cost effectiveness was identified.

Although all the studies provided very low certainty evidence of the outcomes, there was congruence in the results reported. The studies identified in this review provide evidence, for a range of pre-specified critical and important outcomes, suggesting that sirolimus may be an effective treatment for children and adults with extracranial slow-flow vascular malformations that are refractory to standard therapies.

Appendix A PICO document

The review questions for this evidence review are:

1. In people with extracranial slow-flow vascular malformations that are refractory to standard therapies, what is the clinical effectiveness of sirolimus compared with no sirolimus?
2. In people with extracranial slow-flow vascular malformations that are refractory to standard therapies, what is the safety of sirolimus compared with no sirolimus?
3. In people with extracranial slow-flow vascular malformations that are refractory to standard therapies, what is the cost effectiveness of sirolimus compared with no sirolimus?
4. From the evidence selected, are there any subgroups of patients that may benefit from sirolimus more than the wider population of interest?
5. From the evidence selected what were the ongoing schedules/doses used for sirolimus?

P –Population and Indication	People with extracranial slow-flow vascular malformations affecting any organ system that are refractory to standard care. [Slow-flow vascular malformations can include lymphatic, venous or capillary malformations. Slow-flow vascular malformations can affect any organ system and any part of the body.] [Refractory to standard care would include: - Response to standard care is inadequate eg due to disease progression or where pain, bleeding, thromboses or lesion size are not controlled using standard care - Inability to tolerate side effects of standard care - Contraindications to standard care due to co-morbidities.] [Standard care could include all, some or none of the following: - Supportive measures (which may include compression devices, psychosocial care and analgesics) - Medical (which may include anticoagulation, analgesics and antibiotics) - Interventional (which may include sclerotherapy) - Surgical] [Syndromes associated with malformations that might be referred to in literature are 1) Venous malformation: • Blue rubber bleb naevus syndrome (BRBN) • Multifocal venous malformations (MVMs) • Inherited cutaneomucosal venous malformation (VMCM) • Glomuvenous malformation (GVM) • Verrucous venous malformation (VVM) 2) Lymphatic malformation: • Gorham-Stout Disease (GSD) • Kaposiform Lymphagiomatosis (KLA) • Cystic hygroma 3) Combined vascular malformations • PIK3CA related overgrowth syndrome (PROS); which includes • Congenital lipomatous overgrowth with vascular anomalies (CLOVES)

	• Klippel-Trenaunay Syndrome or Klippel-Trenaunay-Weber Syndrome) (KTS) • Megalencephaly-capillary malformation (MCAP) • Proteus Syndrome • Hyperkeratotic cutaneous capillary-venous malformation • Capillary-venous malformation (CVM) • Capillary-lymphatic malformation (CLM) • Lymphatic venous malformation (LVM) • Capillary-lymphatic-venous malformation (CLVM)] All ages Subgroups of interest: - Paediatrics - Venous vs lymphatic vs combined venous/lymphatic/capillary malformations
I – Intervention	Oral sirolimus (also known as rapamycin) [Sirolimus treatment is in the form of oral capsules or oral solution. Patients could be receiving some supportive care, medical care or interventional treatment (eg sclerotherapy). Patients receive some surgery for lesions where viable.]
C – Comparator	No oral sirolimus [Patients could be receiving some supportive care, medical care or interventional treatment (eg sclerotherapy). Patients receive some surgery for lesions where viable.]
O – Outcomes	**<u>Clinical Effectiveness</u>** Minimally clinically important differences (MCIDs) are not known unless stated. <u>*Critical to decision-making:*</u> ○ **Disease response** *This outcome is important to patients because it can reflect the benefits the treatment may have for a patient. This can be important to control the symptomatic burden of the disease and/or reflect subgroups who may configure additional response benefits, allowing the treatment protocol to be individualised.* [For example, but not limited to: Clinical response, improvement in performance score, lower pain threshold, disease state, objective response rate.] ○ **Overall Survival** *Overall survival is important to patients as individuals with slow-flow vascular malformations which have failed standard therapy can have life-threatening complications. Improved survival is an important marker of effective treatment.* ○ **Symptom alleviation**

	This outcome 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. [Other terms used to describe or indicate symptom alleviation include but are not limited to symptoms, symptomatic response, alleviating disease symptoms.] *Important to decision-making:* ○ **Radiographic changes** *Changes to the appearance of scans of the location of malformations are important to patients as they are used to help determine treatment success and requirement for further treatment. Imaging results might not be expected to return to normal, however, stabilisation may indicate treatment has successfully limited disease progression and may be associated with improvement in clinical features*. ○ ***Organ specific disease response*** *This outcome is important to patients as objective measures of functioning of affected organs. Disease activity results might not be expected to return to normal following treatment; however, stabilisation may indicate treatment has successfully limited disease progression.* ▪ ***Respiratory disease activity*** [Pulmonary function measures commonly used to assess this outcome are Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 second (FEV1), the fraction between FVC and FEV1 (FVC/FEV1), diffusing capacity of the lungs for carbon monoxide (DLCO), peripheral oxygen saturation (SaO2). The 6 minutes walking test (6-MWT) can also be used] ▪ ***Skin and subcutaneous disease activity*** *[*General measures commonly used include the physician global assessment (PGA) and clinical judgement of improvement with the use of clinical examination or photographs. Frequency of cellulitis flares would also be an important marker of disease activity for this subgroup.] ▪ ***Musculoskeletal disease activity*** [General measures commonly used include clinical judgement of functional improvement and clinical improvement with the use of clinical examination or photographs]. ▪ ***Hepatic (liver) disease activity*** [The tools commonly used are ultrasound scan of the liver to assess for liver disease and blood tests that measure liver enzymes [aspartate aminotransferase (AST), Alanine transaminase (ALT), Alkaline phosphatase (ALP), Lactate dehydrogenase (LDH) and gamma-glutamyl transferase (GGT)] and clotting factors [fibrinogen and D-dimer] ▪ ***Gastrointestinal and genitourinary disease activity*** [General measures commonly used include the physician global assessment (PGA) and clinical judgement of improvement particularly reporting on rectal bleeding, oozing and vaginal (PV) bleeding.]

	▪ ***Cardiopulmonary disease activity*** [General measures commonly used include the Physician global assessment (PGA) and clinical judgement of improvement particularly reporting on shortness of breath, murmur, presence of pericardial effusion] ○ **Quality of life** *Quality of life is important to patients as it provides an indication of an individual's general health, their self-perceived well-being and their ability to participate in activities of daily living. Measurement of quality of life can help inform patient-centred decision making.* ○ **Activities of daily living (ADLs)** *ADLs are important outcomes to patients as they facilitate enablement and independence, allowing individuals to function in education, work, home, and recreational settings. They encompass patients' individual needs and facilitate inclusion and participation. The complications of slow-flow vascular malformations can lead to progressively worsening physical symptoms and altered ability to complete ADLs without assistance*. [ADLs can be measured using assessments such as: ○ Timed task completion (e.g., timed repeatable test such as dressing, meal preparation or patient specific ADL goal) ○ ADLs assessment using a tool (e.g., Barthel Index (BI) or Independence in Activities of Daily Living (ADL) ○ Subjective/self-reported assessment (e.g., by the individual, carer, or MDT. This could include self-reported questionnaires such as participation in work and other activities).] • **<u>Safety</u>** *Safety of sirolimus is important to patients as it allows comparison of interventional approaches.* [Examples include, but not limited to: ○ Toxicity ○ Frequency of adverse events ○ Frequency of grade 3 or 4 adverse events ○ Adverse events leading to discontinuation ○ Treatment related adverse events] **<u>Cost effectiveness</u>**
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.
Language	English only

Patients	Human studies only
Age	All ages
Date limits	2013-2023
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-prints and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase, the Cochrane Library and TRIP were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, commentaries, letters, editorials, non-systematic reviews and trial registrations. Case studies with four or fewer participants were also excluded.

Search date: 4 July 2023

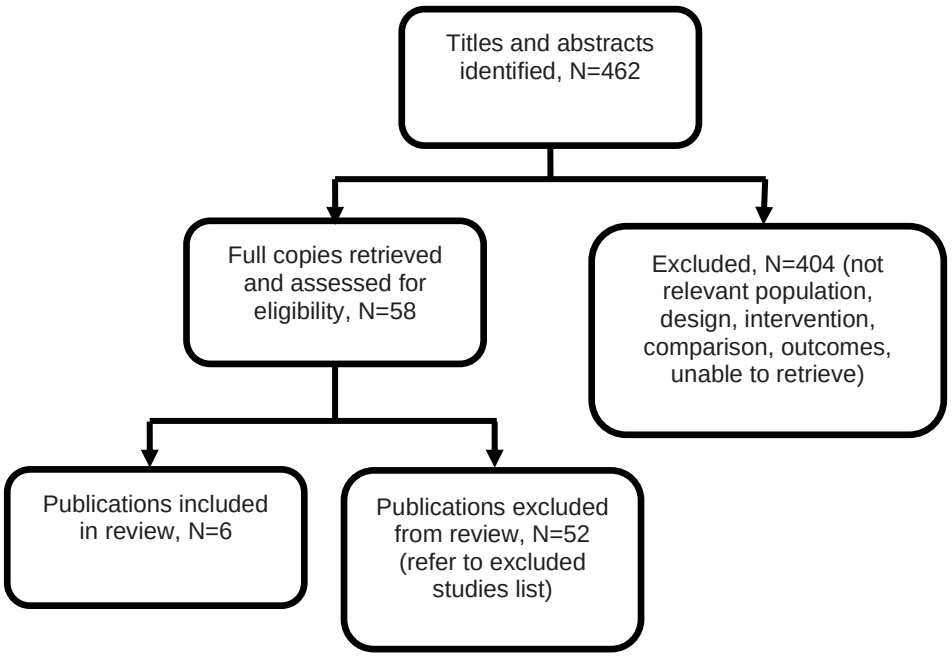
Medline search strategy:

1	vascular malformations/ or arteriovenous malformations/
2	Lymphatic Abnormalities/
3	Lymphangioma, Cystic/
4	Klippel-Trenaunay-Weber Syndrome/
5	(((vascular or vein* or venous or glomuvenous or arteriovenous) adj2 (malformation? or anomal* or abnormal*)) or glomangioma?).ti,ab,kf.
6	blue rubber bleb.ti,ab,kf.
7	((lymph* adj2 (malformation? or anomal* or abnormal*)) or lymphangiomatosis).ti,ab,kf.
8	((gorham adj2 disease) or kaposiform lymph* or cystic hygroma? or cystic lymphangioma?).ti,ab,kf.
9	(overgrowth syndrome or (pik3ca adj3 syndrome?) or congenital lipo* overgrowth or cloves or angioosteohypertrophy syndrome or klippel trenaunay or kts or proteus syndrome or (capillary adj2 (malformation? or anomal* or abnormal*))).ti,ab,kf.
10	or/1-9
11	exp Sirolimus/
12	(sirolimus or rapamycin or rapamune).ti,ab,kf.
13	or/11-12
14	10 and 13
15	limit 14 to (english language and yr="2013 -Current")
16	(comment or editorial or letter or review).pt.
17	15 not 16
18	limit 15 to (meta analysis or "systematic review" or "reviews (maximizes specificity)")
19	17 or 18

Appendix C Evidence selection

The literature searches identified 462 references. These were screened using their titles and abstracts and 58 references were obtained in full text and assessed for relevance. Of these, 6 references are included in the evidence summary. The remaining 52 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection - decision and rationale if excluded
Maruani A, Tavernier E, Boccara O, Mazereeuw-Hautier J, Leducq S, Bessis D, et al. Sirolimus (Rapamycin) for Slow-Flow Malformations in Children: The Observational-Phase Randomized Clinical PERFORMUS Trial. JAMA Dermatology. 2021;157(11):1289-98.	Included
Hammer J, Seront E, Duez S, Dupont S, Van Damme A, Schmitz S, et al. Sirolimus is efficacious in treatment for extensive and/or complex slow-flow vascular malformations: a monocentric prospective phase II study. Orphanet Journal of Rare Diseases. 2018;13(1):191.	n=16, all trials and case studies with fewer than 50 participants were excluded as larger trials and prospective case series were included.
Harbers VEM, Rongen GAPJM, van der Vleuten CJM, Verhoeven BH, de Laat PCJ, van der Horst CMAM, et al. Patients with Congenital Low-Flow Vascular Malformation Treated with Low Dose Sirolimus. Advances in Therapy. 2021;38(6):3465-82.	Narrative synthesis of n=12 case studies, study design excluded by PICO.

Appendix D Excluded studies table

Study reference	Reason for exclusion
Badawy M, Ma Y, Baldrighi C, Oestreich K, Jester A. Efficacy of mTOR inhibitors (sirolimus) in isolated limb overgrowth: a systematic review. The Journal of Hand Surgery, European volume. 2022;47(7):698-704.	n<50, larger trials and prospective case series included.
Bessis D, Vernhet H, Bigorre M, Quere I, Rossler J. Life-Threatening Cutaneous Bleeding in Childhood Klippel-Trenaunay Syndrome Treated With Oral Sirolimus. JAMA Dermatology. 2016;152(9):1058-9.	Letter to the editor, study design excluded by PICO.
Chelliah MP, Do HM, Zinn Z, Patel V, Jeng M, Khosla RK, et al. Management of Complex Arteriovenous Malformations Using a Novel Combination Therapeutic Algorithm. JAMA Dermatology. 2018;154(11):1316-9.	n<50, larger trials and prospective case series included.
Cho YJ, Kwon H, Kwon YJ, Kim SC, Kim DY, Namgoong J-M. Effects of sirolimus in the treatment of unresectable infantile hemangioma and vascular malformations in children: A single-center experience. Journal of Vascular Surgery Venous and Lymphatic Disorders. 2021;9(6):1488-94.	n<50, larger trials and prospective case series included.
Durand R, Reid JR, Belasco JB, Shellikeri S, Calle-Toro JS, Cahill AM, et al. MRI for Response Assessment of Extensive Lymphatic Malformations in Children Treated With Sirolimus. AJR American Journal of Roentgenology. 2021;217(3):741-52.	n<50, larger trials and prospective case series included.
Dvorakova V, Rea D, O'Regan GM, Irvine AD. Generalized lymphatic anomaly successfully treated with long-term, low-dose sirolimus. Pediatric Dermatology. 2018;35(4):533-4.	n=1. Case study design excluded by PICO.
Engel ER, Hammill A, Adams D, Phillips RJ, Jeng M, Tollefson MM, et al. Response to sirolimus in capillary lymphatic venous malformations and associated syndromes: Impact on symptomatology, quality of life, and radiographic response. Pediatric Blood & Cancer. 2023;70(4):e30215.	n<50, larger trials and prospective case series included.
Fernandez Oliveira C, Martinez Roca C, Gomez Tellado M, Salvador Garrido MP, Outeda Macias M, Martin Herranz I. Treatment with oral or topical sirolimus in complex vascular anomalies in pediatrics. Experience in a third-level hospital. Tratamiento con sirolimus oral o topico en anomalias vasculares complejas en pediatria Experiencia en un hospital terciario. 2023;36(2):60-6.	n<50, larger trials and prospective case series included.
Freixo C, Ferreira V, Martins J, Almeida R, Caldeira D, Rosa M, et al. Efficacy and safety of sirolimus in the treatment of vascular anomalies: A systematic review. Journal of Vascular Surgery. 2020;71(1):318-27.	Narrative review of the literature, study design excluded by PICO.
Gao Q, Chen H, Sun B, Cui J, Shen W. Intermittent Administration Regimen of Sirolimus for Refractory Cervicofacial Lymphatic Malformation. The Journal of Craniofacial Surgery. 2022;33(3):850-4.	n<50, larger trials and prospective case series included.

Study reference	Reason for exclusion
Geeurickx M, Labarque V. A narrative review of the role of sirolimus in the treatment of congenital vascular malformations. Journal of Vascular Surgery Venous and lymphatic disorders. 2021.	Narrative review of the literature, study design excluded by PICO.
Gomez Sanchez A, Redondo Sedano JV, Perez Alonso V, Marti Carrera ME, Baro Fernandez M, Palencia Perez SI, et al. Oral rapamycin: an alternative in children with complicated vascular abnormalities. Rapamicina oral: una alternativa en ninos con anomalias vasculares complicadas. 2020;33(4):183-7.	n<50, larger trials and prospective case series included.
Grenier P-O, McCormack L, Alshamekh SA, Adams DM, Trenor CC, 3rd, O'Hare MJ, et al. Mucocutaneous Adverse Events Associated With Oral Sirolimus for the Treatment of Vascular Anomalies. JAMA Dermatology. 2021;157(2):233-5.	Population does not meet PICO. This retrospective case series included patients who were not refractory to standard treatment and, therefore, did not meet the population definition in the PICO (Appendix A).
Hammer J, Seront E, Duez S, Dupont S, Van Damme A, Schmitz S, et al. Sirolimus is efficacious in treatment for extensive and/or complex slow-flow vascular malformations: a monocentric prospective phase II study. Orphanet Journal of Rare Diseases. 2018;13(1):191.	n<50, larger trials and prospective case series included.
Harbers VEM, Rongen GAPJM, van der Vleuten CJM, Verhoeven BH, de Laat PCJ, van der Horst CMAM, et al. Patients with Congenital Low-Flow Vascular Malformation Treated with Low Dose Sirolimus. Advances in Therapy. 2021;38(6):3465-82.	Narrative review of the literature, study design excluded by PICO.
Holm A, Te Loo M, Schultze Kool L, Salminen P, Celis V, Baselga E, et al. Efficacy of Sirolimus in Patients Requiring Tracheostomy for Life-Threatening Lymphatic Malformation of the Head and Neck: A Report From the European Reference Network. Frontiers in Pediatrics. 2021;9:697960.	n<50, larger trials and prospective case series included.
Isoldi S, Belsha D, Yeop I, Uc A, Zevit N, Mamula P, et al. Diagnosis and management of children with Blue Rubber Bleb Nevus Syndrome: A multi-center case series. Digestive and Liver Disease : Official Journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver. 2019;51(11):1537-46.	n<50, larger trials and prospective case series included.
Kalwani NM, Rockson SG. Management of lymphatic vascular malformations: A systematic review of the literature. Journal of Vascular Surgery Venous and Lymphatic Disorders. 2021;9(4):1077-82.	Narrative review of the literature, study design excluded by PICO.
Karastaneva A, Gasparella P, Tschauner S, Crazzolara R, Kropshofer G, Modl M, et al. Indications and Limitations of Sirolimus in the Treatment of Vascular Anomalies-Insights From a Retrospective Case Series. Frontiers in Pediatrics. 2022;10:857436.	n<50, larger trials and prospective case series included.
Mack JM, Verkamp B, Richter GT, Nicholas R, Stewart K, Crary SE. Effect of sirolimus on coagulopathy of slow-flow vascular malformations. Pediatric Blood & Cancer. 2019;66(10):e27896.	n<50, larger trials and prospective case series included.
Maruani A, Moineau AG, Boccara O, Mazereeuw-Hautier J, Leducq S, Bessis D, et al. Vascular endothelial growth factor, tissue factor, coagulation	Letter to the editor, study design excluded by PICO.

Study reference	Reason for exclusion
and fibrinolysis markers in slow-flow vascular malformations: a prospective study of treatment with sirolimus. Br J Dermatol. 2023;188(1):152-4.	
Mehl SC, Kinley A, Todd HF, Mir DI, Iacobas I, Pezeshkmehr A, et al. Institutional Management of Abdominal Lymphatic Malformations: Evolution of Treatment Over a Decade. The Journal of Surgical Research. 2022;280:296-303.	n<50, larger trials and prospective case series included.
Mercouris M, Davidson A, Kahl G, de Quintal H, Hendricks M. The paediatric oncologist and the evolving medical management of complex vascular anomalies: An institutional experience. SA Journal of Oncology. 2022;6:a227.	n<50, larger trials and prospective case series included.
Nadal M, Giraudeau B, Tavernier E, Jonville-Bera A-P, Lorette G, Maruani A. Efficacy and Safety of Mammalian Target of Rapamycin Inhibitors in Vascular Anomalies: A Systematic Review. Acta Dermato-Venereologica. 2016;96(4):448-52.	Population does not meet PICO. This systematic review included vascular tumours and, therefore, did not meet the population definition in the PICO in Appendix A. No pooled results were available for the population of interest.
Nozawa A, Ozeki M, Yasue S, Endo S, Kawamoto N, Ohnishi H, et al. Immunologic Effects of Sirolimus in Patients With Vascular Anomalies. Journal of Pediatric Hematology/Oncology. 2020;42(5):e355-e60.	n<50, larger trials and prospective case series included.
Ozeki M, Nozawa A, Yasue S, Endo S, Asada R, Hashimoto H, et al. The impact of sirolimus therapy on lesion size, clinical symptoms, and quality of life of patients with lymphatic anomalies. Orphanet Journal of Rare Diseases. 2019;14(1):141.	n<50, larger trials and prospective case series included.
Pang C, Evans N, Jethwa P, Papadopoulou A, Khalifa M, Tsui J, et al. Single Center Experience of Sirolimus Therapy in Head and Neck Low-flow Vascular Malformations. Vascular and Endovascular Surgery. 2021;55(5):482-90.	n<50, larger trials and prospective case series included.
Ricci KW, Hammill AM, Mobberley-Schuman P, Nelson SC, Blatt J, Bender JLG, et al. Efficacy of systemic sirolimus in the treatment of generalized lymphatic anomaly and Gorham-Stout disease. Pediatric Blood & Cancer. 2019;66(5):e27614.	n<50, larger trials and prospective case series included.
Rossler J, Baselga E, Davila V, Celis V, Diociaiuti A, El Hachem M, et al. Severe adverse events during sirolimus "off-label" therapy for vascular anomalies. Pediatric Blood & Cancer. 2021;68(8):e28936.	n<50, larger trials and prospective case series included.
Saibene AM, Rosso C, Felisati G, Pignataro L, Schindler A, Ghilardi G, et al. Sirolimus treatment for paediatric head and neck lymphatic malformations: a systematic review. European Archives of Oto-Rhino-Laryngology : Official Journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : Affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 2023;280(8):3529-40.	Population does not meet PICO. This systematic review included patients whose first treatment was sirolimus and, therefore, did not meet the population definition of refractory disease in the PICO (Appendix A).
Sandbank S, Molho-Pessach V, Farkas A, Barzilai A, Greenberger S. Oral and Topical Sirolimus for Vascular Anomalies: a Multicentre Study and Review. Acta Dermato-Venereologica. 2019.	n<50, larger trials and prospective case series included.

Study reference	Reason for exclusion
Sebold AJ, Day AM, Ewen J, Adamek J, Byars A, Cohen B, et al. Sirolimus Treatment in Sturge-Weber Syndrome. Pediatric Neurology. 2021;115:29-40.	Population does not meet PICO. This case series included patients with intracranial capillary malformations and, therefore, did not meet the population definition in the PICO in Appendix A.
Shoji MK, Shishido S, Freitag SK. The Use of Sirolimus for Treatment of Orbital Lymphatic Malformations: A Systematic Review. Ophthalmic Plastic and Reconstructive Surgery. 2020;36(3):215-21.	n<50, larger trials and prospective case series included.
Strychowsky JE, Rahbar R, O'Hare MJ, Irace AL, Padua H, Trenor CC, 3rd. Sirolimus as treatment for 19 patients with refractory cervicofacial lymphatic malformation. The Laryngoscope. 2018;128(1):269-76.	n<50, larger trials and prospective case series included.
Teng JMC, Hammill A, Martini J, Treat J. Sirolimus in the Treatment of Microcystic Lymphatic Malformations: A Systematic Review. Lymphatic Research and Biology. 2023;21(2):101-10.	No pooled result for population of interest.
Tezol O, Alakaya M, Gundogan B, Citak EC. Sirolimus for the Treatment of Benign Vascular Anomalies in Children: A Single Centre Experience. Hong Kong Journal of Paediatrics. 2023;28(1):20-6.	Population does not meet PICO. This retrospective case series included infantile haemangiomas as well as vascular malformations and, therefore, did not meet the population definition in the PICO in Appendix A.
Thirion S, Jamblin P, Demarche M, Boon L, Thiry A, Hoyoux C. A new treatment for vascular anomalies: Six cases treated with rapamycin. Archives de Pediatrie. 2017;24(7):600-6.	Paper not in English.
Tole S, Fantauzzi M, Cottingham D, Amaral JG, John PR, Lara-Corrales I, et al. The use of rapamycin to treat vascular tumours and malformations: A single-centre experience. Paediatrics & Child Health. 2021;26(1):e25-e32.	Population does not meet PICO. This systematic review included vascular tumours and, therefore, did not meet the population definition in the PICO in Appendix A. No pooled results were available for the population of interest.
Triana P, Dore M, Cerezo VN, Cervantes M, Sanchez AV, Ferrero MM, et al. Sirolimus in the Treatment of Vascular Anomalies. European Journal of Pediatric Surgery : Official Journal of Austrian Association of Pediatric Surgery [et al] = Zeitschrift fur Kinderchirurgie. 2017;27(1):86-90.	n<50, larger trials and prospective case series included.
Triana P, Lopez-Gutierrez JC. Menstrual disorders associated with sirolimus treatment. Pediatric Blood & Cancer. 2021;68(3):e28867.	n<50, larger trials and prospective case series included.
Wang J, Zhang X, Sun N, Liu Q, Li Y, Peng Y, et al. Differences in Efficacy and Safety of Sirolimus and Sildenafil in Pediatric Lymphatic Malformations. The Laryngoscope. 2023.	n<50, larger trials and prospective case series included.
Wang Z, Yan H, Ding Y, Gong Y, Ma Y, Yao W, et al. Successful Treatment of Fibro-Adipose Vascular Anomaly with Sirolimus. Journal of Pediatric Surgery. 2023;58(7):1337-41.	n<50, larger trials and prospective case series included.
Wiegand S, Dietz A, Wichmann G. Efficacy of sirolimus in children with lymphatic malformations of the head and neck. European Archives of Oto-Rhino-Laryngology : Official Journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : Affiliated with the German Society for Oto-	Population does not meet PICO. This systematic review included patients whose first treatment was sirolimus and, therefore, did not meet the population definition of refractory disease in the PICO (Appendix A).

Study reference	Reason for exclusion
Rhino-Laryngology - Head and Neck Surgery. 2022;279(8):3801-10.	
Wiegand S, Wichmann G, Dietz A. Treatment of Lymphatic Malformations with the mTOR Inhibitor Sirolimus: A Systematic Review. Lymphatic Research and Biology. 2018;16(4):330-9.	13/25 studies included were case reports, excluded by PICO. 11 case series and 1 prospective cohort were evaluated for inclusion separately.
Wong XL, Phan K, Rodriguez Bandera AI, Sebaratnam DF. Sirolimus in blue rubber bleb naevus syndrome: A systematic review. Journal of Paediatrics and Child Health. 2019;55(2):152-5.	n<50, larger trials and prospective case series included. 2 case series were evaluated for inclusion separately.
Wu C, Song D, Guo L, Wang L. Refractory Head and Neck Lymphatic Malformation in Infants Treated With Sirolimus: A Case Series. Frontiers in Oncology. 2021;11:616702.	n<50, larger trials and prospective case series included.
Yesil S, Tanyildiz HG, Bozkurt C, Cakmakci E, Sahin G. Single-center experience with sirolimus therapy for vascular malformations. Pediatric Hematology and Oncology. 2016;33(3):219-25.	n<50, larger trials and prospective case series included.
Zhang G, Chen H, Zhen Z, Chen J, Zhang S, Qin Q, et al. Sirolimus for treatment of verrucous venous malformation: A retrospective cohort study. J Am Acad Dermatol. 2019;80(2):556-8.	Letter to the editor, study design excluded by PICO.
Zhang Z, Li Y, Zhang G, Yang K, Qiu T, Zhou J, et al. Safety Evaluation of Oral Sirolimus in the Treatment of Childhood Diseases: A Systematic Review. Children (Basel, Switzerland). 2022;9(9).	Subgroup analyses included data for patients that had both refractory and non-refractory vascular anomalies. No separate reporting of results for the population of interest (Appendix A) were available.
Zhou J, Yang K, Chen S, Ji Y. Sirolimus in the treatment of kaposiform lymphangiomatosis. Orphanet Journal of Rare Diseases. 2021;16(1):260.	n<50, larger trials and prospective case series included.
Zhou J, Zhao Z, Sun T, Liu W, Yu Z, Liu J, et al. Efficacy and Safety of Sirolimus for Blue Rubber Bleb Nevus Syndrome: A Prospective Study. The American Journal of Gastroenterology. 2021;116(5):1044-52.	n<50, larger trials and prospective case series included.
Zobel MJ, Nowicki D, Gomez G, Lee J, Howell L, Miller J, et al. Management of cervicofacial lymphatic malformations requires a multidisciplinary approach. Journal of Pediatric Surgery. 2021;56(5):1062-7.	No results reported for the outcomes specified in the PICO.

Appendix E Evidence table

For abbreviations see list after table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Adams DM, Trenor CC, 3rd, Hammill AM, Vinks AA, Patel MN, Chaudry G et al. Efficacy and Safety of Sirolimus in the Treatment of Complicated Vascular Anomalies. Pediatrics. 2016;137(2):e20153257. **Study location** US **Study type** Phase II single-arm, open label clinical trial (single-arm trial) **Study aim** To assess the efficacy and safety of the mTOR inhibitor Sirolimus in the treatment of complicated vascular anomalies in children and young adults	**Children and young adults with complicated vascular anomalies and at least one complication**[24] **Inclusion criteria** • aged between 0 and 31 years • adequate organ function (liver, bone marrow, renal) • adequate lipid panel • Karnofsky or Lansky performance status of ≥50%[25] **Exclusion Criteria** • concurrent use of cytochrome P450 3A4 enzyme inducers or inhibitors • No concurrent steroids (except for	**Interventions** Oral sirolimus on a continuous dosing schedule at a starting dose of 0.8 mg/m^2 twice daily, with one course equivalent to 28 days. Pharmacokinetically guided dosing was used, and trough levels were maintained between 10 and 15 ng/mL Treatment duration: 12 courses; course equivalent to 28 days **Comparators** No comparator	**Critical outcomes** **Disease Response** *Overall Response*[28] Course 6[29], n (%) [95%CI]; n=57 • CR: 0 (0) [N/A] • PR: 47 (83) [70 to 95] • SD: 3 (5) [0 to 13] • PD: 7 (12) [2 to 23] Course 12[30], n (%) [95%CI]; n=53 • CR: 0 (0) [N/A] • PR: 45 (85) [73 to 97] • SD: 0 (0) [N/A] • PD: 8 (15) [3 to 27] *Efficacy by 2014 ISSVA classification* Course 6, n (%); n=57 • Generalized lymphatic anomaly: PR – 7 (100) • Gorham syndrome: PR – 3 (100)	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Yes 4. Unclear 5. Unclear 6. No 7. Yes 8. Yes 9. No 10. Not applicable **Other comments:** This was a single-arm, open label clinical trial that included 61 patients from 2 hospitals in the United States. It was not clear if all potentially eligible patients were included in the study. As this was a phase II clinical trial, all patients received the study drug, sirolimus, so it was not possible to blind participants or assessors.

[24] Patients needed to have at least 1 of 6 predefined complications: 1) coagulopathy, 2) chronic pain, 3) recurrent cellulitis (defined as >3 episodes per year), 4) ulceration, 5) visceral and/or bone involvement or 6) cardiac dysfunction

[25] Karnofsky or Lansky performance statuses are used to quantify cancer patients' general well-being and activities of daily life. The Karnofsky score is used for adults; the Lanksy score is used for children. Both scores use a ranking that run from 100 to 0, where 100 is "perfect" health and 0 is death.

[28] Presented as complete response (CR), partial response (PR), progressive disease (PD) or stable disease (SD). This composite measure is established by changes in at least 1 parameter: response by radiologic imaging, health quality-of-life questionnaire [Paediatric Quality of Live Inventory 4.0 (3-18 years) and Infant Scales (≤2 years) or the Functional Assessment of Chronic Illness System (>18 years)] or using defined clinical criteria in a functional impairment score (measures of organ function).

[29] Disease response after 6 courses of sirolimus. A course of treatment was equal to 28 days. Courses were taken consecutively with no break, thus six courses represented 168 days; 12 courses 336 days / 48 weeks.

[30] Disease response after 12 courses of sirolimus. A course of treatment was equal to 28 days. Courses were taken consecutively with no break, thus six courses represented 168 days; 12 courses 336 days / 48 weeks.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Study dates October 2009 to April 2013	patients with KHE), chemotherapy or radiation • At least 2 weeks since major surgery • At least 4 weeks since receiving myelosuppressive chemotherapy • At least 14 days since receiving hematopoietic growth factors, antineoplastic agents, enzyme-inducing anticonvulsants or cytochrome P450 3A4 inhibitors / inducers • chronic steroid use • known HIV • chronic severe or uncontrolled medical disease • uncontrolled infection • previous mTOR inhibitor use • impaired gastrointestinal function • Pregnant or breastfeeding women (women of childbearing age were required to use contraceptive methods)		• Kaposiform lymphangiomatosis: PR – 5 (71); SD 1 (14); PD – 1 (14) • Microcystic lymphatic malformation: PR – 2 (50); PD – 2 (50); 1 patient removed from trial[31] • KHE with KMP: PR – 10 (100) • KHE without KMP: PR – 1 (33); SD 1 (33); PD – 1 (33) • Capillary lymphatico/ venous malformation: 11 (100); 1 patient removed from trial[32] • Abnormalities of the central conducting lymphatic channels: PD – 3 (100) • PTEN/ AVM: PR – 2 (100) • PTEN/ overgrowth/ VA: PR – 3 (75); SD 1 (25) • Venous lymphatic malformation: PR – 3 (100) • Overall: PR – 47 (82); SD – 3 (5); PD – 7 (12) Course 12, n (%); n=57 • Generalized lymphatic anomaly: PR – 7 (100) • Gorham syndrome: PR – 1 (50); PD – 1 (50) • Kaposiform lymphangiomatosis: PR – 6 (86); PD – 1 (14) • Microcystic lymphatic malformation: PR – 2 (50); PD – 2 (50); 1 patient removed from trial[33]	The PICO for this review defined the population as *refractory* to standard therapies. Eleven patients in this trial had no previous treatment prior to be enrolled in this clinical trial; it is unclear from the documentation if they were refractory to other treatment. The trial was written using Simon's 2-stage design, with an interim analysis after six courses of treatment in the first 23 patients; stoppage of the study would occur if only 1/23 were CR/PR. The full study was powered to demonstrate a response rate of at least 18% at 90% power at the 0.05 level with 60 patients. Several syndromes had 100% partial response during the study period: generalised lymphatic anomaly, KHE with KMP, CLVM, PTEN and venous lymphatic malformation. Those with abnormalities of the central conducting lymphatic channels did not respond to sirolimus and had 100% progressive disease. Fifty percent of patients had a blood/bone marrow adverse event at the Grade 3 or 4 level and 37% had a Grade 3 or 4 infection; however, only two study patients decreased

[31] participant removed from study treatments for reasons other than progressive disease
[32] participant removed from study treatments for reasons other than progressive disease
[33] participant removed from study treatments for reasons other than progressive disease

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Total sample size n=61 **Baseline characteristics (n=60)** *Age years*, median (range): 8.1 (21 days to 28.5 years) *Male*, n (%): 25 (42) *Diagnosis* – 2014 ISSVA classification[26], n (%) • Generalized lymphatic anomaly: 7 (12) • Gorham syndrome: 3 (5) • Kaposiform lymphangiomatosis: 7 (12) • Microcystic lymphatic malformation: 5 (8) • KHE with KMP: 10 (17) • KHE without KMP: 3 (5) • Capillary lymphatico/ venous malformation: 13 (22) • Abnormalities of the central conducting		• KHE with KMP: PR – 10 (100) • KHE without KMP: PR – 2 (66); PD – 1 (33) • Capillary lymphatico/ venous malformation: 11 (100); 1 patient removed from trial[34] • Abnormalities of the central conducting lymphatic channels: PD – 3 (100) • PTEN/ AVM: PR – 1 (100); 1 patient lost to follow-up • PTEN/ overgrowth/ VA: PR – 3 (75); 1 patient removed from trial[35] • Venous lymphatic malformation: PR – 2 (100) • Overall – PR 45 (85); PD (15) **Important outcomes** **Radiographic changes**[36] Course 6, n (%) [95%CI]; n=57 • CR: 0 (0) [N/A] • PR: 20 (35) [20 to 51] • SD: 36 (63) [47 to 79] • PD: 1 (2) [0 to 6] Course 12, n (%) [95%CI]; n=53 • CR: 0 (0) [N/A] • PR: 28 (52) [36 to 69] • SD: 25 (48) [31 to 64] • PD: 0 (0) [N/A]	their sirolimus does and a further two stopped sirolimus due to toxicity. **Source of funding:** This study was supported by the Office of Orphan Products, Harvard Catalyst, The Harvard Clinical and Translational Science Center (National Center for Research Resources and National Center for advancing Translational Sciences, National Institutes of Health Award, Harvard University and the National Institutes of Health. Pfizer provided the drug but had no role in designing, conduction, analysing or reporting the study results. The authors declared no conflicts of interest.

[26] ISSVA classification: International Society for the Study of Vascular Anomalies. Earliest version developed in Rome in 1996, Adams et al used the 2014 revised classification.
[34] participant removed from study treatments for reasons other than progressive disease
[35] participant removed from study treatments for reasons other than progressive disease
[36] Radiographic changes were measured as
CR: no evidence of disease on radiologic imaging; PR: >20% reduction in size of target vascular lesion evident on radiologic imaging; PD: >20% increase in size of target vascular lesion evident on radiologic imaging; SD: ≤20% change in either direction of target vascular lesion evident on radiologic imaging

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	lymphatic channels: 3 (5) • PTEN/ AVM: 2 (3) • PTEN/ overgrowth/ VA: 4 (7) • Venous lymphatic malformation: 3 (5) *Previous Therapies*, n (%) • No previous therapy: 11 (18) • Medical therapy: 12 (20) • Surgery 9 (15) • Intervention[27] 6 (10) • Medical therapy and intervention: 1 (2) • Medical therapy and surgery: 1 (2) • Surgery and intervention: 16 (27) • Medical therapy, surgery and intervention: 4 (7)		**Organ specific disease response**[37] Course 6, n (%) [95%CI]; n=57 • CR: 0 (0) [N/A] • PR: 40 (71) [56 to 85] • SD: 17 (29) [15 to 44] • PD: 0 (0) [N/A] Course 12, n (%) [95%CI]; n=53 • CR: 0 (0) [N/A] • PR: 42 (80) [67 to 94] • SD: 11 (16) [4 to 28] • PD: 0 (0) [N/A] **Quality of Life (QoL)**[38] Course 6, n (%) [95%CI]; n=57 • CR: 18 (32) [17 to 47] • PR: 30 (52) [36 to 68] • SD: 9 (16) [4 to 28] • PD: 0 (0) [N/A] Course 12, n (%) [95%CI]; n=53 • CR: 21 (39) [23 to 55] • PR: 26 (50) [34 to 67] • SD: 5 (9) [0 to 19] • PD: 1 (2) [not reported] **Safety** *Adverse Events* • Dose reduction, n (%): 2 (3)	

[27] defined as any radiologic interventional procedure

[37] The functional impairment score was adopted from the measures of organ function that have been validated in the quantification of adverse event results from medical therapies and procedures. The instrument was piloted in the present study. Changes were defined as:

CR: no evidence of organ dysfunction due to disease; PR: improvement in target organ dysfunction by at least 1 grade; PD: worsening in target organ dysfunction by at least 1 grade; SD: no change in target organ dysfunction

[38] Quality-of-Life (QoL) changes were measured as

CR: normalisation of QoL criteria; PR: improvement of self-report PedsQL by >4.4 or proxy-report PedsQL by >4.5 or FACT-G by >3.99 compared with baseline; PD: worsening of self-report PedsQL by >4.4 or proxy-report PedsQL by >4.5 or FACT-G by >3.99 compared with baseline; SD: ≤4.4 change in self-report of PedsQL or ≤4.5 change in proxy-report PedsQL or ≤3.99 change in FACT-G compared with baseline

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			• AEs leading to drug discontinuation, n (%): 2 (3) *Grade 2 or Higher Adverse Events (AEs) by attributability to sirolimus*, n=60[39] Blood/ bone marrow, n (%) • Possible: 17 (28) • Probable: 11 (18) • Definite: 2 (3) Gastrointestinal, n (%) • Possible: 12 (20) • Probable: 18 (30) • Definite: 3 (5) Metabolic/ laboratory, n (%) • Possible: 5 (8) • Probable: 6 (10) • Definite: 1 (2) Pain, n (%) • Possible: 5 (8) • Probable: 5 (8) • Definite: 1 (2) *Grade 3 or 4 AE[40]* Blood/ bone marrow, n (%)41 • Grade 3/4: 30 (50) • Suspected to be sirolimus related (grade 3/4): 16 (27)	

[39] Presenting 4 AEs most likely to be attributable to sirolimus. Additional AEs can be found in the full paper.
[40] AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0: Grade 1, Mild - asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated; Grade 2, Moderate - minimal, local or non-invasive intervention indicated, limiting age-appropriate instrumental activities of daily living; Grade 3, Severe or medically significant but not immediately life-threatening - hospitalization or prolongation of hospitalization indicated, disabling, limiting self-care activities of daily living; Grade 4, Life-threatening consequences - urgent intervention indicated; Grade 5, Death related to AE
[41] Presenting 6 AEs most likely to be attributable to sirolimus. Additional AEs can be found in the full paper.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Gastrointestinal, n (%) • Grade 3/4: 10 (17) • Suspected to be sirolimus related (grade 3/4): 2 (3) Infection, n (%) • Grade 3/4: 22 (37) • Suspected to be sirolimus related (grade 3/4): 1 (2) Metabolic / laboratory, n (%) • Grade 3/4: 11 (18) • Suspected to be sirolimus related (grade 3/4): 2 (3) Pulmonary/ upper respiratory, n (%) • Grade 3/4: 7 (1) • Suspected to be sirolimus related (grade 3/4): 1 (2)	
Harbers VEM, Zwerink LGJM, Rongen GA, Klein WM, van der Vleuten CJM, van Rijnsoever IMP et al. Clinical differences in sirolimus treatment with low target levels between children and adults with vascular malformations - A nationwide trial. Clinical and translational science. 2023;16(5):781-96. **Study location** The Netherlands	**Children and adults with a diagnosis of a slow-flow vascular malformation that was refractory to standard care** **Inclusion criteria** • aged above 1 year • normal clinical screening[42] • Karnosfsky score >50 **Exclusion Criteria** • patients with other treatment alternatives	**Interventions** sirolimus children: starting dose of 0.8mg/m^2 in two doses adults: starting does of 1mg twice daily Dose adjustments, based on plasma levels of sirolimus, to reach target levels of 4-10ng/mL **Comparators** No comparator	**Results are following the challenge phase of the trial (six months of sirolimus therapy)** **Critical outcomes** **Disease Response** *Overall Response*[47] All Patients, n (%); n=67 • CR: 0 (0) • PR: 53 (79.1) • SD: 11 (16.4) • PD: 3 (4.5) Children, n (%); n=32 • CR: 0 (0)	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Yes 4. Unclear 5. Unclear 6. No 7. Yes 8. Yes 9. No 10. Yes **Other comments:** This was a phase IIB single-arm, open label clinical trial that included

[42] no signs of infection and normal bone marrow, liver and kidney function and glucose metabolism
[47] Presented as complete response (CR), partial response (PR), progressive disease (PD) or stable disease (SD). This composite measure is established by changes in at least 1 parameter: response to pain symptoms, health related quality of life (Pediatric Quality of Life Inventory / SF-36 / Physical Component Summary), clinical symptoms related to the vascular malformation – excluding pain, response to imaging (MRI).

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Study type Phase IIB open-label, single-arm clinical trial (single-arm trial) **Study aim** To investigate the efficacy and toxicity of sirolimus **Study dates** September 2017 to February 2021	• cardiac impairment • underlying medical disorders like Down's syndrome or other syndromes • hypersensitivity to drugs or metabolites from similar classes as trial treatment • acute or chronic pancreatitis • liver cirrhosis • active chronic hepatitis • severely impaired lung function[43] • recent history (≤5 years) of malignancy • immunocompromised patients, including known seropositivity for HIV • pregnant or lactating women **Total sample size** n=74 **Baseline characteristics (n=60)** *Age years*, median (SD): 23.0 (16.4) *Male*, n (%): 24 (35.3) *Vascular malformation type*, n (%)		• PR: 30 (93.8) • SD: 2 (6.3) • PD: 0 (0) Adults, n (%); n=35 • CR: 0 (0) • PR: 23 (65.7) • SD: 9 (25.7) • PD: 3 (8.6) *Responder / Non-Responder*[48] All Patients, n (%); n=67 • Responders: 53 (79.1) • Non-Responders: 14 (20.9) Children, n (%); n=32 • Responders: 30 (93.8) • Non-Responders: 2 (6.3) Adults, n (%); n=35 • Responders: 23 (65.7) • Non-Responders: 12 (34.3) **Symptom alleviation** *Change in pain symptoms*[49] All Patients, n (%); n=67 • No change in pain: 29 (43.3) • Improvement of pain: 37 (55.2) • Worsening of pain: 1 (1.5) Children, n (%); n=32 • No change in pain: 13 (40.6) • Improvement of pain: 19 (59.4)	74 patients from a single tertiary hospital in the Netherlands. It was not clear if all potentially eligible patients were included in the study. As this was a phase II clinical trial, all patients received the study drug, sirolimus, so it was not possible to blind participants or assessors. The study was designed as a challenge-dechallenge-rechallenge design. The challenge and dechallenge phases were each six months in length and the rechallenge phase was 12 months. The authors compared results between children and adults and reported that children in the study responded more often and earlier to sirolimus when compared with adults; these results were statistically significant. **Source of funding:** This study was funded by ZonMW. Pfizer supported the study by providing the sirolimus. The authors declared no conflicts of interest.

[43] Measured with spirometry where ≤50% of the normal predicted value and/or O2 saturation ≤88% at rest
[48] Responders are comprised of those that had complete or partial response (CR/PR); non-responders were those that had stable or progressive disease (SD/PD).
[49] Pain was recorded using the Children and Infants Postoperative Pain Scale for children aged 0–3 years, visual analogue scale (VAS) clinical pictures for children aged 4–7 years, VAS for patients aged 8–17 years and numeric pain rating scale (NRS) for adults.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	• lymphatic malformation: 26 (38.2) • venous malformation: 29 (42.6) • combined malformation: 11 (16.2)[44] • other: 2 (2.9)[45] *Previous Therapies*, n (%) • No previous therapy: 11 (18) • Medical therapy: 12 (20) • Surgery 9 (15) • Intervention[46] 6 (10) • Medical therapy and intervention: 1 (2) • Medical therapy and surgery: 1 (2) • Surgery and intervention: 16 (27) • Medical therapy, surgery and intervention: 4 (7)		• Worsening of pain: 0 (0) Adults, n (%); n=35 • No change in pain: 16 (45.7) • Improvement of pain: 1 (51.4) • Worsening of pain: 1 (2.9) *Pain score* All patients, EMM[50] (95%CI); n=67 • Baseline: 5.4 (4.5 to 6.2) • After challenge: 3.6 (2.8 to 4.4) • Difference: -1.8 (-2.8 to -0.8); p<0.001[51] Children, EMM (95%CI); n=32 • Baseline: 4.1 (2.9 to 5.4) • After challenge: 2.7 (1.4 to 4.0) • Difference: -1.5 (-3.1 to 0.08); p>0.05 Adults, EMM (95%CI); n=35 • Baseline: 6.2 (5.2 to 7.2) • After challenge: 4.3 (3.2 to 5.4) • Difference: -1.9 (-3.2 to -0.5); p<0.001 *Change of symptoms to the vascular malformation – excluding pain*[52] All Patients, n (%); n=67 • No change: 17 (25.4)	

[44] combined malformations include Kippel Trenaunay Syndrome (KTS), veno-lymphatic malformation and capillary and venous malformation.
[45] other vascular malformations: fibro adipose vascular malformation (FAVA), multiple spindle-cell hemangioma
[46] defined as any radiologic interventional procedure
[50] EMM: estimated marginal mean
[51] Mixed linear regression with a patient random effect and trial phase as fixed effect, with Bonferroni correction to account for multiple testing.
[52] Improvement of clinical symptoms was defined as clinical size decrease, improvement of activities/functioning, and improvement of energy/condition/endurance.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			• Improvement of symptoms: 50 (74.6) • Worsening of symptoms: 0 (0) Children, n (%); n=32 • No change: 4 (12.5) • Improvement of symptoms: 28 (87.5) • Worsening of symptoms: 0 (0) Adults, n (%); n=35 • No change: 13 (37.1) • Improvement of symptoms: 22 (62.9) • Worsening of symptoms: 0 (0) **Important outcomes** **Radiographic changes** *Change in size of the vascular malformation at 2D-MRI* All patients, n (%); n=62 • No change in volume: 39 (62.9) • Decreased volume: 22 (35.5) • Increased volume: 1 (1.6) Children, n (%); n=31 • No change in volume: 19 (61.3) • Decreased volume: 12 (38.7) • Increased volume: 0 (0) Adults, n (%); n=31 • No change in volume: 20 (64.5) • Decreased volume: 10 (32.3) • Increased volume: 1 (3.2)	

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Organ specific disease response *Hepatic (liver) disease activity: D-dimer level (ng/mL)* Children, median (95%CI); n=32 • Baseline: 1345 (620 to 2770) • After challenge: 1070 (860 to 2580) Adults, median (95%CI); n=35 • Baseline: 1315 (820 to 2300) • After challenge: 1030 (600 to 2280) **Quality of life** *Change in HRQoL*[53] All Patients, n (%); n=44 • No change: 11 (25.0) • Improved HRQoL: 29 (65.9) • Worsening of HRQoL: 4 (9.1) Children, n (%); n=18 • No change: 3 (16.7) • Improved HRQoL: 15 (83.3) • Worsening of HRQoL: 0 (0) Adults, n (%); n=26 • No change: 8 (30.8) • Improved HRQoL: 14 (53.3) • Worsening of HRQoL: 4 (15.4) **Safety** *Adverse Events* Occurrence of Grade 1-4 AEs attributable to sirolimus All Patients, n (%)[54]; n=67	

[53] HRQOL was assessed by Research and Development-36 (RAND-36) for adults, the TNO-AZL (Nederlandse Organisatie voor toegepast-natuurwetenschappelijk onderzoek van het Academisch Ziekenhuis in Leiden Preschool Children) Quality of Life Questionnaire for parents of 1-year-old children, the parents' version of the Paediatric Quality of Life Inventory 4.0 Generic Core Scales for the parents of children aged 2–17 years and the children's PedsQL version for children aged 5–17 years.
[54] % of total AEs, i.e. % of Grade 2 AEs attributable to sirolimus.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			• Grade 1: 202 (73.2) • Grade 2: 67 (24.3) • Grade 3: 6 (2.2) • Grade 4: 1 (0.4) • Total: 276 (100) Children, n (%); n=32 • Grade 1: 72 (72.7) • Grade 2: 22 (22.2) • Grade 3: 4 (4.0) • Grade 4: 1 (1.0) • Total: 99 (35.9) Adults, n (%); n=35 • Grade 1: 130 (73.4) • Grade 2: 45 (25.4) • Grade 3: 2 (1.1) • Grade 4: 0 (0.0) • Total: 177 (64.1) *Specific AEs by Grade and attributability to sirolimus* n=67[55] Infection, n (%) • Grade II: possible 11 (16.4); probable 1 (1.5); definitely 0 (0) • Grade III: possible 0 (0); probable 0 (0); definitely 0 (0) • Grade IV: possible 1 (1.5); probable 0 (0); definitely 0 (0) Neurologic toxicity, n (%) • Grade II: possible 7 (10.5); probable 4 (6.0); definitely 0 (0) • Grade III: possible 0 (0); probable 0 (0); definitely 0 (0) Gastrointestinal toxicity, n (%)	

[55] Presenting top 5 AEs most likely to be attributable to sirolimus. Additional AEs can be found in the full paper.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			• Grade II: possible 4 (6.0); probable 4 (6.0); definitely 2 (3.0) • Grade III: possible 0 (0); probable 0 (0); definitely 0 (0) General symptoms, n (%) • Grade II: possible 7 (10.5); probable 0 (0); definitely 0 (0) • Grade III: possible 0 (0); probable 0 (0); definitely 0 (0) Metabolic / laboratory toxicity, n (%) • Grade II: possible 5 (7.5); probable 1 (1.5); definitely 0 (0) • Grade III: possible 3 (4.5); probable 1 (1.5); definitely 0 (0) *Grade 3 or 4 AEs*[56] Suspected to be sirolimus related (grade 3/4), n • All patients: 3 • Children: 3 • Adults: 0	
Harbers VEM, Bouwman FCM, van Rijnsoever IMP, Verhoeven BH, van der Vleuten CJM, Schultze Kool LJ et al. Magnitude and relevance of change in health-related quality of life	**Children and adults with a diagnosis of a slow-flow vascular malformation that was refractory to standard care**	**Interventions** sirolimus children: starting dose of 0.8mg/m^2 in two doses adults: starting does of 1mg twice daily	**Results are following the challenge phase of the trial (six months of sirolimus therapy).** **Important outcomes** **Quality of life** *Change in HRQoL*[61]	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Yes 4. Unclear 5. Unclear

[56] AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0: Grade 1, Mild - asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated; Grade 2, Moderate - minimal, local or non-invasive intervention indicated, limiting age-appropriate instrumental activities of daily living; Grade 3, Severe or medically significant but not immediately life-threatening - hospitalization or prolongation of hospitalization indicated, disabling, limiting self-care activities of daily living; Grade 4, Life-threatening consequences - urgent intervention indicated; Grade 5, Death related to AE

[61] HRQOL was assessed by Research and Development-36 (SF-36) for adults, the parents' version of the Paediatric Quality of Life Inventory 4.0 Generic Core Scales for the parents of children aged 2–17 years and the children's PedsQL version for children aged 5–17 years. For all HRQoL measures a higher score indicates a better QoL.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
in patients with vascular malformations treated with sirolimus. Frontiers in medicine. 2023;10:1155476. **Study location** The Netherlands **Study type** Phase IIB open-label, single-arm clinical trial (single-arm trial) **Study aim** To investigate the efficacy and toxicity of sirolimus. The aim of this sub-paper was to analyse the magnitude of the HRQoL changes following the sirolimus treatment **Study dates** September 2017 to February 2021	**Inclusion criteria** • aged above 2 years • normal clinical screening[57] • Karnosfsky score >50 **Exclusion Criteria** • patients with other treatment alternatives • cardiac impairment • underlying medical disorders like Down's syndrome or other syndromes • hypersensitivity to drugs or metabolites from similar classes as trial treatment • acute or chronic pancreatitis • liver cirrhosis • active chronic hepatitis • severely impaired lung function[58] • recent history (≤5 years) of malignancy • immunocompromised patients, including known seropositivity for HIV • pregnant or lactating women **Total sample size** n=56	Dose adjustments, based on plasma levels of sirolimus, to reach target levels of 4-10ng/mL **Comparators** HRQoL scores were compared with the general Dutch population	Child-reported, mean (SD); n=16 • Baseline: 66.3 (17.7) • After treatment: 76.2 (18.1) • Change in HRQoL: +9.9 (12.6); p<0.05 Parent-reported, mean (SD); n=18 • Baseline: 64.0 (16.2) • After treatment: 74.9 (17.0) • Change in HRQoL: +10.9 (10.7); p<0.05 Adults: MCS score, mean (SD); n=26 • Baseline: 48.9 (9.3) • After treatment: 52.5 (8.7) • Change in HRQoL: +3.6 (8.3); p<0.005 Adults: PCS score, mean (SD); n=26 • Baseline: 32.8 (10.7) • After treatment: 39.0 (13.1) • Change in HRQoL: +6.2 (9.5); p<0.005 *Magnitude of HRQoL Change*[62] Children, parent reported, n=18 • physical functioning: 0.88 • emotional functioning: 0.44 • social functioning: 0.76 • school functioning: 0.74 • psychosocial: 0.78 • total score: 1.02 Children, child reported, n=16 • physical functioning: 0.58	6. No 7. Yes 8. Yes 9. No 10. Yes **Other comments:** This was a phase IIB single-arm, open label clinical trial that included 74 patients from a single tertiary hospital in the Netherlands. It was not clear if all potentially eligible patients were included in the study. As this was a phase II clinical trial, all patients received the study drug, sirolimus, so it was not possible to blind participants or assessors. The study was designed as a challenge-dechallenge-rechallenge design. The challenge and dechallenge phases were each six months in length and the rechallenge phase was 12 months. The authors compared HRQoL results to the Dutch general population. At baseline the HRQoL scores of children with vascular malformations were lower than that of the general population; following treatment with sirolimus the difference between the groups was smaller. The adult patients with vascular malformations had significantly lower HRQoL scores

[57] No signs of infection and normal bone marrow, liver and kidney function and glucose metabolism
[58] Measured with spirometry where ≤50% of the normal predicted value and/or O2 saturation ≤88% at rest
[62] Effect sizes at the end of the challenge period as categorised by the PedsQL (child and parent scores) and the SF-36 scores. Effect sizes were categorised as small 0.20 – 0.49, moderate 0.50 – 0.79, or high ≥0.80. An effect size of more than 0.5 was considered clinically relevant.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Baseline characteristics (n=51) *Age groups*, years; n (%): • under 2: 0 (0) • 2-4: 2 (4) • 5-7: 3 (6) • 8-12: 11 (22) • 13-17: 4 (8) • ≥18: 31 (61) *Male*, n (%): 15 (29) *Vascular malformation type*, n (%) • lymphatic malformation: 16 (31) • venous malformation: 25 (49) • combined malformation: 8 (16)[59] • other: 2 (4)[60] *Total HRQoL Score* Children's reports (n=17): 73.91 (IQR 55.43 to 77.17) Parent's reports (n=20): 59.24 (IQR 55.71 to 75.54) Adult Mental Component Summary (MCS) (n=31): 47.5 (95%CI 43.4 to 51.5) Adult Physical Component Summary		• emotional functioning: 0.86 • social functioning: 0.66 • school functioning: 0.40 • psychosocial: 0.81 • total score: 0.79 Adults, n=26 • physical functioning: 0.62 • social functioning: 0.73 • role limitations – physical: 0.47 • role limitations – emotional: 0.19 • mental health: 0.52 • energy levels/vitality: 0.66 • pain: 0.60 • general health perception: 0.29 • PCS: 0.43 • MCS: 0.65 *Comparison of HRQoL to Dutch General Population, Total Scale Score*[63] Children aged 2-4 years, parent report • Baseline, median (IQR); n=2: 52.08 (38.89 to NA) • After treatment, median (IQR; n=3: 70.83 (44.44 to NA) • Dutch population, median; n=275: 90.48 Children aged 5-7 years, parent report	across all domains, except for mental health, when compared to the general Dutch population; however, after six months of sirolimus treatment the scores for social functioning, role limitations – emotional and energy levels/vitality normalised to that of the general populus. **Source of funding:** This study was funded by ZonMW. Pfizer supported the study by providing the sirolimus. The authors declared no conflicts of interest.

[59] combined malformations include Kippel Trenaunay Syndrome (KTS), venolymphatic malformation and capillary and venous malformation.
[60] other vascular malformations: fibro adipose vascular malformation (FAVA), multiple spindle-cell haemangioma
[63] PedsQL parent or child reported score or SF-36 for adults

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	(PCS) (n=31): 33.1 (95%CI 29.1 to 37.1)		• Baseline, median (IQR); n=3: 66.30 (38.89 to NA) • After treatment, median (IQR; n=3: 83.70 (75.00 to NA) • Dutch population, median; n=251: 89.13 Children aged 8-12 years, child report • Baseline, median (IQR); n=10: 69.02 (53.80 to 79.89) • After treatment, median (IQR; n=10: 79.35 (65.22 to 90.22) • Dutch population, median (SD); n=219: 84.18 (8.87) Children aged 13-16 years, child report • Baseline, median (IQR); n=4: 78.26 (69.84 to 86.68) • After treatment, median (IQR; n=3: 78.26 (69.84 to 86.68) • Dutch population, median (SD); n=185: 82.24 (9.15) Adults, physical functioning, mean (95%CI) • Baseline, n=31: 49.0 (39.4 to 58.7) • After treatment, n=27: 63.9 (50.9 to 76.8) • Dutch population, n=1063: 81.9 • mean difference at baseline: p<0.005 • mean difference after treatment: p<0.05 Adults, social functioning, mean (95%CI)	

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			• Baseline, n=31: 57.7 (47.0 to 68.4) • After treatment, n=27: 77.3 (67.2 to 87.4) • Dutch population, n=1063: 86.9 • mean difference at baseline: p<0.005 • mean difference after treatment: p>0.05 Adults, role limitations - physical, mean (95%CI) • Baseline, n=31: 25.0 (12.9 to 37.1) • After treatment, n=27: 43.5 (25.6 to 61.4) • Dutch population, n=1063: 79.4 • mean difference at baseline: p<0.005 • mean difference after treatment: p<0.005 Adults, role limitations - emotional, mean (95%CI) • Baseline, n=31: 65.6 (50.6 to 80.6) • After treatment, n=27: 77.8 (61.8 to 93.7) • Dutch population, n=1063: 84.1 • mean difference at baseline: p<0.05 • mean difference after treatment: p>0.05 Adults, mental health, mean (95%CI)	

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			• Baseline, n=31: 72.5 (67.0 to 78.0) • After treatment, n=27: 81.6 (76.5 to 86.8) • Dutch population, n=1063: 76.8 • mean difference at baseline: p>0.05 • mean difference after treatment: p>0.05 Adults, energy levels/vitality, mean (95%CI) • Baseline, n=31: 47.1 (40.9 to 53.3) • After treatment, n=27: 62.6 (53.8 to 71.4) • Dutch population, n=1063: 67.4 • mean difference at baseline: p<0.005 • mean difference after treatment: p>0.05 Adults, pain, mean (95%CI) • Baseline, n=31: 43.4 (33.1 to 53.6) • After treatment, n=27: 64.8 (53.7 to 75.8) • Dutch population, n=1063: 79.5 • mean difference at baseline: p<0.005 • mean difference after treatment: p<0.05 Adults, general health perception, mean (95%CI) • Baseline, n=31: 49.0 (40.7 to 57.3)	

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			• After treatment, n=27: 55.0 (46.4 to 63.6) • Dutch population, n=1063: 72.7 • mean difference at baseline: p<0.005 • mean difference after treatment: p<0.005	
Ji Y, Chen S, Yang K, Zhou J, Zhang X, Jiang X et al. A prospective multi-center study of sirolimus for complicated vascular anomalies. Journal of vascular surgery. 2021;74(5):1673-81.e3. **Study location** China **Study type** Prospective, open-label, multi-centre, phase II clinical trial (single-arm trial) **Study aim** To measure the efficacy and safety of sirolimus in paediatric patients with complicated vascular anomalies	**Children with complicated vascular anomalies and at least one complication**[64] **Inclusion criteria** • aged between 0 and 14 years • clinical diagnosis of vascular anomaly and/or the presence of clinically complicated lesions (defined as life-threatening or potentially life-threatening, impinged on a vital structure, impaired the patients QoL or had the potential to cause substantial complications)	**Interventions** sirolimus children: starting dose of 0.8mg/m^2 in two doses adults: starting does of 1mg twice daily Dose adjustments, based on plasma levels of sirolimus, to reach target levels of 10-15ng/mL **Comparators** No comparator	**All the patients received ≥12 months of treatment. The mean length of follow-up was 3.0 years (range 0.4 to 4.5 years).** **Critical outcomes** **Disease Response** *Overall Response*[66] six months, n (%); n=126 • CR: 0 (0) • GR: 5 (4.0) • PR: 86 (68.3) • SD: 30 (23.8) • PD: 5 (4.0) 24 months, n (%); n=126 • CR: 0 (0) • GR: 28 (22.2) • PR: 71 (56.3) • SD: 14 (11.1) • PD: 13 (10.3)	JBI checklist for case series. 1. Yes 2. Yes 3. Yes 4. Unclear 5. Unclear 6. No 7. No 8. Yes 9. No 10. Not applicable **Other comments:** This was a single-arm, open label clinical trial that included 126 patients from 5 tertiary hospitals in China. It was not clear if all potentially eligible patients were included in the study. As this was a phase II clinical trial, all patients received the study drug, sirolimus, so it was not possible to blind participants or assessors.

[64] Patients needed to have at least 1 of 6 predefined complications: 1) coagulopathy, 2) chronic pain, 3) recurrent cellulitis (defined as >3 episodes per year), 4) ulceration, 5) visceral and/or bone involvement or 6) cardiac dysfunction

[66] Presented as complete response (CR), good response (GR), partial response (PR), stable disease (SD) or progressive disease (PD). This measure was determined based on changes in the volumetric measurements of VA lesions on MRI. CR = complete resolution of measured VAs at 12 months; GR = decrease of ≥75% but <100%; PR = decrease of ≥20% but <75%; SD = Increase of <20% but decrease of <20% in volumes of VA lesions; PD = Increase of ≥20% in volume of index LMs compared with baseline volume

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Study dates October 2014 to September 2019	**Exclusion Criteria** • At least 2 weeks since major surgery • At least 4 weeks since receiving chemotherapy, embolization, sclerotherapy or any other therapeutic agents • allergy to sirolimus or other rapamycin analogue **Total sample size** n=126 **Baseline characteristics (n=60)** *Age years*, median (range): 4.8 (0.1 to 14.0) *Male*, n (%): 64 (50.8) *Diagnosis* – 2018 ISSVA classification[65], n (%) • KHE: 25 (19.8) • VM: 19 (15.1) • AVM: 5 (4.0) • Common LM: 20 (15.9) • PL: 2 (1.6) • GLA: 8 (6.3) • KLA: 4 (3.2) • PIL: 4 (3.2) • CCLA: 1 (0.8)		*Total responses / No response*[67] six months, n (%); n=126 • Total responses: 91 (72.2) • No response: 35 (27.8) 24 months, n (%); n=126 • Total responses: 99 (78.6) • No response: 27 (21.4) *Total responses by VA diagnosis, six months, n* • KHE: 22/25 • VM: 14/19 • AVM: 3/5 • Common LM: 17/20 • PL: 0/2 • GLA: 5/8 • KLA: 2/4 • PIL: 2/4 • CCLA: 0/1 • GSD: 1/2 • CVM: 5/6 • CLM: 2/5 • LVM: 8/10 • CLVM: 2/3 • CVAVM: 2/3 • KTS: 5/7 • CLOVES syndrome: 1/2 *Total responses by VA diagnosis, 24 months, n* • KHE: 11/25 • VM: 17/19 • AVM: 1/5 • Common LM: 18/20 • PL: 0/2	The PICO for this review defined the population as *refractory* to standard therapies. Twenty-seven patients (21%) in this trial had no previous treatment prior to be enrolled in this clinical trial; it is unclear from the documentation if they were refractory to other treatment. Some arteriovenous malformations were also included in this study, which were not included in the PICO population of *slow-flow* vascular malformations. Efficacy was assessed as intention-to-treat; five patients withdrew before the end of the study. Two patients died during follow-up due to disease progression and one patient required prednisolone combination therapy so was no longer eligible for the trial; two additional patients were removed from the protocol due to concerns about disease progression. Several syndromes had 100% partial response during the study period. No patients exhibited a complete response during the follow-up period. Sirolimus was able to deliver an effective clinical responses in those with venous malformation, common lymphatic malformation and combined malformations with a prominent venous and/or lymphatic

[65] ISSVA classification: International Society for the Study of Vascular Anomalies. Earliest version developed in Rome in 1996, Ji et al used the 2018 revised classification.
[67] Total responses are comprised of those that had complete, good or partial response (CR/GR/PR); those with no response were those that had stable or progressive disease (SD/PD).

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	• GSD: 2 (1.6) • CVM: 6 (4.8) • CLM: 5 (4.0) • LVM: 10 (7.9) • CLVM: 3 (2.4) • CVAVM: 3 (2.4) • KTS: 7 (5.6) • CLOVES syndrome: 2 (1.6) *Severity Score, 2 or 3*, n (%): 109 (86.5)		• GLA: 6/8 • KLA: 2/4 • PIL: 3/4 • CCLA: 0/1 • GSD: 1/2 • CVM: 6/6 • CLM: 4/5 • LVM: 9/10 • CLVM: 3/3 • CVAVM: 3/3 • KTS: 4/7 • CLOVES syndrome: 1/2 VM, n=19 • Total responses: 14 • No response: 3 **Overall survival** • **Two patients died of disease progression during follow-up, one with KLA and one with PIL** **Symptom alleviation** *Mean severity score*[68], mean; n=126 • baseline: 2.6 • six months: 2.0 • 12 months: 1.3 • Change from baseline to six months: p<0.001 • Change from six months to 12 months: p<0.001 *Improvement in severity score by VA diagnosis, 12 months, n* • KHE: 21/25 • VM: 17/19 • AVM: 2/5	component. The authors reported that sirolimus had no effect for two patients with primary lymphedema. **Source of funding:** This study was supported by the National Natural Science Foundation of China, Key Project in the Science and Technology Program of Sichuan Province, Science Foundation for the Excellent Youth Scholars of Sichuan University and the 1-3-5 Project for Disciplines of Excellence – Clinical Research Incubation Project. The authors declared no conflicts of interest.

[68] Disease severity was recorded using a scale of 0 to 5 with higher values representing more profound symptoms and/or functional disability.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			• Common LM: 19/20 • PL: 0/2 • GLA: 7/8 • KLA: 3/4 • PIL: 3/4 • CCLA: 0/1 • GSD: 1/2 • CVM: 5/6 • CLM: 45 • LVM: 9/10 • CLVM: 3/3 • CVAVM: 3/3 • KTS: 4/7 • CLOVES syndrome: 2/2 **Important outcomes** **Radiographic changes** Please see disease response above **Quality of life** *Change in HRQoL[69],* 12 months, %; n=126 • Improvement from baseline: 100 (79.4) • Worsening from baseline: 18 (14.3) *Improvement in QoL score by VA diagnosis, 12 months, n* • KHE: 20/25 • VM: 16/19 • AVM: 1/5 • Common LM: 17/20 • PL: 0/2 • GLA: 7/8 • KLA: 2/4 • PIL: 3/4	

[69] HRQOL was assessed by Research and Development-36 (SF-36) for adults, the parents' version of the Paediatric Quality of Life Inventory 4.0 Generic Core Scales for the parents of children aged 2–17 years and the children's PedsQL version for children aged 5–17 years. For all HRQoL measures a higher score indicates a better QoL.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			• CCLA: 0/1 • GSD: 1/2 • CVM: 6/6 • CLM: 45 • LVM: 9/10 • CLVM: 3/3 • CVAVM: 3/3 • KTS: 6/7 • CLOVES syndrome: 2/2 **Safety** *Adverse Events* Occurrence of Grade 1-4 AEs[70], n (%); n=126[71] • Total AEs: 290 • Total Grade 3 AEs: 23 • Total Grade 4 AEs: 4 • Most common AEs: mucositis, diarrhoea, vomiting, rash and pneumonitis • AEs leading to temporary discontinuation: 12 (9.5) • AEs leading to target reduction of sirolimus: 7 (5.6) *Specific AEs by Grade, possibly related to sirolimus* n=126[72] Mucositis • All grades: 47 • Grade III: 2 • Grade IV: 0	

[70] AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0: Grade 1, Mild - asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated; Grade 2, Moderate - minimal, local or non-invasive intervention indicated, limiting age-appropriate instrumental activities of daily living; Grade 3, Severe or medically significant but not immediately life-threatening - hospitalization or prolongation of hospitalization indicated, disabling, limiting self-care activities of daily living; Grade 4, Life-threatening consequences - urgent intervention indicated; Grade 5, Death related to AE

[71] The safety population included all patients who had received at least one dose of sirolimus. It was possible for each person to have more than one adverse event, whereby the total will be >126

[72] Presenting top 5 AEs most likely to be attributable to sirolimus. Additional AEs can be found in the full paper.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Upper respiratory infection • All grades: 33 • Grade III: 7 • Grade IV: 1 Nausea/vomiting • All grades: 27 • Grade III: 1 • Grade IV: 0 Increased liver enzyme levels • All grades: 25 • Grade III: 6 • Grade IV: 0 Thrombocytosis • All grades: 25 • Grade III: 0 • Grade IV: 0	
Maruani A, Tavernier E, Boccara O, Mazereeuw-Hautier J, Leducq S, Bessis D et al. Sirolimus (Rapamycin) for Slow-Flow Malformations in Children: The Observational-Phase Randomized Clinical PERFORMUS Trial. JAMA dermatology. 2021;157(11):1289-98. **Study location** France **Study type**	**children with a slow-flow vascular malformation** **Inclusion criteria** • aged between 6 and 18 years • complicated slow-flow malformation[73] extending to underlying tissues, confirmed by MRI **Exclusion Criteria**	**Interventions** oral sirolimus, 0.08 mg/kg/d twice daily, with dose adjustments to reach a serum target of 4-12 ng/mL at day 15 **Comparators** Patients acted as their own comparator and were randomised to length of observation period. All patients had a 4 month observation period and were randomised to start sirolimus at month 4, 5, 6, 7 or 8.	**Patients were followed for 12 months. 63 patients were enrolled in the trial; 59 were included in the analysis.**[76] **Critical outcomes** **Disease Response** *Difference in volume*[77]*,* 12 months, median (IQR) • all vascular malformations (n=59): -0.002 (-0.004 to 0.001); p=0.24 • VM (n=22): 0 (-0.002 to 0.002); p=0.73	JBI checklist for RCTs. 1. No 2. Yes 3. Yes 4. No 5. No 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes 11. Yes 12. Yes 13. No **Other comments:**

[73] Venous malformation, lymphatic malformation apart from pure macrocytic malformation and combined venolymphatic malformations, including syndromic forms
[76] Four patients withdrew before receiving randomised intervention: 3 withdrawn from study by medical team, 1 patient withdrew consent to participate.
[77] Difference in the volume of the vascular malformation between the observational period and the interventional period

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Multicentre, open-label observational-phase randomised clinical trial (randomised trial) **Study aim** To assess the efficacy and safety of sirolimus for children with complicated slow-flow vascular malformations **Study dates** September 2015 to November 2020	• vascular malformation requiring immediate medical treatment • individuals with a contraindication to MRI • sirolimus is contraindicated[74] **Total sample size** n=63 **Baseline characteristics (n=63)** *Malformation type*, n (%) • vascular (VM): 22 (37.3) • lymphatic (LM): 18 (30.5) • venolymphatic (combined): 19 (32.2) *Age*, years; mean (SD) • VM: 10.3 (3.9) • LM: 11.7 (3.3) • combined: 12.9 (3.7) • total: 11.6 (3.8) *Male*, n (%) • VM: 9 (40.9) • LM: 5 (27.8) • combined: 10 (52.6) • total: 24 (40.7)		• LM (n=17): -0.004 (-0.006 to -0.002); p<0.001 • combined (n=19): -0.001 (-0.004 to 0.003); p=0.70 **Symptom alleviation** *Pain*[78] VM, mean±SD; n=22 • baseline: 3.62±2.96 • at transition to sirolimus: 3.24±3.03 • 12 months: 2.40±2.39 LM, mean±SD; n=18 • baseline: 1.52±2.54 • at transition to sirolimus: 2.21±2.98 • 12 months: 0.58±1.25 combined, mean±SD; n=19 • baseline: 3.67±3.12 • at transition to sirolimus: 5.08±3.18 • 12 months: 2.14±2.61 total, mean±SD; n=59 • baseline: 3.01±3.01 • at transition to sirolimus: 3.49±3.23 • 12 months: 1.76±2.29 *Oozing and bleeding*[79] VM, n (%); n=22 • baseline: 0 (0)	This was an open label clinical trial that included 63 paediatric patients from 11 tertiary hospitals in France. Patients acted as their own control (stepped-wedge design) and were randomised to the length of the observation period. Patients and clinicians were not blinded; however, radiographers assessing the primary outcome via MRI were blinded to treatment period. This was a randomised trial; however, patients were not randomised to a treatment arm but instead to a treatment length. Randomisation determined the length of the observation period prior to the start of sirolimus treatment. The study was powered to detect an effect size of 0.4 with 80% power with 2-sided type I error of 5% with a sample size of n=50. A total of 59 patients were included in the final analysis. The PICO for this review defined the population as *refractory* to standard therapies. Not all patients in this trial had previous treatment (range 32.2% to 93.3%). It is unclear from the publication if the included patients were refractory to other treatment.

[74] Immunosuppression, chronic infectious disease, cancer, liver insufficiency, cytopenia, hypercholesterolemia, pregnancy and women of childbearing age not using birth control
[78] Pain was self-assessed using a visual analogue scale 0 – 10, where 0 means no pain and 10 signifies the worst pain imaginable
[79] Data on bleeding and oozing was collected at three timepoints as a binary variable

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Previous therapies, n (%)[75] • surgery – partial resection: 19 (32.2) • surgery – epiphysiodesis: 3 (5.1) • sclerotherapy: 18 (30.5) • carbon dioxide laser: 4 (6.8) • anticoagulation: 6 (10.2) *Genetic Mutations*, 18 patients underwent genetic analysis; n (%) • *TEK*: 5 (27.8) • *PIK3CA*: 11 (61.1) • no variants: 2 (11.1)		• at transition to sirolimus: 1 (4.5) • 12 months: 2 (9.1) LM, n (%); n=18 • baseline: 8 (44.4) • at transition to sirolimus: 10 (55.6) • 12 months: 4 (22.2) combined, n (%); n=19 • baseline: 10 (52.6) • at transition to sirolimus: 9 (47.4) • 12 months: 2 (10.5) total, n (%); n=59 • baseline: 18 (30.5) • at transition to sirolimus: 20 (33.9) • 12 months: 8 (13.6) **Important outcomes** **Radiographic changes** *Volume of vascular malformations, mm^3* VM, median (IQR); n=22 • baseline: 128 (24 to 276) • at transition to sirolimus: 110 (23 to 327) • 12 months: 135 (23 to 311) LM, median (IQR); n=18 • baseline: 173 (47 to 343) • at transition to sirolimus: 308 (50 to 343) • 12 months: 145 (17 to 373)	Efficacy was assessed as intention-to-treat; eight patients withdrew before the end of the study. Six patients discontinued due to medical advice; 2 patients decided to withdraw due to adverse events. A key limitation of the analysis was a lack of controlling for time in the data analysis, a key criteria of stepped-wedge data trials. Those that had sirolimus for a longer period are not noted in the paper nor is that accounted for in the analysis. The study found that sirolimus had no overall treatment effect on slow-flow vascular malformations. A statistically significant reduction in the volume of lymphatic malformations was observed when this sub-group was analysed. **Source of funding:** The study was funded by the French Ministry of Social Affairs and Health. The funder had no role in the design and conduct of the study, including collection, management, analysis, interpretation of the data, preparation, review or approval of the manuscript. The authors report receiving personal fees from Pierre Fabre, Almirall, Sanofi-Genzyme, AbbVie, Pfizer, LEO Pharma, Sanofi-Aventis, Lilly, Novartis, Amgen, Takeda and Janssen. One researcher received further grants from the French

[75] Several answers might be possible for each patient

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			combined, median (IQR); n=19 • baseline: 189 (79 to 832) • at transition to sirolimus: 217 (72 to 672) • 12 months: 151 (49 to 800) total, median (IQR); n=59 • baseline: 164 (49 to 485) • at transition to sirolimus: 158 (48 to 510) • 12 months: 151 (31 to 420) **Organ specific disease response** **Skin and subcutaneous disease activity** *Global assessment of efficacy by physician, patient and parent*[80], mean ± SD Venous malformations (VM), n=22[81] Physician assessment • Visit 3: 1.77±2.05 • Visit 4: 3.55±2.69 • 12 months: 4.60±2.16 Patient assessment • Visit 3: 2.73±2.79 • Visit 4: 4.39±3.12 • 12 months: 5.72±2.63 Parent assessment • Visit 3: 2.43±2.40 • Visit 4: 4.05±2.49 • 12 months: 4.727±2.10	Health Ministry National Programme Hospitalier de Recherche Clinique.

[80] Score was assessed using a visual analogue scale at each visit (0=no efficacy; 10=complete resolution) by the physician, parent and patient. Visit 3 was 1 month after the introduction of sirolimus; visit 4 was 3 months after the introduction of sirolimus; the final visit was at the end of the study (12 months follow-up)
[81] p<0.001

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Lymphatic malformations (LM), n=18[82] Physician assessment • Visit 3: 3.64±2.82 • Visit 4: 5.07±2.27 • 12 months: 5.08±2.75 Patient assessment • Visit 3: 6.13±3.58 • Visit 4: 6.99±3.18 • 12 months: 7.03±3.30 Parent assessment • Visit 3: 3.82±2.68 • Visit 4: 5.83±2.97 • 12 months: 5.87±2.77 Combined malformations (combined), n=19[83] Physician assessment • Visit 3: 2.94±2.70 • Visit 4: 4.46±2.93 • 12 months: 5.00±3.14 Patient assessment • Visit 3: 3.64±3.50 • Visit 4: 5.28±3.36 • 12 months: 5.19±3.61 Parent assessment • Visit 3: 3.78±3.30 • Visit 4: 5.70±3.75 • 12 months: 5.59±3.54 Total, n=59[84] Physician assessment	

[82] p<0.001
[83] p<0.001
[84] p<0.001

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			• Visit 3: 2.64±2.56 • Visit 4: 4.22±2.67 • 12 months: 4.85±2.58 Patient assessment • Visit 3: 4.04±3.52 • Visit 4: 5.39±3.33 • 12 months: 5.95±3.18 Parent assessment • Visit 3: 3.24±2.81 • Visit 4: 5.00±3.04 • 12 months: 5.32±2.77 **Quality of Life (QoL)**[85] *Proportion of children with a C-DLQI score of 0 or 1, indicating condition has "no effect on their life"* VM, n (%); n=22 • baseline: 4 (18.2) • at transition to sirolimus: 4 (18.2) • 12 months: 10 (45.5) LM, n (%); n=18 • baseline: 10 (55.6) • at transition to sirolimus: 6 (33.3) • 12 months: 14 (77.8) combined, n (%); n=19 • baseline: 2 (10.5) • at transition to sirolimus: 4 (21.1) • 12 months: 8 (42.1) total, n (%); n=59	

[85] Quality-of-Life (QoL) was measured using the Children-Dermatological Life Quality Index (C-DLQI). There are 10 questions with a maximum score of 30. A score of 0-1 indicates "no effect on a child's life"; 2-6 "small effect", 7-12 "moderate effect", 13-18 "very large effect" and 19-30 "extremely large effect."

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			• baseline: 16 (27.1) • at transition to sirolimus: 14 (23.7) • 12 months: 32 (54.2) **Safety** *Nonserious Adverse Events* • Number of events: 231 • Number of patients experiencing an AE: 56 (95%) *AEs possibly related to sirolimus* Nonserious AEs • Number of events: 101 • Number of patients experiencing an AE: 43 (73%) • Median age: 14 (IQR 11-17) Serious AEs • Number of events: 5 • Number of patients experiencing an AE: 5 (8%) • Median age: 15 (IQR 10-19) *AEs probably related to sirolimus* Nonserious AEs • Number of events: 89 • Number of patients experiencing an AE: 35 (59%) • Median age: 12 (IQR 8-14) Serious AEs • Number of events: 0 • Number of patients experiencing an AE: 0 (0%)	
Tian R, Liang Y, Zhang W, Wang J, Shan Y, Gao H et al. Effectiveness of	**Children with complex lymphatic**	**Interventions** sirolimus	**Patients were divided into three groups based on treatment length: Group 1 = 1-6 months (n=15);**	JBI checklist for case series. 1. No 2. Yes

Study details	Population	Interventions	Study outcomes	Appraisal and funding
sirolimus in the treatment of complex lymphatic malformations: Single center report of 56 cases. Journal of pediatric surgery. 2020;55(11):2454-8. **Study location** China **Study type** Prospective case series **Study aim** Investigate the efficacy and safety of sirolimus in children with lymphatic malformations at a single hospital centre **Study dates** June 2016 to March 2019	**malformations treated with sirolimus** **Inclusion criteria** • aged between 0 and 18 years • diagnosis of complex lymphatic malformation (pathology or enhanced MRI) and treated with oral sirolimus **Exclusion Criteria** • None listed **Total sample size** n=56 **Baseline characteristics** *Age*, months; median (range): 24.0 (2 -194) *Male*, n (%): 32 (57.1) *Diagnosis method*, n (%) • pathology: 44 (78.6) • enhanced MRI: 12 (21.4) *Previous treatment*, n (%) • biopsy: 9 (16.1)	children: starting dose of 0.8mg/m^2 (body surface per dose), administered every 12 hours Dose adjustments, based on plasma levels of sirolimus, to reach target levels of 10-15ng/mL Patients were also given SMZ (400 mg sulfamethoxazole & 80 mg trimethoprim / piece), dosed at 20-30 mg/kg, dived into two oral doses and given three days per week **Comparators** No comparator	**Group 2 = 7-12 months (16); Group 3 = 13-24 months (n=25).** **Critical outcomes** **Disease Response** *Overall Response*[86], n (%) • CR: 2 (3.6) • PR: 48 (85.7) • SD: 0 (0) • PD: 6 (10.7) *Effective / Ineffective responses*[87] Group 1, n (%); n=15 • Effective: 11 (73.3) • Ineffective: 4 (26.7) Group 2, n (%); n=16 • Effective: 15 (93.8) • Ineffective: 1 (6.2) Group 3, n (%); n=25 • Effective: 24 (96) • Ineffective: 1 (4) **Safety** *Adverse Events*	3. Yes 4. Unclear 5. Unclear 6. No 7. No 8. Yes 9. No 10. No **Other comments:** This was a prospective case series from a single paediatric hospital in China. It was not clear if all potentially eligible patients were included in the study. As this was a prospective case series, no comparator data were available. The PICO for this review defined the population as *refractory* to standard therapies. Thirteen patients (23.2%) in this trial had no previous treatment prior to be enrolled in this clinical trial; it is unclear from the documentation if they were refractory to other treatment. Following oral sirolimus, nearly 90% of patients in the prospective case series had an effective response to treatment. Three patients had a severe adverse event. No statistical analyses were presented.

[86] Presented as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). This measure was determined based on changes in the volumetric measurements of VA lesions on MRI, clinical changes in the lesion and/or changes in symptoms. CR = complete disappearance of either the lesion (clinical and/or radiological), and the symptoms; PR = reduction of >20% in size of the lesion (clinical and/or radiological) and improvement in symptoms; PD = enlargement of >20% in size of the lesion (clinical and/or radiological) or as new lesions appearing; SD = none of the above

[87] Effective group is comprised of those that had complete or partial response (CR/PR); those in the ineffective group were those that had stable or progressive disease (SD/PD).

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	• partial excision: 22 (39.3) • sclerotherapy: 7 (12.5) • other treatment: 5 (8.9) • total: 43 (76.8)		Occurrence of Grade 1-4 AEs[88], n (%); n=56[89] • Total AEs: 37 • Total Grade 3 AEs: 3 • Total Grade 4 AEs: 0 *Specific AEs by Grade[90]* Oral mucositis • All grades: 17 • Grade III: 1 • Grade IV: 0 Upper respiratory infection • All grades: 6 • Grade III: 0 • Grade IV: 0 Pneumonia • All grades: 2 • Grade III: 2[91] • Grade IV: 0 Cystic haemorrhage • All grades: 4 • Grade III: 0 • Grade IV: 0 Rash • All grades: 3 • Grade III: 0 • Grade IV: 0	The authors noted that during the study not all patients had consistent treatment approaches, due to ethical concerns, which limits the comparability and generalisability of the results. **Source of funding:** The study was funded by two Chinese government grants: Project of Shanghai Science and Technology Committee and Science and Technology Development Fund of Shanghai Pudong New Area. The authors declared no conflicts of interest.

[88] AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0: Grade 1, Mild - asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated; Grade 2, Moderate - minimal, local or non-invasive intervention indicated, limiting age-appropriate instrumental activities of daily living; Grade 3, Severe or medically significant but not immediately life-threatening - hospitalization or prolongation of hospitalization indicated, disabling, limiting self-care activities of daily living; Grade 4, Life-threatening consequences - urgent intervention indicated; Grade 5, Death related to AE

[89] The safety population included all patients who had received at least one dose of sirolimus. It was possible for each person to have more than one adverse event, whereby the total will be >56

[90] Presenting top 5 AEs. Additional AEs can be found in the full paper.

[91] Two children were admitted to paediatric ITU for pneumonia (Grade III AE)

Study details	Population	Interventions	Study outcomes	Appraisal and funding

Abbreviations
2D: two dimensional; AE: adverse event; AVM: arteriovenous malformation; CCLA: central conducting lymphatic anomaly; C-DLQI: Children-Dermatological Life Quality Index; CI: confidence interval; CLM: capillary lymphatic malformation; CLOVES: congenital lipomatous overgrowth, vascular malformation, epidermal nevus, spinal/skeletal anomalies/scoliosis; CLVM: capillary lymphatic venous malformation; CR: complete response; CVAVM: capillary venous arteriovenous malformation; CVM: capillary venous malformation; EMM: estimated marginal mean; FACT-G: Functional Assessment of Cancer Therapy – General; FAVA: fibro adipose vascular malformation; GLA: generalized lymphatic anomaly; GR: good response; GSD: Gorham-Stout disease; HIV: human immunodeficiency virus; HRQoL: health related quality of life; IQR: interquartile range; ISSVA: International Society for the Study of Vascular Anomalies; ITU: intensive therapy unit; kg: kilograms; KHE: kaposiform haemangioendothelioma; KLA: kaposiform lymphangiomatosis; KMP: Kasabach-Merritt Phenomenon; KTS: Klippel-Trenaunay syndrome; LM: lymphatic malformation; LVM: lymphatic venous malformation; m: metre; MCS: mental component summary; mg: milligram; mL: millilitres; mm: millimetres; MRI: magnetic resonance imaging; mTOR: mammalian target of rapamycin; n: number; N/A: not applicable; ng: nanograms; NRS: numeric rating scale; PCS: physical component summary; PD: progressive disease; PedsQL: Paediatric Quality of Life Inventory; PIL: primary intestinal lymphangiectasia; PL: primary lymphedema; PR: partial response; PTEN: PTEN Hamartoma Tumour Syndrome; QoL: quality of life; RAND-36: Research and Development-36; SD: stable disease; SD: standard deviation; SF-36: Short Form 36; SMZ: sulfamethoxazole & trimethoprim; *TEK*: tyrosine kinase receptor gene; TNO-AZL: Nederlandse Organisatie voor toegepast-natuurwetenschappelijk onderzoek van het Academisch Ziekenhuis in Leiden Preschool Children; US: United States; VA: vascular anomalies; VAS: visual analogue scale; VM: venous malformation

Appendix F Quality appraisal checklists

JBI critical appraisal checklist for RCTs

1. Was true randomisation used for assignment of participants to treatment groups?
2. Was allocation to treatment groups concealed?
3. Were treatment groups similar at the baseline?
4. Were participants blinded to treatment assignment?
5. Were those delivering treatment blind to treatment assignment?
6. Were outcomes assessors blind to treatment assignment?
7. Were treatment groups treated identically other than the intervention of interest?
8. Was follow-up complete and if not, were differences between groups in terms of their follow-up adequately described and analysed?
9. Were participants analysed in the groups to which they were randomised?
10. Were outcomes measured in the same way for treatment groups?
11. Were outcomes measured in a reliable way?
12. Was appropriate statistical analysis used?
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomisations, parallel groups) accounted for in the conduct and analysis of the trial

JBI Critical Appraisal Checklist for Case Series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series
3. Were valid methods used for the identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

Appendix G GRADE profiles

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sirolimus	Best supportive care	Result		
Disease Response (1 randomised trial, 3 single-arm trials, 1 prospective case series)									
Overall Response[A], six months of treatment (benefit is indicated by complete response – CR or partial response – PR); n (%)									
1 single-arm trial Harbers, Zwerink et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	total=67; children=32; adults=35		*All patients* • CR: 0 (0) • PR: 53 (79.1) • SD: 11 (16.4) • PD: 3 (4.5) *Children* • CR: 0 (0) • PR: 30 (93.8) • SD: 2 (6.3) • PD: 0 (0) *Adults* • CR: 0 (0) • PR: 23 (65.7) • SD: 9 (25.7) • PD: 3 (8.6)	Critical	Very low
Overall Response[B], six months of treatment (benefit is indicated by responder); n (%)									
1 single-arm trial Harbers, Zwerink et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	total=67; children=32; adults=35		*All patients* • Responders: 53 (79.1) • Non-Responders: 14 (20.9) *Children* • Responders: 30 (93.8) • Non-Responders: 2 (6.3) *Adults* • Responders: 23 (65.7) • Non-Responders: 12 (34.3)	Critical	Very low
Overall Response[C], six months (benefit is indicated by complete response – CR or partial response – PR); n (%)									
1 single-arm trial Ji et al 2021	Very serious limitations[1]	Very serious indirectness[3]	Not applicable	Not calculable	126		• CR: 0 (0) • GR: 5 (4.0) • PR: 86 (68.3) • SD: 30 (23.8)	Critical	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sirolimus	Best supportive care	Result		
							• PD: 5 (4.0)		
Overall Response[D], six months (benefit is indicated by responder); n (%)									
1 single-arm trial Ji et al 2021	Very serious limitations[1]	Very serious indirectness[3]	Not applicable	Not calculable	126		• Total responses: 91 (72.2) • No response: 35 (27.8)	Critical	Very low
Overall Response[E], Course six[F] / 168 days (benefit is indicated by complete response – CR or partial response – PR); n (%) [95%CI]									
1 single-arm trial Adams et al 2016	Serious limitations[4]	Very serious indirectness[3]	Not applicable	Not calculable	57		• CR: 0 (0) [N/A] • PR: 47 (83) [70 to 95] • SD: 3 (5) [0 to 13] • PD: 7 (12) [2 to 23]	Critical	Very low
Overall Response[E], Course 12[G] / 336 days (benefit is indicated by complete response – CR or partial response – PR); n (%) [95%CI]									
1 single-arm trial Adams et al 2016	Serious limitations[4]	Very serious indirectness[3]	Not applicable	Not calculable	53		• CR: 0 (0) [N/A] • PR: 45 (85) [73 to 97] • SD: 0 (0) [N/A] • PD: 8 (15) [3 to 27]	Critical	Very low
Difference in volume of vascular malformation, 12 months (benefit is indicated by a smaller volume); mm^3; median (IQR)									
1 randomised trial Maruani et al 2021	Very serious limitations[5]	Very serious indirectness[3]	Not applicable	Not calculable	59		• all vascular malformations (n=59): -0.002 (-0.004 to 0.001); p=0.24 • VM (n=22): 0 (-0.002 to 0.002); p=0.73 • LM (n=17): -0.004 (-0.006 to -0.002); p<0.001 • combined (n=19): -0.001 (-0.004 to 0.003); p=0.70	Critical	Very low
Overall Response[C], 24 months (benefit is indicated by complete response – CR, good response – GR or partial response – PR); n (%)									
1 single-arm trial Ji et al 2021	Very serious limitations[1]	Very serious indirectness[3]	Not applicable	Not calculable	126		• CR: 0 (0) • GR: 28 (22.2) • PR: 71 (56.3) • SD: 14 (11.1) • PD: 13 (10.3)	Critical	Very low
Overall Response[D], 24 months (benefit is indicated by responder); n (%)									
1 single-arm trial	Very serious limitations[1]	Very serious indirectness[3]	Not applicable	Not calculable	126		• Total responses: 99 (78.6) • No response: 27 (21.4)	Critical	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Sirolimus**	**Best supportive care**	**Result**		
Ji et al 2021									
Overall Response[H], 24 months (benefit is indicated by complete response – CR or partial response – PR); n (%)									
1 prospective case series Tian et al 2020	Very serious limitations[1]	Very serious indirectness[3]	Not applicable	Not calculable	56		• CR: 2 (3.6) • PR: 48 (85.7) • SD: 0 (0) • PD: 6 (10.7)	Critical	Very low
Overall Response[I], 24 months; n (%)									
1 prospective case series Tian et al 2020	Very serious limitations[1]	Very serious indirectness[3]	Not applicable	Not calculable	56 Group 1=15, Group 2=16, Group 3=25		Group 1: • Effective: 11 (73.3) • Ineffective: 4 (26.7) Group 2: • Effective: 15 (93.8) • Ineffective: 1 (6.2) Group 3: • Effective: 24 (96) • Ineffective: 1 (4)	Critical	Very low
Overall Survival (1 single-arm trial)									
Died during follow up, 24 months; n									
1 single-arm trial Ji et al 2021	Very serious limitations[1]	Very serious indirectness[3]	Not applicable	Not calculable	126		Two patients died of disease progression during follow up	Critical	Very low
Symptom alleviation (1 randomised trial, 2 single-arm trials)									
Change in pain symptoms[J], six months of treatment; n (%)									
1 single-arm trial Harbers, Zwerink et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	67; children=32; adults=35		*All patients* • No change in pain: 29 (43.3) • Improvement of pain: 37 (55.2) • Worsening of pain: 1 (1.5) *Children* • No change in pain: 13 (40.6) • Improvement of pain: 19 (59.4) • Worsening of pain: 0 (0)	Critical	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Sirolimus**	**Best supportive care**	**Result**		
							Adults • No change in pain: 16 (45.7) • Improvement of pain: 1 (51.4) • Worsening of pain: 1 (2.9)		
Pain score, six months of treatment; EMM[K] (95%CI)									
1 single-arm trial Harbers, Zwerink et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	67; children=32; adults=35		*All patients* • Baseline: 5.4 (4.5 to 6.2) • After challenge: 3.6 (2.8 to 4.4) • Difference: -1.8 (-2.8 to -0.8); p<0.001 *Children* • Baseline: 4.1 (2.9 to 5.4) • After challenge: 2.7 (1.4 to 4.0) • Difference: -1.5 (-3.1 to 0.08); p>0.05 *Adults* • Baseline: 6.2 (5.2 to 7.2) • After challenge: 4.3 (3.2 to 5.4) • Difference: -1.9 (-3.2 to -0.5); p<0.001	Critical	Very low
Change in symptoms to the vascular malformation excluding pain[L], six months of treatment; n (%)									
1 single-arm trial Harbers, Zwerink et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	67; children=32; adults=35		*All patients* • No change: 17 (25.4) • Improvement of symptoms: 50 (74.6) • Worsening of symptoms: 0 (0) *Children* • No change in symptoms: 4 (12.5) • Improvement of symptoms: 28 (87.5)	Critical	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sirolimus	Best supportive care	Result		
							• Worsening of symptoms: 0 (0) *Adults* • No change in symptoms: 13 (37.1) • Improvement of symptoms: 22 (35.5) • Worsening of symptoms: 0 (0)		
Pain; 12 months (benefit is indicated by a lower score); mean±SD									
1 randomised trial Maruani et al 2021	Very serious limitations[5]	Very serious indirectness[3]	Not applicable	Not calculable	59 VM=22; LM=18; combined= 19		VM: • baseline: 3.62±2.96 • at transition to sirolimus: 3.24±3.03 • 12 months: 2.40±2.39 LM: • baseline: 1.52±2.54 • at transition to sirolimus: 2.21±2.98 • 12 months: 0.58±1.25 combined: • baseline: 3.67±3.12 • at transition to sirolimus: 5.08±3.18 • 12 months: 2.14±2.61 total: • baseline: 3.01±3.01 • at transition to sirolimus: 3.49±3.23 • 12 months: 1.76±2.29	Critical	Very low
Oozing and bleeding; 12 months (benefit is indicated by a null value / 1 indicates presence of bleeding or oozing); n (%)									
1 randomised trial Maruani et al 2021	Very serious limitations[5]	Very serious indirectness[3]	Not applicable	Not calculable	59 VM=22; LM=18; combined= 19		VM: • baseline: 0 (0) • at transition to sirolimus: 1 (4.5) • 12 months: 2 (9.1)	Critical	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sirolimus	Best supportive care	Result		
							LM: • baseline: 8 (44.4) • at transition to sirolimus: 10 (55.6) • 12 months: 4 (22.2) combined: • baseline: 10 (52.6) • at transition to sirolimus: 9 (47.4) • 12 months: 2 (10.5) total: • baseline: 18 (30.5) • at transition to sirolimus: 20 (33.9) • 12 months: 8 (13.6)		
Severity score,[M] 12 months (higher scores indicate more profound symptoms and/or functional disability); score									
1 single-arm trial Ji et al 2021	Serious limitations[4]	Very serious indirectness[3]	Not applicable	Not calculable	126		• Baseline: 2.6 • six months: 2.0 • 12 months: 1.3 • Change from baseline to six months: p<0.001 • Change from six months to 12 months: p<0.001	Critical	Very low
Radiographic changes (1 randomised trial, 2 single-arm trials)									
Radiographic Changes on MRI, six months (benefit is indicated by decreased volume); n (%) [95%CI]									
1 single-arm trial Harbers, Zwerink et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	62; children=31; adults=31		*All patients* • No change in volume: 39 (62.9) • Decreased volume: 22 (35.5) • Increased volume: 1 (1.6) *Children* • No change in volume: 19 (61.3)	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sirolimus	Best supportive care	Result		
							• Decreased volume: 12 (38.7) • Increased volume: 0 (0) *Adults.* • No change in volume: 20 (64.5) • Decreased volume: 10 (32.3) • Increased volume: 1 (3.2)		
Radiographic Changes[N], Course six[F] / 168 days (benefit is indicated by complete response – CR or partial response – PR); n (%) [95%CI]									
1 single-arm trial Adams et al 2016	Serious limitations[4]	Very serious indirectness[3]	Not applicable	Not calculable	57		• CR: 0 (0) [N/A] • PR: 20 (35) [20 to 51] • SD: 36 (63) [47 to 79] • PD: 1 (2) [0 to 6]	Important	Very low
Radiographic Changes[N], Course 12[G] / 336 days (benefit is indicated by complete response – CR or partial response – PR); n (%) [95%CI]									
1 single-arm trial Adams et al 2016	Serious limitations[4]	Very serious indirectness[3]	Not applicable	Not calculable	53		• CR: 0 (0) [N/A] • PR: 28 (52) [36 to 69] • SD: 25 (48) [31 to 64] • PD: 0 (0) [N/A]	Important	Very low
Volume of vascular malformations, mm^3, 12 months (benefit is indicated by decreased volume); median (IQR)									
1 randomised trial Maruani et al 2021	Very serious limitations[5]	Very serious indirectness[3]	Not applicable	Not calculable	59 VM=22; LM=18; combined=19		VM: • baseline: 128 (24 to 276) • at transition to sirolimus: 110 (23 to 327) • 12 months: 135 (23 to 311) LM: • baseline: 173 (47 to 343) • at transition to sirolimus: 308 (50 to 343) • 12 months: 145 (17 to 373) combined: • baseline: 189 (79 to 832)	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sirolimus	Best supportive care	Result		
							• at transition to sirolimus: 217 (72 to 672) • 12 months: 151 (49 to 800) total: • baseline: 164 (49 to 485) • at transition to sirolimus: 158 (48 to 510) • 12 months: 151 (31 to 420)		
Organ specific disease response (1 randomised trial and 2 single-arm trials)									
Hepatic (liver) disease activity: D-dimer level, six months (benefit is indicated lower result); ng/mL; median (95%CI)									
1 single-arm trial Harbers, Zwerink et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	Children n=32; Adults n=35		Children • Baseline: 1345 (620 to 2770) • After challenge: 1070 (860 to 2580) Adults • Baseline: 1315 (820 to 2300) • After challenge: 1030 (600 to 2280)	Important	Very low
Functional Impairment Score[O], Course six[F] / 168 days (benefit is indicated by complete response – CR or partial response – PR); n (%) [95%CI]									
1 single-arm trial Adams et al 2016	Serious limitations[4]	Very serious indirectness[3]	Not applicable	Not calculable	57		• CR: 0 (0) [N/A] • PR: 40 (71) [56 to 85] • SD: 17 (29) [15 to 44] • PD: 0 (0) [N/A]	Important	Very low
Functional Impairment Score[O], Course 12[G] / 336 days (benefit is indicated by complete response – CR or partial response – PR); n (%) [95%CI]									
1 single-arm trial Adams et al 2016	Serious limitations[4]	Very serious indirectness[3]	Not applicable	Not calculable	53		• CR: 0 (0) [N/A] • PR: 42 (80) [67 to 94] • SD: 11 (16) [4 to 28] • PD: 0 (0) [N/A]	Important	Very low
Skin and subcutaneous disease activity: Global assessment of efficacy by physician, patient and parent[P], 12 months (benefit is indicated higher result); mean±SD									
1 randomised trial	Very serious limitations[5]	Very serious indirectness[3]	Not applicable	Not calculable	59		Venous malformations (VM), p<0.001	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sirolimus	Best supportive care	Result		
Maruani et al 2021					VM=22; LM=18; combined= 19		*Physician assessment* • Visit 3: 1.77±2.05[a] • Visit 4: 3.55±2.69[b] • 12 months: 4.60±2.16 *Patient assessment* • Visit 3: 2.73±2.79 • Visit 4: 4.39±3.12 • 12 months: 5.72±2.63 *Parent assessment* • Visit 3: 2.43±2.40 • Visit 4: 4.05±2.49 • 12 months: 4.727±2.10 <u>Lymphatic malformations (LM), p<0.001</u> *Physician assessment* • Visit 3: 3.64±2.82 • Visit 4: 5.07±2.27 • 12 months: 5.08±2.75 *Patient assessment* • Visit 3: 6.13±3.58 • Visit 4: 6.99±3.18 • 12 months: 7.03±3.30 *Parent assessment* • Visit 3: 3.82±2.68 • Visit 4: 5.83±2.97 • 12 months: 5.87±2.77 <u>Combined malformations (combined)</u>, p<0.001 *Physician assessment* • Visit 3: 2.94±2.70 • Visit 4: 4.46±2.93 • 12 months: 5.00±3.14 *Patient assessment* • Visit 3: 3.64±3.50		

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sirolimus	Best supportive care	Result		
							• Visit 4: 5.28±3.36 • 12 months: 5.19±3.61 *Parent assessment* • Visit 3: 3.78±3.30 • Visit 4: 5.70±3.75 • 12 months: 5.59±3.54 <u>Total, p<0.001</u> *Physician assessment* • Visit 3: 2.64±2.56 • Visit 4: 4.22±2.67 • 12 months: 4.85±2.58 *Patient assessment* • Visit 3: 4.04±3.52 • Visit 4: 5.39±3.33 • 12 months: 5.95±3.18 *Parent assessment* • Visit 3: 3.24±2.81 • Visit 4: 5.00±3.04 • 12 months: 5.32±2.77		
Quality of Life (QoL; 1 randomised trial, 4 single-arm trials)									
HRQoL[Q], six months of treatment; n (%)									
1 single-arm trial Harbers, Zwerink et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	44; children=18; adults=26		*All patients* • No change: 11 (25.0) • Improved HRQoL: 29 (65.9) • Worsening of HRQoL: 4 (9.1) *Children* • No change: 3 (16.7) • Improved HRQoL: 15 (83.3) • Worsening of HRQoL: 0 (0) *Adults* • No change: 8 (30.8)	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sirolimus	Best supportive care	Result		
							• Improved HRQoL: 14 (53.3) • Worsening of HRQoL: 4 (15.4)		
Change in HRQoL[Q], six months of treatment (benefit is indicated by a higher result); mean (SD)									
1 single-arm trial Harbers, Bouwman et al 2023	Serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	child-reported HRQoL=16; parent-reported HRQoL=18; adults=26		*Child-reported* • Baseline: 66.3 (17.7) • After treatment: 76.2 (18.1) • Change in HRQoL: +9.9 (12.6); p<0.05 *Parent-reported* • Baseline: 64.0 (16.2) • After treatment: 74.9 (17.0) • Change in HRQoL: +10.9 (10.7); p<0.05 *Adults: MCS score* • Baseline: 48.9 (9.3) • After treatment: 52.5 (8.7) • Change in HRQoL: +3.6 (8.3); p<0.005 *Adults: PCS score* • Baseline: 32.8 (10.7) • After treatment: 39.0 (13.1) • Change in HRQoL: +6.2 (9.5); p<0.005	Important	Very low
Magnitude of HRQoL Change, six months (benefit is indicated by a higher results); effect size									
1 single-arm trial Harbers, Bouwman et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	child-reported HRQoL=16; parent-reported HRQoL=18; adults=26		• Children, parent reported, total score: 1.02 • Children, child reported, total score: 0.79 • Adults, PCS: 0.43 • Adults, MCS: 0.65	Important	Very low
Comparison of HRQoL to Dutch General Population, Total HRQoL Score, six months (benefit is indicated by a higher results); median (IQR) / median (SD) / mean (95%CI)									
1 single-arm trial	Serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	children aged 2-4 years=3;	Dutch population	*Children aged 2-4 years, parent report*	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sirolimus	Best supportive care	Result		
Harbers, Bouwman et al 2023					children aged 5-7 years=3; children aged 8-12=10; children aged 13-16 years=3; adults=27	children aged 2-4 years=275; children aged 5-7 years=251; children aged 8-12=219; children aged 13-16=185; adults=1063	• After treatment: 70.83 (44.44 to NA) • Dutch population: 90.48 *Children aged 5-7 years, parent report* • After treatment: 83.70 (75.00 to NA) • Dutch population: 89.13 *Children aged 8-12 years, child report* • After treatment: 79.35 (65.22 to 90.22) • Dutch population: 84.18 (8.87) *Children aged 13-16 years, child report* • After treatment: 78.26 (69.84 to 86.68) • Dutch population: 82.24 (9.15) *Adults, physical functioning* • After treatment: 63.9 (50.9 to 76.8) • Dutch population: 81.9 • mean difference: p<0.05 *Adults, social functioning* • After treatment: 77.3 (67.2 to 87.4) • Dutch population: 86.9 • mean difference: p>0.05 *Adults, role limitations - physical* • After treatment: 43.5 (25.6 to 61.4) • Dutch population: 79.4 • mean difference: p<0.005 *Adults, role limitations - emotional* • After treatment: 77.8 (61.8 to 93.7) • Dutch population: 84.1		

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sirolimus	Best supportive care	Result		
							• mean difference: p>0.05 *Adults, mental health* • After treatment: 81.6 (76.5 to 86.8) • Dutch population: 76.8 • mean difference: p>0.05 *Adults, energy levels/vitality* • After treatment: 62.6 (53.8 to 71.4) • Dutch population: 67.4 • mean difference: p>0.05 *Adults, pain* • After treatment: 64.8 (53.7 to 75.8) • Dutch population: 79.5 • mean difference: p<0.05 *Adults, general health perception* • After treatment: 55.0 (46.4 to 63.6) • Dutch population: 72.7 • mean difference: p<0.005		
QoL[S], Course six[F] / 168 days (benefit is indicated by complete response – CR or partial response – PR); n (%) [95%CI]									
1 single-arm trial Adams et al 2016	Serious limitations[4]	Very serious indirectness[3]	Not applicable	Not calculable	57		• CR: 18 (32) [17 to 47] • PR: 30 (52) [36 to 68] • SD: 9 (16) [4 to 28] • PD: 0 (0) [N/A]	Important	Very low
QoL[S], Course 12[G] / 366 days (benefit is indicated by complete response – CR or partial response – PR); n (%) [95%CI]									
1 single-arm trial Adams et al 2016	Serious limitations[4]	Very serious indirectness[3]	Not applicable	Not calculable	53		• CR: 21 (39) [23 to 55] • PR: 26 (50) [34 to 67] • SD: 5 (9) [0 to 19] • PD: 1 (2) [not reported]	Important	Very low
Change in HRQoL[T], 12 months (benefit is indicated by a higher result); n (%)									
1 single-arm trial Ji et al 2021	Very serious limitations[1]	Very serious indirectness[3]	Not applicable	Not calculable	126		• Improvement from baseline: 100 (79.4) • Worsening from baseline: 18 (14.3)	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Sirolimus**	**Best supportive care**	**Result**		
Children where QoL is not impacted by VA condition[U], 12 months; n (%)									
1 randomised trial Maruani et al 2021	Very serious limitations[5]	Very serious indirectness[3]	Not applicable	Not calculable	59 VM=22; LM=18; combined=19		VM: • baseline: 4 (18.2) • at transition to sirolimus: 4 (18.2) • 12 months: 10 (45.5) LM: • baseline: 10 (55.6) • at transition to sirolimus: 6 (33.3) • 12 months: 14 (77.8) combined: • baseline: 2 (10.5) • at transition to sirolimus: 4 (21.1) • 12 months: 8 (42.1) total: • baseline: 16 (27.1) • at transition to sirolimus: 14 (23.7) • 12 months: 32 (54.2)	Important	Very low
Safety (1 randomised trial, 3 single-arm trials, 1 prospective case series)									
Adverse Events (AEs) attributable to sirolimus, six months of treatment; n (%)[V]									
1 single-arm trial Harbers, Zwerink et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	67; children=32; adults=35		*All patients* • Grade 1: 202 (73.2) • Grade 2: 67 (24.3) • Grade 3: 6 (2.2) • Grade 4: 1 (0.4) • Total: 276 (100) *Children* • Grade 1: 72 (73.4) • Grade 2: 22 (22.2) • Grade 3: 4 (4.0) • Grade 4: 1 (1.0) • Total: 99 (35.9)	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sirolimus	Best supportive care	Result		
							Adults • Grade 1: 130 (73.4) • Grade 2: 45 (25.4) • Grade 3: 2 (1.1) • Grade 4: 0 (0.0) • Total: 177 (64.1)		
Specific AEs by Grade and attributability to sirolimus, six months of treatment; n (%)									
1 single-arm trial Harbers, Zwerink et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	67		Infection, n (%) • Grade II: possible 11 (16.4); probable 1 (1.5); definitely 0 (0) • Grade III: possible 0 (0); probable 0 (0); definitely 0 (0) • Grade IV: possible 1 (1.5); probable 0 (0); definitely 0 (0) Neurologic toxicity, n (%) • Grade II: possible 7 (10.5); probable 4 (6.0); definitely 0 (0) • Grade III: possible 0 (0); probable 0 (0); definitely 0 (0) Gastrointestinal toxicity, n (%) • Grade II: possible 4 (6.0); probable 4 (6.0); definitely 2 (3.0) • Grade III: possible 0 (0); probable 0 (0); definitely 0 (0) General symptoms, n (%) • Grade II: possible 7 (10.5); probable 0 (0); definitely 0 (0)	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sirolimus	Best supportive care	Result		
							• Grade III: possible 0 (0); probable 0 (0); definitely 0 (0) Metabolic / laboratory toxicity, n (%) • Grade II: possible 5 (7.5); probable 1 (1.5); definitely 0 (0) • Grade III: possible 3 (4.5); probable 1 (1.5); definitely 0 (0)		
Grade 3 or 4 AEs attributable to sirolimus, six months of treatment; n (%)									
1 single-arm trial Harbers, Zwerink et al 2023	Very serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	67		• All patients: 3 • Children: 3 • Adults: 0	Important	Very low
Adverse Events (AEs), Course 12[G] / 366 days; n (%)									
1 single-arm trial Adams et al 2016	Very serious limitations[1]	Very serious indirectness[3]	Not applicable	Not calculable	60		• Dose reduction, n (%): 2 (3) • AEs leading to drug discontinuation, n (%): 2 (3)	Important	Very low
Grade 2+ Adverse Events (AEs) and their attributability to sirolimus, Course 12[G] / 366 days; n (%)									
1 single-arm trial Adams et al 2016	Very serious limitations[1]	Very serious indirectness[3]	Not applicable	Not calculable	60		Blood/ bone marrow • Possible: 17 (28) • Probable: 11 (18) • Definite: 2 (3) Gastrointestinal • Possible: 12 (20) • Probable: 18 (30) • Definite: 3 (5) Metabolic/ laboratory • Possible: 5 (8) • Probable: 6 (10) • Definite: 1 (2)	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sirolimus	Best supportive care	Result		
							Pain • Possible: 5 (8) • Probable: 5 (8) • Definite: 1 (2)		
Grade 3 or 4 Adverse Events (AEs), Course 12[G] / 366 days; n (%)									
1 single-arm trial Adams et al 2016	Very serious limitations[1]	Very serious indirectness[3]	Not applicable	Not calculable	60		Blood/ bone marrow • Grade 3/4: 30 (50) • Suspected to be sirolimus related (grade 3/4): 16 (27) Gastrointestinal • Grade 3/4: 10 (17) • Suspected to be sirolimus related (grade 3/4): 2 (3) Infection • Grade 3/4: 22 (37) • Suspected to be sirolimus related (grade 3/4): 1 (2) Metabolic / laboratory • Grade 3/4: 11 (18) • Suspected to be sirolimus related (grade 3/4): 2 (3) Pulmonary/ upper respiratory • Grade 3/4: 7 (1) • Suspected to be sirolimus related (grade 3/4): 1 (2)	Important	Very low
Adverse Events (AEs), 12 months; n (%)									
1 single-arm trial Ji et al 2021	Very serious limitations[1]	Very serious indirectness[3]	Not applicable	Not calculable	126		• Total AEs: 290 • Total Grade 3 AEs: 23 • Total Grade 4 AEs: 4 • AEs leading to temporary discontinuation: 12 (9.5) • AEs leading to target reduction of sirolimus: 7 (5.6)	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Sirolimus**	**Best supportive care**	**Result**		
Specific AEs possibly related to sirolimus, 12 months; n									
1 single-arm trial Ji et al 2021	Very serious limitations[1]	Very serious indirectness[3]	Not applicable	Not calculable	126		Mucositis • All grades: 47 • Grade III: 2 • Grade IV: 0 Upper respiratory infection • All grades: 33 • Grade III: 7 • Grade IV: 1 Nausea/vomiting • All grades: 27 • Grade III: 1 • Grade IV: 0 Increased liver enzyme levels • All grades: 25 • Grade III: 6 • Grade IV: 0 Thrombocytosis • All grades: 25 • Grade III: 0 • Grade IV: 0	Important	Very low
AEs possibly related to sirolimus, 12 months; n (%)									
1 randomised trial Maruani et al 2021	Very serious limitations[5]	Very serious indirectness[3]	Not applicable	Not calculable	59		Nonserious AEs • Number of events: 101 • Number of patients experiencing an AE: 43 (73%) • Median age: 14 (IQR 11-17) Serious AEs • Number of events: 5 • Number of patients experiencing an AE: 5 (8%) • Median age: 15 (IQR 10-19)	Important	Very low
AEs probably related to sirolimus, 12 months; n (%)									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Sirolimus**	**Best supportive care**	**Result**		
1 randomised trial Maruani et al 2021	Very serious limitations[5]	Very serious indirectness[3]	Not applicable	Not calculable	59		Nonserious AEs • Number of events: 89 • Number of patients experiencing an AE: 35 (59%) • Median age: 12 (IQR 8-14) Serious AEs • Number of events: 0 • Number of patients experiencing an AE: 0 (0%)	Important	Very low
Adverse Events (AEs), 24 months; n (%)									
1 prospective case series Tian et al 2020	Very serious limitations[1]	Very serious indirectness[3]	Not applicable	Not calculable	56		• Total AEs: 37 • Total Grade 3 AEs: 3 • Total Grade 4 AEs: 0	Important	Very low
Specific AEs possibly by Grade, 24 months; n									
1 prospective case series Tian et al 2020	Very serious limitations[1]	Very serious indirectness[3]	Not applicable	Not calculable	56		Oral mucositis • All grades: 17 • Grade III: 1 • Grade IV: 0 Upper respiratory infection • All grades: 6 • Grade III: 0 • Grade IV: 0 Pneumonia • All grades: 2 • Grade III: 2 • Grade IV: 0 Cystic haemorrhage • All grades: 4 • Grade III: 0 • Grade IV: 0 Rash • All grades: 3 • Grade III: 0 • Grade IV: 0	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sirolimus	Best supportive care	Result		

Abbreviations
AE: adverse event; C-DLQI: Children-Dermatological Life Quality Index; CI: confidence interval; CR: complete response; EMM: estimated marginal mean; FACT-G: Functional Assessment of Cancer Therapy – General; GR: good response; HRQoL: health related quality of life; IQR: interquartile range; ISSVA: International Society for the Study of Vascular Anomalies; ITU: intensive therapy unit; LM: lymphatic malformation; MCS: mental component summary; mL: millilitres; mm: millimetres; MRI: magnetic resonance imaging; n: number; N/A: not applicable; ng: nanograms; NRS: numeric rating scale; PCS: physical component summary; PD: progressive disease; PedsQL: Paediatric Quality of Life Inventory; PR: partial response; QoL: quality of life; RAND-36: Research and Development-36; SD: stable disease; SD: standard deviation; SF-36: Short Form 36; TNO-AZL: Nederlandse Organisatie voor toegepast-natuurwetenschappelijk onderzoek van het Academisch Ziekenhuis in Leiden Preschool Children; US: United States; VA: vascular anomalies; VAS: visual analogue scale; VM: venous malformation

A Presented as complete response (CR), partial response (PR), progressive disease (PD) or stable disease (SD). This composite measure is established by changes in at least 1 parameter: response to pain symptoms, health related quality of life (Paediatric Quality of Life Inventory / SF-36 / Physical Component Summary), clinical symptoms related to the vascular malformation – excluding pain, response to imaging (MRI).
B Responders are comprised of those that had complete or partial response (CR/PR); non-responders were those that had stable or progressive disease (SD/PD).
C Presented as complete response (CR), good response (GR), partial response (PR), stable disease (SD) or progressive disease (PD). This measure was determined based on changes in the volumetric measurements of VA lesions on MRI. CR = complete resolution of measured VAs at 12 months; GR = decrease of ≥75% but <100%; PR = decrease of ≥20% but <75%; SD = Increase of <20% but decrease of <20% in volumes of VA lesions; PD = Increase of ≥20% in volume of index LMs compared with baseline volume.
D Total responses are comprised of those that had complete, good or partial response (CR/GR/PR); those with no response were those that had stable or progressive disease (SD/PD)
E Presented as complete response (CR), partial response (PR), progressive disease (PD) or stable disease (SD). This composite measure is established by changes in at least 1 parameter: response by radiologic imaging, health quality-of-life questionnaire [Paediatric Quality of Live Inventory 4.0 (3-18 years) and Infant Scales (≤2 years) or the Functional Assessment of Chronic Illness System (>18 years)] or using defined clinical criteria in a functional impairment score (measures of organ function). Patients that responded to treatment were those designated as CR or PR.
F Disease response after 6 courses of sirolimus. Trial included a total of 12 courses of treatment with each course lasting 28 days.
G Disease response after 12 courses of sirolimus. Trial included a total of 12 courses of treatment with each course lasting 28 days.
H Presented as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). This measure was determined based on changes in the volumetric measurements of VA lesions on MRI, clinical changes in the lesion and/or changes in symptoms. CR = complete disappearance of either the lesion (clinical and/or radiological), and the symptoms; PR = reduction of >20% in size of the lesion (clinical and/or radiological) and improvement in symptoms; PD = enlargement of >20% in size of the lesion (clinical and/or radiological) or as new lesions appearing; SD = none of the above
I Patients were divided into three groups based on treatment length: Group 1 = 1-6 months (n=15); Group 2 = 7-12 months (16); Group 3 = 13-24 months (n=25). Effective group is comprised of those that had complete or partial response (CR/PR); those in the ineffective group were those that had stable or progressive disease (SD/PD).
J Pain was recorded using the Children and Infants Postoperative Pain Scale for children aged 0–3 years, visual analogue scale (VAS) clinical pictures for children aged 4–7 years, VAS for patients aged 8–17 years and numeric pain rating scale (NRS) for adults.
K EMM: estimated marginal mean.
L Improvement of clinical symptoms was defined as clinical size decrease, improvement of activities/functioning, and improvement of energy/condition/endurance
M Disease severity was recorded using a scale of 0 to 5 with higher values representing more profound symptoms and/or functional disability.
N Radiographic changes were measured as - CR: no evidence of disease on radiologic imaging; PR: >20% reduction in size of target vascular lesion evident on radiologic imaging; PD: >20% increase in size of target vascular lesion evident on radiologic imaging; SD: ≤20% change in either direction of target vascular lesion evident on radiologic imaging.
O The functional impairment score was adopted from the measures of organ function that have been validated in the quantification of adverse event results from medical therapies and procedures. The instrument was piloted in the present study. Changes were defined as: CR: no evidence of organ dysfunction due to disease; PR: improvement in target organ dysfunction by at least 1 grade; PD: worsening in target organ dysfunction by at least 1 grade; SD: no change in target organ dysfunction.
P Score was assessed using a visual analogue scale at each visit (0=no efficacy; 10=complete resolution) by the physician, parent and patient.

Q HRQOL was assessed by Research and Development-36 (RAND-36) for adults, the TNO-AZL (Nederlandse Organisatie voor toegepast-natuurwetenschappelijk onderzoek van het Academisch Ziekenhuis in Leiden Preschool Children) Quality of Life Questionnaire for parents of 1-year-old children, the parents' version of the Paediatric Quality of Life Inventory 4.0 Generic Core Scales for the parents of children aged 2–17 years and the children's PedsQL version for children aged 5–17 years.
R HRQoL was assessed by Research and Development-36 (SF-36) for adults, the parents' version of the Paediatric Quality of Life Inventory 4.0 Generic Core Scales for the parents of children aged 2–17 years and the children's PedsQL version for children aged 5–17 years. For all HRQoL measures a higher score indicates a better QoL
S Quality-of-Life (QoL) changes were measured as CR: normalisation of QoL criteria; PR: improvement of self-report PedsQL by >4.4 or proxy-report PedsQL by >4.5 or FACT-G by >3.99 compared with baseline; PD: worsening of self-report PedsQL by >4.4 or proxy-report PedsQL by >4.5 or FACT-G by >3.99 compared with baseline; SD: ≤4.4 change in self-report of PedsQL or ≤4.5 change in proxy-report PedsQL or ≤3.99 change in FACT-G compared with baseline.
T HRQOL was assessed by Research and Development-36 (SF-36) for adults, the parents' version of the Paediatric Quality of Life Inventory 4.0 Generic Core Scales for the parents of children aged 2–17 years and the children's PedsQL version for children aged 5–17 years
U Quality-of-Life (QoL) was measured using the Children-Dermatological Life Quality Index (C-DLQI). There are 10 questions with a maximum score of 30. A score of 0-1 indicates “no effect on a child’s life”; 2-6 “small effect”, 7-12 “moderate effect”, 13-18 “very large effect” and 19-30 “extremely large effect.” The children reported here all had a score of 0-1.
V % of total AEs, i.e. % of Grade 2 AEs attributable to sirolimus.

1 Risk of bias: very serious limitations due to unclear reporting of study participants (in relation to non-consecutive and/or incomplete inclusion) and a lack of any statistical analysis or summary statistic.
2 Indirectness: serious indirectness due to no comparison across treatment arms.
3 Indirectness: very serious indirectness as the population were not all refractory to standard care / unclear if refractory to standard care (the PICO states population must be refractory to standard care) and lack of comparator.
4 Risk of bias: serious limitations due to unclear reporting of study participants (in relation to non-consecutive and/or incomplete inclusion).
5 Risk of bias: very serious limitations due to both a lack of blinding of patients and clinicians and potential confounding in the statistical analysis due to lack of adjustment for the stepped-wedge design.

a Visit 3 was 1 month after the introduction of sirolimus
b Visit 4 was 3 months after the introduction of sirolimus

Glossary

Term	Definition
Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether or not the event is suspected to be related to or caused by the drug, treatment or intervention.
Baseline	The set of measurements at the beginning of a study (after any initial 'run-in' period with no intervention), with which subsequent results are compared.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias.
Case series	Reports of several patients with a given condition, usually covering the course of the condition and the response to treatment. There is no comparison (control) group of patients.
Clinical importance	A benefit from treatment that relates to an important outcome such as length of life and is large enough to be important to patients and health professionals.
Confidence interval (CI)	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
Control group	A group of people in a study who do not have the intervention or test being studied. Instead, they may have the standard intervention. The results for the control group are compared with those for a group having the intervention being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible to those in the intervention group, to make it as easy as possible to detect any effects due to the intervention.
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.

Term	Definition
Intention-to-treat analysis (ITT)	An assessment of the people taking part in a trial, based on the group they were initially (and randomly) allocated to. This is regardless of whether or not they dropped out, fully adhered to the treatment or switched to an alternative treatment. ITT analyses are often used to assess clinical effectiveness because they mirror actual practice, when not everyone adheres to the treatment, and the treatment people have may be changed according to how their condition responds to it. Studies of drug treatments often use a modified ITT analysis, which includes only the people who have taken at least one dose of a study drug.
Minimal clinically important difference	The smallest change in a treatment outcome that people with the condition would identify as important (either beneficial or harmful), and that would lead a person or their clinician to consider a change in treatment.
Objective measure	A measurement that follows a standardised procedure which is less open to subjective interpretation by potentially biased observers and people in the study.
Per-protocol analysis	A comparison of treatment groups in a trial that includes only those patients who completed the treatment they were originally allocated to. If done alone, this analysis leads to bias.
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
Prospective study	A research study in which the health or other characteristic of patients is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
P-value (p)	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug,

Term	Definition
	treatment or other intervention. One group (the experimental group) has the intervention being tested, the other (the comparison or control group) has an alternative intervention, a dummy intervention (placebo) or no intervention at all. The groups are followed up to see how effective the experimental intervention was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Standard deviation (SD)	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.

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NHS England

Wellington House

133-155 Waterloo Road

London

SE1 8UG