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Clinical evidence review of everolimus for refractory partial-onset seizures associated with tuberous sclerosis complex

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About this clinical evidence review

Clinical evidence reviews provide a summary of the best available evidence for a single technology within a licensed indication for which the responsible commissioner is NHS England. The clinical evidence review supports NHS England in producing clinical policies but is **not NICE guidance or advice**.

Summary

Evidence review

The focus of this review is on everolimus (Votubia, Novartis Pharmaceuticals) as adjunctive treatment of patients aged 2 years and older who have refractory partial-onset seizures associated with tuberous sclerosis complex (TSC). The evidence review was undertaken in line with NHS England's methods for undertaking clinical evidence reviews.

A literature search was undertaken, which identified 329 references (see appendix 2 for search strategy). The company also provided a submission of evidence. Seven studies were included in the review; including one phase III extension study (Franz, 2018).

Results

Evidence of the effect of everolimus comes from one 12-week double-blinded, placebo-controlled randomised control trial (RCT) including 366 patients (French, 2016), together with a long-term (up to 48 months) uncontrolled extension study of that trial (Franz, 2018). Patients in these studies had a confirmed diagnosis of tuberous sclerosis complex and epilepsy that was not responding to treatment with antiepileptic drugs (AED). Five additional studies with smaller sample sizes (6-20 patients) also provide evidence.

Effectiveness

Evidence from the 12-week regulatory trial (French, 2016) suggests that both low exposure and high exposure everolimus, when given as adjunctive therapy to between 1 and 3 AEDs, are associated with a statistically significantly greater reduction in seizure frequency than placebo (28.2% [low exposure everolimus], 40.0% [high exposure everolimus] and 15.1% [placebo]). Evidence from the phase III extension study (Franz et al. 2018) indicates that the benefit improves over time (in the extension study, the percentage of people with a reduction in seizure frequency of at least 50% was 31% at week 18, 46.6% at 1 year and 57.7% at 2 years of treatment with everolimus. A sensitivity analysis was performed assuming all drop outs were

due to lack of effect in which everolimus was found to reduce seizure frequency by at least 50% in 41% (95%CI, 34.6-47.7; N=229) of people at 2 years. The greatest benefit was observed in patients initially randomised to high exposure everolimus in the registration study; those initially randomised to low exposure everolimus or placebo had a similar pattern of efficacy outcomes over time. The authors of the extension study report that reductions in seizure frequency are dependent on both the length of treatment duration (longer treatment being associated with better outcomes) and exposure to everolimus (higher exposure being associated with better outcomes). .

There is limited evidence of a difference in behavioural outcomes, and changes in AED usage from additional studies.

Safety and tolerability

Evidence from the extension study, which studied 361 patients up to 2 years, indicates that the most frequent treatment-related adverse effects were stomatitis (33.5%), mouth ulceration (26.0%), diarrhoea (10.5%), aphthous ulcer (10.2%), and pyrexia (10.2%). The occurrence of adverse effects did not increase over time. Adverse events led to treatment discontinuation in 47 patients (13%), primarily due to pneumonia (1.7%) and stomatitis (1.4%). There were 4 deaths, 2 were thought to be treatment-related deaths (pneumonia and septic shock; both in children).

Evidence gaps

The patients included in the registration trial and extension study (French, 2016 and Franz, 2018) had a high baseline seizure rate (34.5 to 42 seizures in a 28 day period) and almost half of the included patients had not gained seizure control after treatment with 6 or more previous AEDs. In NHS clinical practice, the disease is considered refractory after at least 2 appropriate AEDs, given at a therapeutic dose, have not resulted in a reduction in seizure frequency and severity. Furthermore, the majority (>80%) of patients were aged under 18 years (median age 10.1 years [range 2.2 years to 56.3 years]); the marketing authorisation permits use in those aged 2 years and older.

None of the included studies provide evidence of everolimus in comparison with surgery, vagus nerve stimulation (VNS) or the ketogenic diet.

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Abbreviations

Term	Definition
AED	Antiepileptic drug
AML	Angiomyolipomas
BSA	Body surface area
EEG	Electroencephalogram
ITT	Intention to treat
MTOR	Mammalian target of rapamycin
NCBRF	Nisonger child behaviour rating form
QOLCE	Quality of life in children with epilepsy
QOLIE	Quality of life in epilepsy
RCT	Randomised controlled trial
SEGA	Subependymal giant cell astrocytomas
SEN	Subependymal nodule
SPC	Summary of product characteristics
SUDEP	Sudden unexplained death in epilepsy
TSA	Tuberous Sclerosis Association
TSC	Tuberous sclerosis complex
VNS	Vagus nerve stimulation

Introduction

Disease background

Tuberous sclerosis complex (TSC) is a condition that people are born with that often leads to non-cancerous growths developing in the brain, eye, heart, kidney, skin and lungs. TSC tumours of the brain can cause seizures. Seizures are one of the most common symptoms of TSC and occur in approximately 84% of people (Kingswood et al, TOSCA data, 2017).

The rate of psychiatric problems in people with TSC is high. The four main disorders reported are depression, anxiety, attention deficit disorder and aggressive/disruptive behaviours (Muzykewicz, et al., 2007). Treatment with certain AEDs is known to increase the degree of cognitive and behavioural disorders in people with TSC-related seizures (French and Staley, 2012).Facial angiofibromas occur in about 75% of TSC patients with onset typically between ages 2 and 5 years (Northrup and Krueger, 2013). Angiofibromas can cause facial disfigurement which can lead to social isolation and depression (Crall, et al. 2016). Everolimus has also been reported to improve the appearance of skin lesions (facial angiofibromas) in these patients (Franz et al. 2016).

In infants and children with TSC, seizures are closely related to development. Specifically, intellectual disability is associated with a history of infantile spasm (seizures which occur in infants) and refractory seizures (Wang and Fallah, 2014). The rate of learning disability in people with epilepsy population is high, especially in children who develop epilepsy early in life (NICE CG137). Early management of seizures is important in preventing and reducing the cognitive and neurological and psychiatric consequences from refractory seizures (Bombadieri, 2010). Long term intellectual development is thought to be improved if seizure treatment starts as soon as a child is diagnosed with epilepsy and when that treatment provides a prompt response (NICE CG137). Sudden unexpected death in epilepsy (SUDEP) is an important cause of mortality in people with TSC-related refractory epilepsy (Amin et al., 2016). Analysis of epilepsy studies have identified frequent convulsive seizures (3 or more in a year) as a major risk factor for SUDEP (Hesdorffer et al., 2011;

Ryvlin et al., 2013) and several studies indicate that unsupervised night-time seizures significantly contribute to SUDEP risk (Lamberts et al., 2012). The aim of treatment, therefore, is to stop or reduce the number and frequency of seizures in patients with TSC as much as possible to limit the cognitive and neuropsychiatric consequences of refractory epilepsy and also ultimately to reduce the risk of SUDEP.

Focus of review

In line with the marketing authorisation, the focus of this review is on everolimus as an adjunctive (add-on) treatment for patients aged 2 years and older who have refractory focal onset seizures including those which evolve to bilateral tonic clonic seizures (formerly known as refractory partial-onset seizures with or without secondary generalisation) associated with TSC. A tonic clonic seizure (also called a convulsion) is a combination of tonic (meaning stiffening) and clonic (meaning rhythmical jerking) seizures. Focal onset seizures are those that start in an area on one side of the brain. When the seizure starts, the person may be aware or have some impaired awareness; if it spreads to both sides of the brain (that is, evolving to a bilateral tonic clonic seizure), the person would be unaware during the seizure. As the majority of TSC seizures have a focal origin, 'focal onset seizures' will be used throughout this document to refer to focal onset seizures with or without evolution to bilateral tonic clonic seizures.

Seizures can progress to become refractory, which is when the seizures no longer respond to anti-seizure treatment (also known as uncontrolled or intractable). In UK clinical practice, this means that 2 different anti-epileptic drugs (AEDs), given at therapeutic doses, have failed to reduce the frequency and severity of a person's seizures.

People with refractory seizures associated with TSC currently have care tailored to their needs. The most common treatment used in UK practice is AEDs, however these are not disease modifying treatment option. Alternative symptom control treatment options for TSC-related refractory seizures include surgical resection (where it is possible to identify a dominant tumour that is

causing the seizures), vagus nerve stimulation (VNS) or a ketogenic (low carbohydrate) diet.

Everolimus is a drug that has a different mechanism of action to the currently available treatments. It targets the mammalian target of rapamycin (mTOR) pathway, which is disrupted in TSC and causes a number of the symptoms of TSC. It is intended to be given as an adjunctive treatment, in addition to current standard of care. The Summary of product characteristics (SPC) states that treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs (see also 'Product Overview' below).

Epidemiology

The estimated prevalence of the condition in the UK ranges between 8.8 per 100,000 (O'Callaghan et al., 1998) up to 10 in 100,000 (Committee for Medicinal Products for Human Use, European Medicines Agency, 2011).

Based on this, it is estimated there are between 4,900 and 5,500 patients in England with TSC. However, this is likely to be an underestimation of the true prevalence, because prevalence is increasing with better identification of less severe cases.

Approximately 84% of people with TSC have epilepsy and the majority of these people have focal onset seizures (equating to between 4,100 and 4,600 people).

The proportion of patients with TSC-related refractory epilepsy varies depending on the evidence source between 36% (Kingswood et al., 2017) and 63% (Chu-Shore et al., 2010). Based on this, the number of people with TSC-related refractory epilepsy in England is between 1,500 and 3,000 people, see Table 1.

Table 1 Patient numbers

Estimates	Data source	Number of people
Population in England in mid-2016	Office for National Statistics	55,268,100
8.8 to 10 in 100,000 with TSC	Previous NHS England clinical policies on SEGA and AML, and company submission	4,864 – 5,527
Epilepsy is in 84% of TSC patients	(Kingswood et al, TOSCA data, 2017) – from company submission	4,086 – 4,643
Refractory to treatment - 36% to 63%	(Kingswood et al, TOSCA data, 2017) – from company submission (Chu-Shore et al. 2010)	1,471 – 2,925

Product overview

Mode of action

The company state that everolimus works by inhibiting mTOR, a protein that regulates multiple cellular functions. TSC is caused by mutations in the TSC1 or TSC2 genes, resulting in hyperactive signalling of the mTOR pathway which can lead to increased cellular growth and proliferation, neuronal hyper-excitability, abnormalities in cortical architecture and network function and impaired synaptic plasticity.

Regulatory status

Everolimus received a marketing authorisation from the European Medicines Agency in January 2017 for the 'adjunctive treatment of patients aged 2 years and older whose refractory partial-onset seizures, with or without secondary generalisation, are associated with tuberous sclerosis complex (TSC)'.

Dosing information

Everolimus is available in the following formulations for the treatment of refractory seizures associated with TSC:

- Votubia 2 mg dispersible tablets
- Votubia 3 mg dispersible tablets

- Votubia 5 mg dispersible tablets

Everolimus is given once daily. The following starting doses are recommended:

Without co-administration of CYP3A4/PgP inducer

- 6mg/m2 for patients aged less than 6 years
- 5mg/m2 for patients aged 6 years or over

With co-administration of CYP3A4/PgP inducer

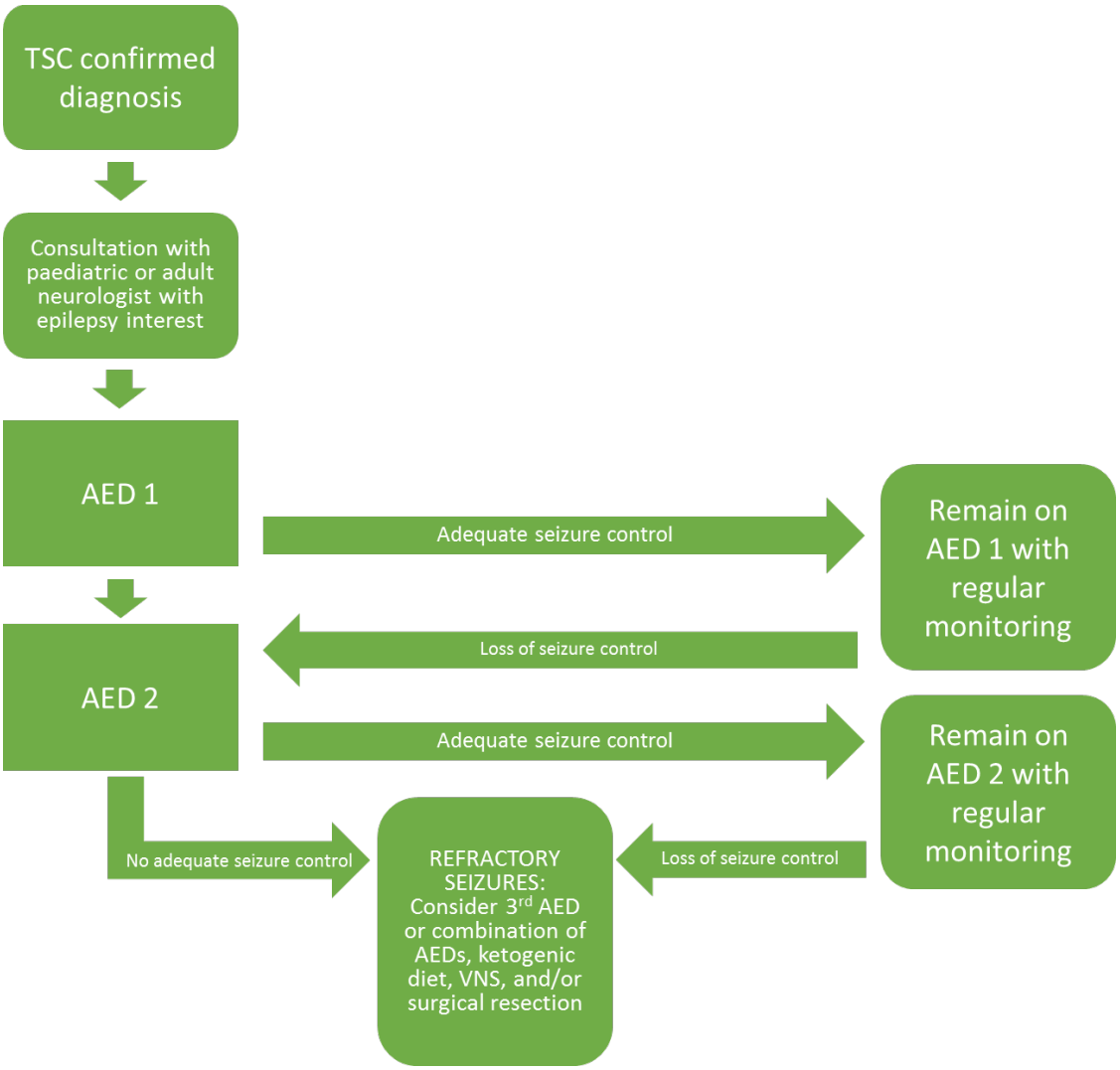
- 9mg/m2 for patients aged less than 6 years
- 8mg/m2 for patients aged 6 years or over

The SPC notes that treatment should be initiated by a physician experienced in the treatment of patients with TSC and therapeutic drug monitoring. It states that doses that will be tolerated and effective vary between patients. Dosing is individualised based on body surface area. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs. Please see SPC for further details of the dosing recommendations.

Treatment pathway and current practice

The most common treatment used in UK clinical practice is AEDs. According to NICE clinical guideline 137, AED treatment strategy should be individualised according to the seizure type, epilepsy syndrome, co-medication and co-morbidity, the child, young person or adult's lifestyle, and the preferences of the person and their family and/or carers as appropriate. In children, other treatment options for refractory seizures include a ketogenic diet, vagus nerve stimulation (VNS) or surgical resection. In adults, other treatments for refractory seizures include VNS and less commonly a ketogenic diet (due to the difficulty of remaining on the strict diet indefinitely) or surgical resection. A pathway of care for the treatment of refractory seizures associated with TSC in England is shown in Figure 1 below.

Figure 1 Pathway of care for refractory seizures associated with TSC



Innovation and unmet need

Everolimus is understood to target the molecular pathology of TSC, and to modify the disease processes thought to be involved in the development of TSC symptoms.

The company estimate that there is a large unmet need, as up to 37% of patients are refractory, and that there is a need for a well-tolerated disease-modifying therapy that suppresses seizure symptoms and treats the disease.

Equality

No equalities issues relating to people with particular characteristics covered by the Equalities Act 2010 (including race, age, sex, disability, religion or belief, sexual orientation, gender reassignment, pregnancy, maternity,

marriage and civil partnership) were identified during this review of the clinical evidence.

Evidence review

Identification of studies

The review was done in line with NHS England's methods for carrying out clinical evidence reviews.

A literature search was undertaken, which identified 329 references (see appendix 2 for search strategy). These references were screened using titles and abstracts and nine full text references were obtained and assessed for relevance. Full text inclusion and exclusion criteria were applied to the identified studies and six studies were included in the clinical evidence review (see appendix 3 for inclusion/exclusion criteria, flow of included studies, and a list of studies excluded at full text with reasons).

The company submission identified five references to published studies in their submission. All of these studies were identified in the literature search, and as such no additional unique references were identified. The company also provided data for one study (Franz, 2018), which was selected for inclusion. Franz (2018) was unpublished at time of inclusion, but has since been published.

In summary seven studies met the inclusion/exclusion criteria and were subsequently included. The European public assessment report (EPAR) was also used to supplement the published data from the pivotal registration trial (French, 2016).

Results

Overview of included studies

The highest grade (according to the National Service Framework Long-term Conditions (NSF-LTC) scoring system, see appendix 6) of available evidence comes from one phase III double-blinded, placebo-controlled RCT (EXIST-3) including 366 patients (French, 2016), together with a long-term uncontrolled

extension study of the trial (Franz, 2018). Five uncontrolled studies with smaller sample sizes (6-20 patients) also provide evidence. A summary of the characteristics of the included studies is shown in Table 2. More detailed evidence and results tables can be found in appendices 4 and 5.

Table 2 Summary of included studies

Study	Population	Intervention and comparator	Follow-up
French et al, 2016. (EXIST 3) Pivotal Phase III double-blind RCT	Patients aged 2–65 years with a confirmed diagnosis of tuberous sclerosis complex and treatment resistant epilepsy 366 patients enrolled Across all treatment groups, the median age of patients was 10.1 years (range 2.2 to 56.3 years), 82% of patients were under 18 years old, 48% were female, and 65% of patients were Caucasian	Low exposure - everolimus target trough of 3-7 ng/mL High exposure– everolimus target trough of 9–15 ng/mL Placebo	12 weeks
Franz et al, 2018. Extension of Phase III RCT	Patients aged 2-65 years with a definitive diagnosis of TSC and refractory epilepsy 361 patients included (256 with ongoing treatment) See French et al, 2016 below for details of population age and sex	Everolimus 3–15 ng/mL target trough range No comparator	Up to 2 years
Kilincaslan et al, 2017. Case series (appears to be retrospective)	Patients with TSC and refractory epilepsy 6 patients were included Patient age ranged from 7.5 to 23 years	Everolimus 5–15 ng/mL target trough No comparator	Median 17.5 months (range 7-26)
Krueger et al, 2013 Phase I/II prospective uncontrolled study	Patients aged 2 years or older with a confirmed diagnosis of tuberous sclerosis complex and treatment resistant epilepsy 20 patients were enrolled The median age of patients was 8 years (range 2 to 21 years), and 50% were female	Everolimus 5–15 ng/mL target trough range No comparator	12 weeks

Study	Population	Intervention and comparator	Follow-up
Krueger et al, 2016 Long-term extension of phase I/II prospective uncontrolled study	Patients aged 2 years or older with a confirmed diagnosis of tuberous sclerosis complex and treatment resistant epilepsy 18 patients entered the extension study See Krueger et al, 2013 above for details of population age and sex	Everolimus 5–15 ng/mL target trough range No comparator	48 months
Samueli et al, 2016 Prospective uncontrolled before and after study	Patients aged 18 years or younger with a confirmed diagnosis of tuberous sclerosis complex and treatment resistant TSC-associated epilepsy 15 patients were enrolled All of the enrolled patients were children with a median age of 6 years (range 1 to 18 years), and 40% were female	Everolimus 5–15 ng/mL target trough range No comparator	Median 22 months (range 6-50)
Wiegand et al, 2013 Prospective uncontrolled before and after (compassionate use) study	Patients with a confirmed diagnosis of tuberous sclerosis complex and treatment resistant epilepsy 7 patients were enrolled All of the enrolled patients were children with a median age of 5 years (range 2 to 12 years), and 57% were female	Everolimus 5–10 ng/mL target trough range No comparator	9 months

French (2016) was a double-blind, randomised, multi-centre trial evaluating the efficacy and safety of everolimus in patients age 2 (1 in Europe, however no one under age 2 was recruited to the study) to 65 who have TSC-related refractory seizures. At the time the patients joined the study, they were being treated with a stable regimen of 1 to 3 AEDs. To remain in the study, patients could not change the type or amount of AED medication they had been taking during the 8 week lead-in period before the study began (to ensure that the responses to treatment observed during the trial would mainly be due to the treatment effect of everolimus or placebo). The trial was conducted according to published protocols, reported clearly and included 366 patients. A majority (>80%) of patients included in the trial were aged under 18 years of age. Patients received a high exposure of everolimus, a low exposure of everolimus or placebo.

For the first 6 weeks of the study, the dose of everolimus was slowly increased to the therapeutic dose (as is reflected in the marketing authorisation for everolimus). That therapeutic dose was then maintained for the following 12 weeks. The study inclusion criteria required that people have a clinically definitive diagnosis of TSC and refractory epilepsy (in the trial, the inclusion criterion relating to refractory epilepsy was 'a prior history of failure to control partial-onset seizures despite having been treated with two or more sequential regimens of single or combined antiepileptic drugs' [See https://clinicaltrials.gov/ct2/show/NCT01713946?term=_EXIST-3&rank=1 accessed October 2017]). For the purposes of the study, only patients who had more than 16 seizures (with no continuous 21-day seizures-free period) during the baseline period of the study were included. The patients recruited to the study had a baseline seizure rate of 34.5 to 42 seizures in a 28 day period and half of the included patients had been treated with 6 or more AEDs.

In Franz (2018), the follow up study to French (2016), 361 of the patients from the EXIST-3 study were followed for up to 2 years. Patients who had originally received everolimus during the main trial remained on everolimus, and patients that originally received placebo were switched to everolimus. Patients were allowed to change AED or alter their AED dose during the follow up period. However, 47% of patients remained for a year or more on stable doses of the AEDs they were using throughout the study.

Overview of key results

Table 3 below provides a grade of evidence summary of the outcomes identified in the scope. The key effectiveness and safety outcomes are discussed below.

Effectiveness

The primary outcome in the French (2016) study was change from baseline in seizure frequency for each of the two everolimus dose groups (low and high exposure) compared with placebo during the 12-week maintenance period. Both response rate (that is, reduction in seizure frequency) and median percentage reduction in seizure frequency were assessed. Seizure frequency

was defined as the ratio between the number of seizures and the number of days on which seizure information was known within the 12-week period.

Evidence from this study suggests that everolimus as add-on treatment is effective at reducing the frequency of seizures compared to treatment with AEDs alone. In the trial, 28.2% [95% CI 20.3 to 37.3, p=0.0077] of patients receiving the lower dose of everolimus and 40.0% [31.5 to 49.0, p<0.0001] of patients receiving the higher dose of everolimus experienced at least a 50% reduction in the number of seizures, compared to 15.1% [95% CI 9.2 to 22.8] of patients receiving placebo. A reduction in seizure frequency of 25% or greater was seen in 52.1% (95% CI 42.7–61.5) of patients in the low exposure everolimus group, and in 70.0% (95% CI 61.3–77.7) of the patients the high-exposure everolimus group, compared to 37.8% (95% CI 29·1–47·2) in the placebo group. Across each treatment group, there was a 29.3% [95% CI 18.8 to 41.9, p=0.0028] and 39.6% [35.0 to 48.7, p<0.0001] median reduction in seizure frequency at 12 weeks in the lower dose and higher dose of everolimus compared with baseline, and a 14.9% [95% CI 0.1 to 21.7] median reduction in seizure frequency compared with baseline in the group receiving placebo.

Evidence from the phase III extension study (Franz, 2018) which studied 361 patients up to 2 years indicates that the benefit of treatment with everolimus increases over time. In the study, the percentage of people with a reduction in seizure frequency of at least 50% was 31% at week 18, 46.6% at 1 year and 57.7% at 2 years of treatment with everolimus. For patients that were able to continue treatment with everolimus (in other words, patients who did not discontinue treatment for any reason), median seizure frequency reduced by 31.7% at week 18, 46.7% at 1 year, and 56.9% at 2 years treatment. The median number of additional seizure-free days (per 28-day period) was 6.15 days at 2 years of everolimus exposure. The greatest benefit was reportedly observed in patients initially randomised to high exposure everolimus, leading the study authors to report that the benefit of everolimus is dependent on length of treatment (longer treatment durations corresponded with better

outcomes) and exposure to everolimus (higher exposure corresponded with better outcomes).

Ninety-five patients (26.3%) discontinued everolimus before the end of 2 years. The authors did a sensitivity analysis assuming that patients who discontinued everolimus for any reason had done so because their seizures had not responded to treatment (regardless of the reported reason). Even using this assumption, everolimus was found to reduce seizure frequency by at least 50% in 30.2% (95%CI, 25.5-35.2; N=361) of people at week 18, 38.8% (95%CI, 33.7-44.1; N=358) at 1 year, and 41% (95%CI, 34.6-47.7; N=229) at 2 years, which suggests sustained benefit over time.

Behaviour and quality of life

The French study investigators had intended to report the effect of everolimus on patient behaviour using the Vineland Adaptive Behavior Scale Survey. However, investigators were unable to perform the survey at baseline for many of the patients due to the severity of the patient's disability.

Evidence from the other studies included in the clinical evidence review for everolimus, suggested that behaviour improved during everolimus treatment. The Krueger 2013 study was a single arm study which included 20 patients which assessed the benefit of everolimus on seizure control in patients with TSC-related refractory epilepsy. The study showed there was a statistically significant reduction in negative domain behaviour (which include conduct problems, anxiety, hyperactivity, self-injury, self-isolation and oversensitivity). There was also an improvement in positive domain behaviour (which includes compliance and social adaptiveness) although this was not statistically significant. There was a statistically significant increase in the overall QOLCE score (+1.0, $p<0.001$), which was driven by changes in attention, behaviour, social interaction, other cognitive, stigma, physical restrictions and social activity domains. It should be noted that patients in the Krueger 2013 study had to their current stable dose of AEDs throughout the study.

In the 48 month follow up study (Krueger, 2016), quality of life measured by the QOLCE composite score improved an average of 14% (43.7 ± 13.4 at

baseline compared to 52.0 ± 17.8 after 48 months). There were positive changes in stigma, self-rated quality of life, attention/concentration, anxiety, language, and general health but the results did not reach statistical significance due to individual variation and cohort size. Trends in behaviour improvement in both positive and negative domains were also observed after 48 months of treatment, but similarly did not reach statistical significance. Patients in the Krueger 2016 extension study were allowed changes to their AED medication. For example, one patient stopped AED treatment during the extension phase of the Krueger study and maintained seizure control with everolimus alone. However, the overall number of AEDs used by patients during the 48 months remained unchanged (median 5 2, range 0–4).

Safety and tolerability

Evidence from the phase III extension study (Franz, 2018) which studied 361 patients up to 2 years indicated that the most frequent treatment-related adverse effects were stomatitis (33.5%), mouth ulceration (26.0%), diarrhoea (10.5%), aphthous ulcer (10.2%), and pyrexia (10.2%). The occurrence of adverse effects did not increase over time. Grade 3 or 4 adverse events were reported in 145 patients (40.2%) and most frequent (≥2.5%) were pneumonia (6.9%), status epilepticus (3.3%), seizures (2.8%), and stomatitis (2.5%). Adverse events led to treatment discontinuation in 47 patients (13%), primarily due to pneumonia (1.7%) and stomatitis (1.4%). There were 4 deaths; 2 were thought to be treatment-related deaths (one due to pneumonia and one due to septic shock; both in children).

Evidence gaps

The evidence base available for everolimus provides a comparison of everolimus in combination with AEDs against a comparison/baseline of AED therapy. As everolimus was evaluated as an add-on to current treatment, it is not intended to replace current therapies. Therefore comparative evidence does not exist.

The trial population included the population covered by the marketing authorisation with respect to seizure burden and prior AED use at baseline,

however, the median values for seizure burden and AED use at baseline were higher than would be expected in NHS clinical practice (median seizure frequency per 28 days at baseline was 37·8 seizures [1 to 874] and just under half of the population had tried 6 or more AEDs at baseline).

There is limited long term evidence (2 years or more) for everolimus use in people with TSC related refractory focal onset seizures. Therefore, consideration should be given to regular monitoring of patients receiving everolimus beyond 2 years for TSC-related refractory focal onset seizures in order to promptly identify any adverse effects of treatment with everolimus.

Key ongoing studies

The following study is ongoing until 2028 to collect long-term safety data:

Trial NCT02962414; CRAD001M2X02B: Roll-over Study to Collect and Assess Long-term Safety of Everolimus in Patients With TSC and Refractory Seizures Who Have Completed the EXIST-3 Study [CRAD001M2304] and Who Are Benefitting From Continued Treatment. Currently recruiting. Estimated completion date: January 2028.

Table 3 Grade of evidence for key outcomes

Outcome measure	Study	Critical appraisal score	Applicability to decision problem	Grade of evidence	Interpretation of evidence
Response rate of 50% reduction in seizures	Franz, 2018	7/10	Directly applicable	A	Response rate of 50% reduction in seizures is the percentage of patients who had at least half the number of seizures they were having at the start of the study. The largest study (French, 2016) with 366 patients reported a response rate of 50% reduction in seizures in 40% of patients treated with high dose everolimus and 28% of patients treated with low dose everolimus, compared to 15% of patients receiving AEDs only (the placebo group) after 12 weeks follow-up. The longest-term evidence from the largest extension trial available (Franz et al., 2018) included 361 patients from the original trial who were all given everolimus. The trial reported a 50% reduction in seizure frequency in 31% of patients at week 18, 46.6% at 1 year, and 57.7% at 2 years. These calculations only included patients that remained on treatment with everolimus during the extension period. The authors did another analysis which took account of patients who dropped out of the study at each time point. Everolimus was still found to reduce seizure frequency by 50% in 30.2% (number of people [n] = 361) of people at week 18, 38.8% (n = 358) at 1 year, and 41% (n = 229) at 2 years. The results from French (2016) and Franz (2018) suggest that 30% of patients treated with everolimus can expect a 50% reduction in seizure frequency from baseline at week 12 after starting treatment. The results
	French, 2016	9/10	Directly applicable		
	Krueger, 2016	4/10	Directly applicable		
	Krueger, 2013	6/10	Directly applicable		
	Samueli, 2016	3/10	Directly applicable		
	Wiegand, 2013	3/10	Directly applicable		

Outcome measure	Study	Critical appraisal score	Applicability to decision problem	Grade of evidence	Interpretation of evidence
					also suggest that the benefit of treatment can increase over time. The greatest benefit was reported in patients initially randomised to high dose everolimus.). It should be noted that the patients included in the study had a higher seizure frequency rate than expected in patients in England and just under half had tried 6 or more AEDs previously.
Median % reduction in seizures	Franz, 2018	7/10	Directly applicable	A	Median percentage reduction in seizures is a measure of the reduction in seizure frequency relative to baseline seizure frequency at the start of the study. The largest study (French, 2016) with 366 patients reported a median 40% and 29% reduction in seizures in the high and low dose everolimus groups, respectively at 12 weeks follow-up. In the AED only (placebo) group, there was a median 15% reduction in seizures in patients. The longest-term evidence from the largest extension trial (Franz, 2018) reported a median 31.7% reduction in seizure frequency at week 18, a median 46.7% reduction at 1 year, and a median 56.9% reduction at 2 years. The results from the French (2016) and Franz (2018) suggest that patients treated with everolimus can expect a 29% reduction in seizure frequency at week 12. The results also suggest that the benefit of treatment can increase over time. The greatest benefit was reported in patients initially randomised to high dose everolimus.
	French, 2016	9/10	Directly applicable		
	Kilincaslan, 2017	2/10	Directly applicable		
	Krueger, 2016	4/10	Directly applicable		
	Krueger, 2013	6/10	Directly applicable		

Outcome measure	Study	Critical appraisal score	Applicability to decision problem	Grade of evidence	Interpretation of evidence
					It should be noted that the patients included in the study had a higher seizure frequency rate than expected in patients in England and just under half had tried 6 or more AEDs previously.
Median number of additional seizure free days per 28 days	Franz, 2018	7/10	Directly applicable	A	The median number of additional seizure free days per 28 days a measure of the additional number of days without any countable seizures in a 28 day period. The largest and longest study (Franz, 2018) reported that the median number of seizure-free days (per 28-day period) increased from 2.5 days at week 18, to 4.32 at 1 year, and 6.15 days at 2 years of everolimus treatment. Data from French 2017 are captured in this analysis. The results from the Franz study (2018) suggest that patients treated with everolimus can expect 2.5 seizure-free days at week 18 with everolimus. The results also suggest that the benefit of treatment can increase over time. The greatest benefit was reported in patients initially randomised to high dose everolimus, leading the study authors to report that the benefit of everolimus is dependent on length of treatment (longer treatment durations corresponded with better outcomes) and exposure to everolimus (higher exposure corresponded with better outcomes). It should be noted that the patients included in the study had a higher seizure frequency rate compared to the expected seizure frequency rate for patients with refractory TSC-related seizures in England and just under half had tried 6 or more AEDs previously.
	French, 2016	9/10	Directly applicable		
	Samueli, 2016	3/10	Directly applicable		

Outcome measure	Study	Critical appraisal score	Applicability to decision problem	Grade of evidence	Interpretation of evidence
Patients remaining seizure free	Franz, 2018	7/10	Directly applicable	A	Patients remaining seizure free is a measure of the number of patients in the trial who had no countable seizures during the trial. The largest study (French, 2016) with 366 patients reported that 6 out of 117 (5%) patients in the low dose everolimus group and 5 out of 130 (4%) patients in the high dose everolimus group had no countable seizures compared to 1 out of 119 (0.8%) patients in the AEDs only (placebo) group at 12 weeks follow up. The longest-term evidence from the largest extension trial (Franz, 2018) included 361 patients from the original trial who were all given everolimus. The trial reported that 15 out of 275 (5%) patients at receiving everolimus were seizure-free over the previous 6 months at year 1 of the study and 13 out of 117 (11%) patients were seizure-free over the previous 6 months at year 2. The results from the French and Franz studies suggest that 4 out of 100 patients treated with everolimus can expect seizure freedom at week 18 of everolimus treatment and that the benefit of treatment with everolimus can increase over time. The greatest benefit was reported in patients who were remained in the study, leading the study authors to report that the benefit of everolimus is dependent on length of treatment (longer treatment durations corresponded with better outcomes). It should be noted that the patients included in the study had a higher seizure frequency rate compared to the expected seizure frequency rate for patients with refractory TSC-related seizures in England and just under half had tried 6 or more AEDs previously.
	French, 2016	9/10	Directly applicable		
	Krueger, 2016	4/10	Directly applicable		
	Krueger, 2013	6/10	Directly applicable		
	Samueli, 2016	3/10	Directly applicable		
	Wiegand, 2013	3/10	Directly applicable		

Outcome measure	Study	Critical appraisal score	Applicability to decision problem	Grade of evidence	Interpretation of evidence
Quality of life	French, 2016	9/10	Directly applicable	B	Quality of life is a measure of a patient's quality of life. It is usually based on a questionnaire which is completed by the patient or parent/carer. Like other outcomes, it is measured at baseline and then again during and at the end of the study. The largest study (French, 2016) with 366 patients reported that there was no difference in quality of life measures. A study with 20 patients (Krueger, 2013) reported a benefit in Quality of Life Childhood Epilepsy (QOLCE) questionnaire, which was driven by improvements in attention, behaviour, and social interaction domains. No improvement in quality of life was reported was during the extension study (Krueger, 2016). The results from the studies suggest that patients treated with everolimus may not see a consistent benefit in quality of life measures. The results from Krueger should be interpreted with caution as they are based on a small single arm study. It means that it did not randomise patients or compare the treatment with any other standard treatment. It should also be noted that the French (2016) study had difficulties in collecting the quality of life data, due to many of the patients enrolled having cognitive impairments which prevented the measurement of quality of life using the questionnaires available.
	Krueger, 2016	4/10	Directly applicable		
	Krueger, 2013	6/10	Directly applicable		
Changes to con-	Franz, 2018	7/10	Directly applicable	B	

Outcome measure	Study	Critical appraisal score	Applicability to decision problem	Grade of evidence	Interpretation of evidence
comitant AED medic-ation	Samueli, 2016	3/10	Directly applicable		Changes to concomitant AED medication means a measurement of changes to the amount and type of AEDs taken by patients in the studies in addition to everolimus or placebo. The largest study with 361 patients was the extension of the main trial (Franz, 2018). In the extension study, patients together with their treating clinician were allowed to make changes to their AED medication. This study reported that the proportion of AEDs patients were receiving at baseline remained the same over 2 years and 47% of patients received the same AED regimen for 1 year or longer during the extension study. The results from the extension study suggest patients being treated with everolimus can expect no change in their AED usage over time. This also suggests that there is less of a need to try a different AED medication as efficacy is maintained with the current AED with everolimus as add on treatment. It should be noted that the just under half of patients in the Franz study had tried 6 or more AEDs previously.
	Wiegand, 2013	3/10	Directly applicable		
Patient behaviour	Kilincaslan, 2017	2/10	Directly applicable	B	Patient behaviour means changes in patient behaviour over time including changes positive (or social) and negative (or antisocial) behaviours. The largest study (Krueger, 2013) with 20 patients reported mixed results indicating an improvement (reduction) in negative behaviour, but no significant improvement in positive behaviours. The results of the extension study (Krueger, 2016) suggested no difference in patient behaviour over 48 months.
	Krueger, 2016	4/10	Directly applicable		
	Krueger, 2013	6/10	Directly applicable		

Outcome measure	Study	Critical appraisal score	Applicability to decision problem	Grade of evidence	Interpretation of evidence
					The results from the studies suggest that patients treated with everolimus may not see a clear improvement in behaviour. The results from Krueger should be interpreted with caution as they are based on a small single arm study. It means that it did not randomise patients or compare the treatment with any other standard treatment. It should also be noted that the French (2016) study had intended on collecting the patient behaviour data, but was unable to do so due to many of the patients enrolled having cognitive impairments which prevented the measurement of patient behaviour using the questionnaires available.
Safety	Franz, 2018	7/10	Directly applicable	A	<u>All Adverse events</u> The largest study (Franz, 2018) which studied 361 patients up to 2 years indicated that all AEs did not increase over time: 77.8% of patients experienced an adverse event within the first 6 months of the study; 46.2% of patients experienced an adverse event between month 6 to month 12 and 45.5% of patients experienced an adverse event between 12 months and 24 months. Grade 3 or 4 adverse events The largest study (Franz, 2018) which studied 361 patients up to 2 years indicated that grade 3 or 4 adverse events were reported in 145 patients (40.2%) and most frequent (≥2.5%) were pneumonia (6.9%), status epilepticus (3.3%), seizures (2.8%), and stomatitis (2.5%). Adverse
	French, 2016	9/10	Directly applicable		
	Kilincaslan, 2017	2/10	Directly applicable		
	Krueger, 2016	4/10	Directly applicable		
	Krueger, 2013	6/10	Directly applicable		

Outcome measure	Study	Critical appraisal score	Applicability to decision problem	Grade of evidence	Interpretation of evidence
	Samueli, 2016	3/10	Directly applicable		events led to treatment discontinuation in 47 patients (13%). The results from the studies suggest that most patients treated with everolimus may experience an adverse event, but that adverse events did not increase over time.
	Wiegand, 2013	3/10	Directly applicable		
Discontin-uation rates	Franz, 2018	7/10	Directly applicable	B	Discontinuation rates means the number of patients who stopped using everolimus for any reason during the trial. The largest study (Franz, 2018) which studied 361 patients up to 2 years indicated that 105/ 361 patients (29%) discontinued everolimus during up to the data cut off of September 2016. The main reasons for discontinuation were adverse events (12.7%), withdrawal of consent (7.2%), and because it was not reducing the frequency or severity of seizures anymore (5.8%). The results from the studies suggest that some patients treated with everolimus may stop taking it due to side effects or because it is no longer reducing the frequency or severity of their seizures. The results should be interpreted with caution as this was a trial setting, and the number of patients stopping treatment clinical practice could vary.
	Krueger, 2016	4/10	Directly applicable		
	Samueli, 2016	3/10	Directly applicable		
	Wiegand, 2013	3/10	Directly applicable		

Relevance to NICE guidelines and NHS England policies

There are no specific NICE guidelines on this topic. The following NICE clinical guideline makes reference to TSC-associated seizures:

- Epilepsies: diagnosis and management (2012 updated 2016) NICE guideline CG137

The following NHS England policies are in TSC but in different indications:

- Clinical Commissioning Policy Statement: Everolimus (Votubia®) for treatment of angiomyolipomas associated with tuberous sclerosis. June 2016. NHS England Reference B14X09.
- Clinical Commissioning Policy: Everolimus for subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex December 2016. NHS England Reference 16066/P.

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Expert advisers

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Declarations of interest

No relevant interests declared.

Appendix 1 Search strategy

Database: Ovid MEDLINE(R) Epub Ahead of Print; In-Process & Other Non-Indexed Citations; Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)
Platform: Ovid
Version: 1946 - date
Search date: 4th July 2017
Number of results retrieved: 63
Search strategy:

1 Tuberous Sclerosis/ (5594)
2 ((tuberous or cerebral or brain or tuberosa or tuberose) adj sclerosis).tw. (7123)
3 tsc.tw. (3178)
4 bourneville*.tw. (479)
5 epiloia.tw. (37)
6 epiloya.tw. (0)
7 "adenoma sebaceum".tw. (174)
8 or/1-7 (9692)
9 exp epilepsy/ (147952)
10 epilep*.tw. (118363)
11 seizur*.tw. (105332)
12 fit*.tw. (271919)
13 convuls*.tw. (26439)
14 or/9-13 (484356)
15 everolimus/ (3642)
16 everolimus.tw. (5018)
17 votubia.tw. (1)
18 (rad adj 001*).tw. (58)
19 rad001*.tw. (494)
20 afinitor.tw. (46)
21 affinitor.tw. (0)
22 certican.tw. (70)
23 zortress.tw. (3)
24 (sdz adj rad).tw. (66)
25 sdzrad.tw. (0)
26 or/15-25 (5866)
27 8 and 14 and 26 (69)
28 animals/ not (humans/ and animals/) (4392318)
29 27 not 28 (66)
30 limit 29 to english language (63)

Database: Embase
Platform: Ovid
Version: 1974 to 3rd July 2017
Search date: 4th July 2017
Number of results retrieved: 239
Search strategy:

1 tuberous sclerosis/ (9521)
2 ((tuberous or cerebral or brain or tuberosa or tuberose) adj sclerosis).tw. (8967)
3 tsc.tw. (4368)
4 bourneville*.tw. (544)
5 epiloia.tw. (32)

6 epiloya.tw. (0)
7 "adenoma sebaceum".tw. (206)
8 or/1-7 (13184)
9 exp epilepsy/ (208150)
10 exp seizure/ (128987)
11 convulsion/ (24549)
12 epilep*.tw. (166063)
13 seizur*.tw. (152070)
14 fit*.tw. (315965)
15 convuls*.tw. (34464)
16 or/9-15 (656290)
17 everolimus/ (21326)
18 everolimus.tw. (11186)
19 votubia.tw. (27)
20 (rad adj 001*).tw. (2136)
21 rad001*.tw. (1098)
22 afinitor.tw. (586)
23 affinitor.tw. (34)
24 certican.tw. (582)
25 zortress.tw. (54)
26 (sdz adj rad).tw. (89)
27 sdzrad.tw. (3)
28 or/17-27 (22272)
29 8 and 16 and 28 (246)
30 nonhuman/ not (human/ and nonhuman/) (4006614)
31 29 not 30 (244)
32 limit 31 to english language (239)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); DARE; CENTRAL; HTA database; NHS EED
Platform: Wiley
Version:
CDSR – 7 of 12, July 2017
DARE – 2 of 4, April 2015 (legacy database)
CENTRAL – 6 of 12, June 2017
HTA – 4 of 4, October 2016
NHS EED – 2 of 4, April 2015 (legacy database)
Search date: 4th July 2017
Number of results retrieved: CDSR – 1; DARE – 0; CENTRAL – 26; HTA – 0; NHS EED – 0.
Search strategy:

ID	Search
#1	[mh ^"tuberous sclerosis"]
#2	((tuberous or cerebral or brain or tuberosa or tuberose) next sclerosis):ti,ab
#3	tsc:ti,ab
#4	bourneville*:ti,ab
#5	epiloia:ti,ab
#6	epiloya:ti,ab
#7	"adenoma sebaceum":ti,ab
#8	{or #1-#7}
#9	[mh epilepsy]
#10	epilep*:ti,ab
#11	seizur*:ti,ab

#12 fit*:ti,ab
#13 convuls*:ti,ab
#14 {or #9-#13}
#15 [mh ^everolimus]
#16 everolimus:ti,ab
#17 votubia:ti,ab
#18 (rad next 001*):ti,ab
#19 rad001*:ti,ab
#20 afinitor:ti,ab
#21 affinitor:ti,ab
#22 certican:ti,ab
#23 zortress:ti,ab
#24 (sdz next rad):ti,ab
#25 sdzrad:ti,ab
#26 {or #15-#25}
#27 #8 and #14 and #26

Trials registries

Clinicaltrials.gov

Search date: 5th July 2017
Number of results retrieved: 29
Search strategy and link to results page:

(Tuberous Sclerosis) OR tuberose OR TSC OR (adenoma sebaceum) *[in indication field]*
AND
everolimus OR votubia OR (rad 001a) OR rad001 OR (rad001a) OR affinitor OR SDZRAD *[in intervention field]*

Results limited to phase 2, 3 or 4 studies.

Clinicaltrialsregister.eu

Search date: 5th July 2017
Number of results retrieved: 10
Search strategy and link to results page:

(((tuberous OR cerebral OR brain OR tuberosa OR tuberose) AND sclerosis) OR TSC OR bourneville OR bournevilles OR epiloia OR epiloya OR (adenoma sebaceum)) AND (everolimus OR votubia OR rad001 OR rad001a OR (rad 001) OR (rad 001a) OR afinitor OR affinitor OR certican OR zortress OR (sdz rad))

Results limited to phase 2, 3 or 4 studies.

Appendix 2 Study selection

The search strategy presented in Appendix 2 yielded 329 studies. Following de-duplication, 249 records were subsequently screened on titles and abstracts in EPPI Reviewer according to the following inclusion/exclusion criteria.

Table 4 Sifting criteria

Sifting criteria	Inclusion	Exclusion
Population	• Seizures associated with TSC	• Non-humans • Studies that focussed on other aspects of TSC, such as SEGA, AML, etc (these studies were grouped together for ease of identification)*
Intervention	• Everolimus	•
Comparator	Any	
Outcomes	N/A	
Other		• Case studies • Abstracts • Non-English language • Duplicates • Opinion pieces, commentaries, epidemiological studies, burden of disease studies

*Please note studies focusing on the use of everolimus in patients with other aspects of TSC such as AML or SEGA were not eligible for inclusion. These trials did not focus on patients with refractory seizures and as such the included patients would not be representative of the decision problem or powered to detect a difference in seizures. For example patients in EXIST 1 which studied everolimus in patients with SEGA did not require patients to have seizures at baseline.

Nine full text articles were ordered and assessed based on the following inclusion/exclusion criteria.

Table 5 Full text criteria

Full text criteria	Inclusion	Exclusion
Population	• **Refractory** seizures associated with TSC	• Studies that focus on other aspects of TSC, such as SEGA, AML, etc (these studies were grouped together for ease of identification)
Intervention	• Everolimus	
Comparator	Any	

Outcomes	See scope	
Other		• Case studies • Non-English language • Reviews that include mixed data on interventions other than everolimus (such as sirolimus) or other indications (such as SEGA) • Opinion pieces, commentaries, epidemiological studies, burden of disease studies

The table of studies excluded at full text is show below.

Table 6 Studies excluded at full text.

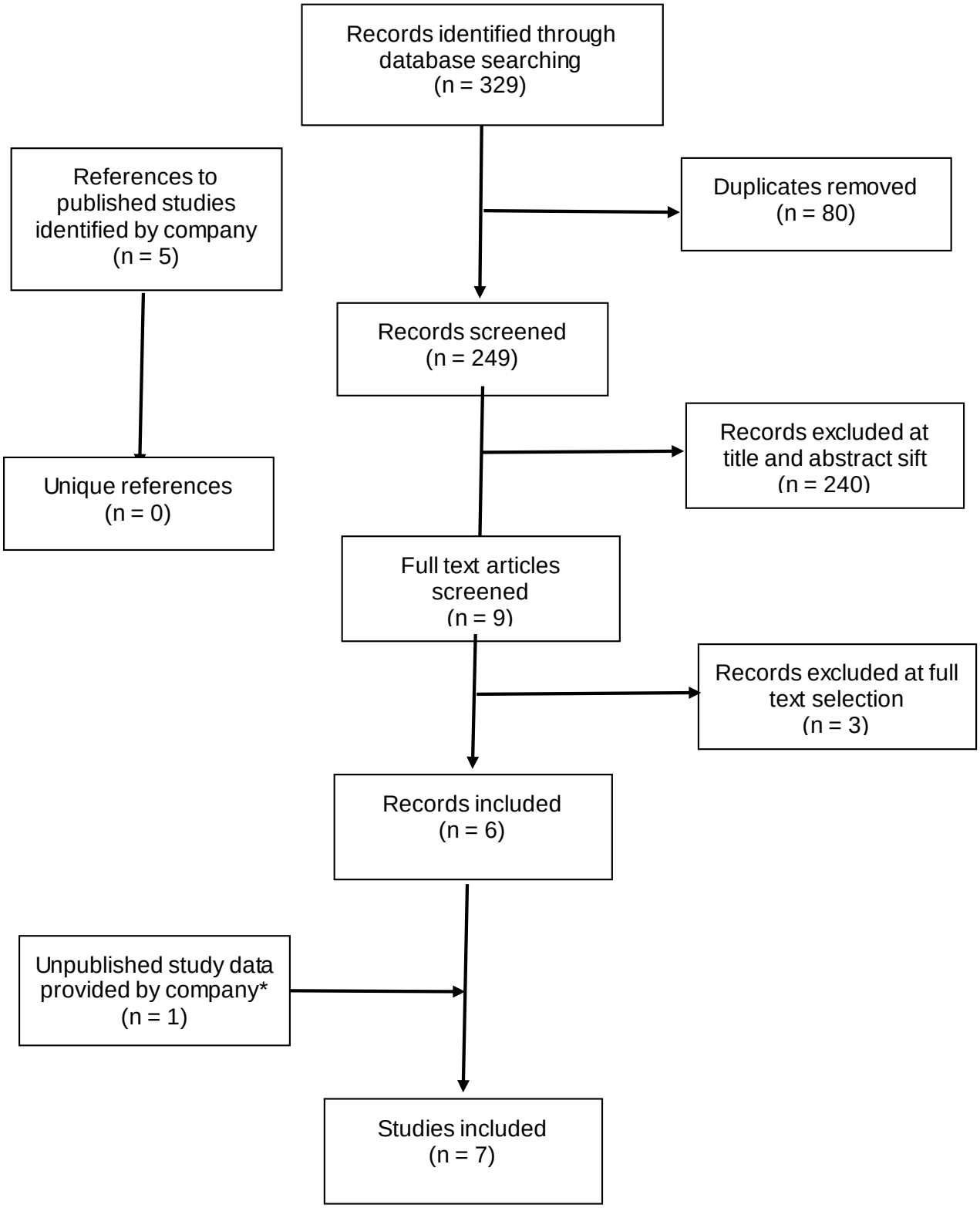
Study reference	Reason for exclusion
Cardamone Michael, Flanagan Danny, Mowat David, Kennedy Sean E, Chopra Maya, and Lawson John A (2014) Mammalian target of rapamycin inhibitors for intractable epilepsy and subependymal giant cell astrocytomas in tuberous sclerosis complex. The Journal of pediatrics 164, 1195-200	Exclude based on target group Case series but only 1 patient received everolimus for seizures
Sasongko Teguh, H , Ismail Nur Farrah, Dila , and Zabidi-Hussin Zamh (2016) Rapamycin and rapalogs for tuberous sclerosis complex. Cochrane Database of Systematic Reviews ,	Exclude based on target group Review and none of the included studies focussed on everolimus for refractory seizures associated with TSC
Yang G, Yang L, Yang X, Shi X, Wang J, Liu Y, Ju J, and Zou L (2015) Efficacy and safety of a mammalian target of rapamycin inhibitor in pediatric patients with tuberous sclerosis complex: A systematic review and meta-analysis. Experimental and Therapeutic Medicine 9, 626-630	Exclude based on target group Review and none of the included studies focussed on everolimus for refractory seizures associated with TSC

The company submission identified 5 references to published studies in their submission. All of these studies were included in the database searches, and as such 0 additional unique references were identified.

The company also provided data for 1 study which was selected for inclusion.

As such, seven studies met the inclusion/exclusion criteria and were subsequently included. Please note, the EPAR was also used to supplement the published data from the pivotal trial (French, 2016).

Figure 2 Flow chart of included studies



* Franz (2018) was unpublished at the time of inclusion, but has since been published.

Appendix 3 Evidence tables

Table 7 Franz (2018) data from EXIST-3 extension

Study reference	Franz David N, Lawson John A, Yapici Zuhal, MD, Ikeda Hiroko, Polster Tilman, Nabbout Rima, Curatolo Paolo, de Vries Petrus J, Dlugos Dennis J, Voi Maurizio, Fan Jenna, Vaury Alexandra, Pelov Diana, French Jacqueline A. Everolimus for treatment-refractory seizures in TSC: extension of a randomised controlled trial. Neurology Clinical Practice. Oct 2018, 8 (5) 412-420.
Unique identifier	NCT01713946
Study type (NSF-LTC category of research)	Prospective non-comparative long term extension of pivotal phase III trial (EXIST-3) (P1 Primary research using quantitative methods)
Aim of the study	To evaluate the long-term efficacy and safety of everolimus as adjunctive therapy for TSC-associated treatment-refractory seizures from EXIST-3 when all patients have completed at least 48 weeks of the extension phase of the study
Study dates	Data cut-off was September 2016
Setting	103 study sites across the world (8 in the UK)
Number of participants	361 256 with ongoing treatment
Population	The dataset was based on 361 patients from core phase of the EXIST -3 study (including those on placebo arm) entering the extension phase who had received at least one dose of everolimus and had at least one efficacy assessment during the core phase and /or extension phase of the study. All subjects had completed at least 48 weeks of the extension phase of the study, or had discontinued earlier. See French et al above for details of the population enrolled in EXIST-3. The included patients had a median age of 10 years (2.2 to 56.3 years), and 81% were under 18 years of age. 48% were female, 64.5% were Caucasian, and the median BSA was 1.09 (range 0.53 to 2.60). Please see French et al for more details of the population characteristics for patients entering EXIST-1 trial.
Inclusion criteria	Key inclusion criteria for core phase: • Patients aged 2-65 years a with definitive diagnosis of TSC • At least 16 treatment- refractory seizures during initial 8-week baseline phase (with no continuous 21-day seizure-free period) • 1-3 AEDs at stable dose for 4 weeks prior to baseline phase Patients were allowed to change AEDs or modify dose during the extension phase.

Exclusion criteria	Key exclusion criteria: • Patients with seizures secondary to metabolic, toxic, infectious or psychogenic disorder or drug abuse or current seizures related to an acute medical illness • subependymal giant-cell • astrocytomas requiring immediate surgical intervention • active infantile spasms • an episode of status epilepticus within 1 year before study inclusion
Intervention(s)	Everolimus 3–15 ng/mL target trough range. Target trough at follow-up not reported.
Comparator(s)	Not applicable
Length of follow-up	Up to 2 year follow-up data presented
Outcomes	Primary outcomes • Long-term efficacy endpoints were 50% response rate, • % reduction from baseline in TSC-seizure frequency •
	Secondary outcomes • Seizure freedom rate • Seizure free days
	Safety outcomes: • Frequency of adverse events
Source of funding	Novartis Pharmaceuticals

NSF-LTC

Criteria	Score	Narrative description of study quality
1. Are the research questions / aims and design clearly stated?	2/2	Clear and appropriate
2. Is the research design appropriate for the aims and objectives of the research?	2/2	Clear and appropriate for type of study.
3. Are the methods clearly described?	1/2	Methods are well described. Appears to be a well conducted extension study. Large sample size for this indication. However, limitations in study methods, such as large dropout rates, and some potential for bias, and confounding (due to changes in AED medications allowed).
4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	This study had a large sample size for this indication. However, limitations in study methods, such as large drop out

		rates, reduce the confidence in the data, and thus the conclusions. Authors do acknowledge study limitations in their conclusions
5. Are the results generalisable?	1/2	Inclusion criteria based on EXIST-3 which was restrictive on entry criteria for participants, which may reduce generalisability.
Total	7/10	
Applicability	Directly applicable	The intervention and indication are directly relevant to the decision problem

Table 8 French, 2016

Study reference	French Jacqueline A, Lawson John A, Yapici Zuhal, Ikeda Hiroko, Polster Tilman, Nabbout Rima, Curatolo Paolo, de Vries , Petrus J, Dlugos Dennis J, Berkowitz Noah, Voi Maurizio, Peyrard Severine, Pelov Diana, and Franz David N (2016) Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study. Lancet (London, and England) 388, 2153-2163[1]
Unique identifier	NCT01713946
Study type (NSF-LTC category of research)	Randomised double-blind placebo-controlled phase III trial (P1 Primary research using quantitative methods)
Aim of the study	To assess the efficacy and safety of two trough exposure concentrations of everolimus, 3–7 ng/mL (low exposure) and 9–15 ng/mL (high exposure), as adjunctive therapy for treatment-resistant focal-onset seizures in tuberous sclerosis complex, compared with placebo.
Study dates	July 2013 to May 2015
Setting	99 centres in 25 countries worldwide (8 UK centres)
Number of participants	432 patients screened 366 patients were enrolled: • N=119 placebo • N=117 low-exposure everolimus • N=130 high exposure everolimus
Population	Patients aged 2–65 years with a confirmed diagnosis of tuberous sclerosis complex and treatment resistant epilepsy.

[1] The EPAR was also used as a date source for this study.

	The population characteristics were generally well balanced across treatment groups. The EMA EPAR noted the following differences between treatment groups at baseline but did not consider them to be a high risk of bias to the results: a higher proportion of patients on 3 AEDs in placebo group (52% for placebo, vs 43-47% for everolimus)); a higher seizure frequency in placebo group (42 for placebo, vs 34.5-37.8 for everolimus); and a higher median number of failed AEDs in placebo group (6 for placebo, vs 5 for everolimus). Across all treatment groups, the median age of patients was 10.1 years (range 2.2 to 56.3 years), 82% of patients were under 18 years old, 48% were female; 65% of patients were white, and the median BSA was 1.10 m^2. The type of seizures at baseline was well balanced across groups, with the 3 most common seizures types at baseline being: focal non-motor with impaired awareness (45%); other focal motor seizures (41%); focal motor with impaired awareness (26%). Generalised onset seizures (EEG confirmed) accounted for 2% of seizures.
Inclusion criteria	• Confirmed diagnosis of TSC according to Gomez criteria • 16 or more seizures during the 8-week baseline phase (with no continuous 21-day seizure-free period) • prior history of failure to control seizures with two or more antiepileptic drug regimens • receiving between one and three antiepileptic drugs at a stable dose for at least 12 weeks before randomisation • prior or concurrent vagal nerve stimulation was allowed, as long as device stimulator remained constant throughout study
Exclusion criteria	• Seizures secondary to drug abuse, metabolic, toxic, infectious or psychogenic disorder, or acute medical illness • presence of non-motor partial seizures • patients with SEGA in need of immediate surgery • patients under 2 with untreated infantile spasms • an episode of status epilepticus within 52 weeks prior to study • patients with a history of seizure clusters • patients who had received a systemic mTOR inhibitor within 24 months of study entry • patients who had received a topical mTOR inhibitor within 4 weeks of study entry • patients who require rescue medication for more than 6 days • patients with non-TSC related progressive encephalopathy. • patients who weigh less than 12 kg. • patients being treated with felbamate, unless treatment has been continuous for ≥ 1 year. • maintenance diet consisting of <40 g of carbohydrate per day within 3 months of screening

	• patients with a score of 4 or 5 on the Suicide Ideation item within 2 years of screening.
Intervention(s)	• Low exposure - everolimus target trough of 3-7 ng/mL • High exposure– everolimus target trough of 9–15 ng/mL At the end of core phase of study the actual achieved troughs and doses were: Low exposure – median trough was 5.1 ng/ml (range 1.4-25.3), and median dose was 5.2 mg/m2/day (range 1.3-14.5) High exposure – median trough was 8.3 ng/ml (range 0.8-22.0), and median dose was 7.5 mg/m2/day (range 1.4-24.4).
Comparator(s)	Placebo
Length of follow-up	12 weeks
Outcomes	Primary outcome: • Response of at least 50% reduction in partial-onset seizure frequency from baseline through to week 12 • Percentage reduction in partial onset seizure frequency from baseline through to week 12
	Secondary outcomes: • Seizure free rate (100% reduction in partial onset seizures) • Proportion of patients with at least 25% reduction in partial onset seizure frequency • Frequency of seizure free days • Treatment duration • Time from randomization until treatment discontinuation in the Core phase • Overall Quality of Life global scores • Sub-test scores for neurocognitive, neurodevelopmental, and neurobehavioral tests • Changes in the Vineland Adaptive Behaviour Scales-II and the Wechsler Non-Verbal Scale of Ability • Percentage reduction in seizure frequency/frequency of selected adverse events • Pre-dose concentrations of anti-epileptic drugs (AEDs) alone and post-baseline (AEDs plus everolimus) • 50% response rate from Baseline by time interval over the extension phase • Seizure free days in partial onset seizure by time interval over the extension phase
	Safety outcomes:

	• Frequency of adverse events • Frequency of abnormal laboratory values • Frequency of Columbia Suicide Severity Rating Scale outcomes • Frequency of serious adverse events referring to a positive suicidal evaluation
Source of funding	Novartis Pharmaceuticals

NSF-LTC

Criteria	**Score**	**Narrative description of study quality**
1. Are the research questions / aims and design clearly stated?	2/2	Clear and appropriate
2. Is the research design appropriate for the aims and objectives of the research?	2/2	Clear and appropriate
3. Are the methods clearly described?	2/2	Clear and appropriate. No change in AED medication allowed which reduces confounding.
4. Are the data adequate to support the authors' interpretations / conclusions?	2/2	Data support authors conclusions
5. Are the results generalisable?	1/2	Key licensing trial, which was conducted in over 25 countries. However, the strict inclusion and exclusion criteria of the trial naturally reduces generalisability of results.
Total	9/10	
Applicability	Directly applicable	The intervention and indication are directly relevant to the decision problem

Table 9 Kilincaslan, 2017

Study reference	Kilincaslan Ayse, Kok Burcu Ece, Tekturk Pinar, Yalcinkaya Cengiz, Ozkara Cigdem, and Yapici Zuhal (2017) Beneficial Effects of Everolimus on Autism and Attention-Deficit/Hyperactivity Disorder Symptoms in a Group of Patients with Tuberous Sclerosis Complex. Journal of child and adolescent psychopharmacology 27, 383-38
Unique identifier	Not found on clinicaltrials.gov
Study type (NSF-LTC category of research)	Case series (appears retrospective) (P1 Primary research using quantitative methods)
Aim of the study	To describe the effects of everolimus on emotional and behavioural symptoms and refractory epilepsy in patients with TSC.
Study dates	2014 to 2016
Setting	1 medical facility in Istanbul, Turkey
Number of participants	6 patients
Population	Six patients, four male and two female, aged 7.5 to 23. The type of seizures prior to everolimus appeared to be predominantly simply partial or complex partial, although other seizure types were noted.
Inclusion criteria	Not applicable although medical notes of patients were reviewed to confirm they had reported at least 8 seizures in 30 days, despite adequate use of at least 2 approved AEDs. All patients were receiving concomitant AEDs and the drug regimen and dose could not be changed during everolimus use
Exclusion criteria	Not applicable
Intervention(s)	Everolimus 5–15 ng/mL target trough The median everolimus dose delivered was 10 mg/day (range 5-20mg)
Comparator(s)	None
Length of follow-up	Median length of follow-up was 17.5 months (range 7-26)
Outcomes	Seizure outcomes • Very good response (90% or more reduction in seizure frequency) • Good response (60-90% reduction in seizure frequency) • Moderate response (30-60% reduction in seizure frequency) • Mild response (<30% reduction in seizure frequency)
	Other outcomes • Psychiatric outcomes

	• Side effects
Source of funding	Not reported

NSF-LTC

Criteria	Score	Narrative description of study quality
1. Are the research questions / aims and design clearly stated?	1/2	Design is not clearly stated.
2. Is the research design appropriate for the aims and objectives of the research?	0/2	The aim was to 'describe' so the case series design is reasonable but study design is itself limited for determining the benefits of an intervention
3. Are the methods clearly described?	0/2	Limited details of methods. But type of study prone to biases and confounding. Small sample size
4. Are the data adequate to support the authors' interpretations / conclusions?	0/2	Limitations in study methods reduce the confidence in the data, and thus the conclusions.
5. Are the results generalisable?	1/2	Too limited details available to be certain if generalisable but population and indication appear generalisable.
Total	2/10	
Applicability	Directly applicable	The intervention and indication are directly relevant to the decision problem

Table 10 Krueger, 2013

Study reference	Krueger Darcy A, Wilfong Angus A, Holland-Bouley Katherine, Anderson Anne E, Agricola Karen, Tudor Cindy, Mays Maxwell, Lopez Christina M, Kim Mi-Ok, and Franz David Neal (2013) Everolimus treatment of refractory epilepsy in tuberous sclerosis complex. Annals of neurology 74, 679-87
Unique identifier	NCT01070316
Study type (NSF-LTC category of research)	Phase I/II prospective uncontrolled study (P1 Primary research using quantitative methods)
Aim of the	To assess the benefit of everolimus on seizures control in patients with tuberous sclerosis complex and refractory epilepsy.

study	
Study dates	January 2010 to December 2015 (for extension phase)
Setting	2 clinics in the USA
Number of participants	23 patients screened 20 patients were enrolled
Population	Patients aged 2 years or older with a confirmed diagnosis of tuberous sclerosis complex and treatment resistant epilepsy. The median age of patients was 8 years (range 2 to 21 years), and 50% were female. The median number of concurrent AEDs was 2 (range 1-4), 25% had VNS present, 20% had prior epilepsy surgery and none were receiving the ketogenic diet.
Inclusion criteria	• Confirmed diagnosis of TSC • 8 or more seizures during the 30 days prior to enrolment • medical refractory epilepsy, defined as having failed on at least 2 approved AEDs • medically stable without evidence of significant infectious, oncological or immunological co-morbidity at enrolment • prior or concurrent vagal nerve stimulation or the ketogenic diet was allowed • prior epilepsy surgery was allowed
Exclusion criteria	• Previously treated with a systemic mTOR inhibitor • changes to AED medication whilst on study was not allowed
Intervention(s)	Everolimus 5–15 ng/mL target trough range. At the end of the maintenance phase of the study the median trough was 6.1 ng/dl (range 1.6-16.1 ng/dl). The median maintenance dose was 8.4mg/m2/day (range 3.4-13.7) or 7.5mg/day (range 2.5-12.5).
Comparator(s)	Not applicable
Length of follow-up	12 weeks
Outcomes	Primary outcome: • Percentage of patients achieving a 50% or greater reduction in seizure frequency from baseline (week 1-4) through to maintenance phase (week 13-16)
	Secondary outcomes: • Seizure response • Seizure response as measured by video EEG • Quality of life in children with epilepsy (QOLCE) • Nisonger child behaviour rating form (NCBRF)
	Safety outcomes: • Frequency of adverse events
Source of funding	Novartis pharmaceuticals

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**
1. Are the research questions / aims and design clearly stated?	2/2	Clear and appropriate
2. Is the research design appropriate for the aims and objectives of the research?	1/2	Clear and appropriate for type of study, but study design is itself limited for determining the benefits of an intervention
3. Are the methods clearly described?	1/2	Methods reasonably clear. Open label studies can be prone to biases. Small sample size. Changes to AED medications were not allowed which reduces confounding
4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	Limitations in study methods reduce the confidence in the data, and thus the conclusions. Authors do acknowledge study limitations in their conclusions
5. Are the results generalisable?	1/2	Inclusion criteria not as strict as EXIST-3, which should increase generalisability. However, few details of study participants so uncertain if fully generalisable. All patients were aged 21 or under
Total	6/10	
Applicability	Directly applicable	The intervention and indication are directly relevant to the decision problem

Table 11 Krueger, 2016

Study reference	Krueger Darcy A, Wilfong Angus A, Mays Maxwell, Talley Christina M, Agricola Karen, Tudor Cindy, Capal Jamie, Holland-Bouley Katherine, and Franz David Neal (2016) Long-term treatment of epilepsy with everolimus in tuberous sclerosis. Neurology 87, 2408-2415
Unique identifier	NCT01070316
Study type (NSF-LTC category of research)	Long term extension of phase I/II prospective uncontrolled study (P1 Primary research using quantitative methods)
Aim of the study	To assess the long-terms benefits and safety of everolimus on seizures control in patients with tuberous sclerosis complex and refractory epilepsy.
Study dates	January 2010 to December 2015 (for extension phase)
Setting	2 clinics in the USA
Number of participants	20 patients were enrolled in phase I/II study 18 patients continued onto extension study 14 patients completed extension study
Population	Patients aged 2 years or older with a confirmed diagnosis of tuberous sclerosis complex and treatment resistant epilepsy. In the initial phase I/II study the median age of patients was 8 years (range 2 to 21 years), and 50% were female. 60% of patients were receiving 2 concurrent AEDs, 25% had VNS present, 20% had prior epilepsy surgery and none were receiving the ketogenic diet. Entering the extension phase the median number of seizures per month was 7 (range 0-46).
Inclusion criteria	Patients demonstrating tolerability and benefits in the initial phase I/II study were eligible to continue onto the extension phase. Dose adjustments and changes of concomitant medications were allowed during the extension phase.
Exclusion criteria	Inefficacy or toxicity during initial phase I/II study
Intervention(s)	Everolimus 5–15 ng/mL target trough range. The serum trough during the extension phase was 7.4-10.8 ng/mL The median daily dose during the extension phase was 0.47-0.56mg/kg/day.
Comparator(s)	Not applicable
Length of follow-up	48 months
Outcomes	Primary outcome:

	• Percentage of patients achieving a 50% or greater reduction in seizure frequency compared to 4-week pre-treatment observation period
	Secondary outcomes: • Reduction in seizures • Quality of life in children with epilepsy (QOLCE) • Nisonger child behaviour rating form (NCBRF)
	Safety outcomes: • Frequency of adverse events
Source of funding	Novartis pharmaceuticals

NSF-LTC

Criteria	Score	Narrative description of study quality
1. Are the research questions / aims and design clearly stated?	2/2	Clear and appropriate
2. Is the research design appropriate for the aims and objectives of the research?	1/2	Clear and appropriate for type of study. Open label prone to biases. Small sample size.
3. Are the methods clearly described?	0/2	Methods not fully described and population characteristics unclear. Open label extension studies can be prone to biases. Changes to AED medication was allowed which increases confounding. Small sample size.
4. Are the data adequate to support the authors' interpretations / conclusions?	0/2	Limitations in study methods reduce the confidence in the data, and thus the conclusions.
5. Are the results generalisable?	1/2	Inclusion criteria not as strict as EXIST-3, which should increase generalisability. However, few details of study participants and seizure types included so uncertain if fully generalizable
Total	4/10	
Applicability	Directly applicable	The intervention and indication are directly relevant to the decision problem

Table 12 Samueli, 2016

Study reference	Samueli Sharon, Abraham Klaus, Dressler Anastasia, Groppel Gudrun, Muhlebner-Fahrngruber Angelika, Scholl Theresa, Kasprian Gregor, Laccone Franco, and Feucht Martha (2016) Efficacy and safety of Everolimus in children with TSC - associated epilepsy - Pilot data from an open single-center prospective study. Orphanet journal of rare diseases 11, 14
Unique identifier	Not found on clinicaltrials.gov
Study type (NSF-LTC category of research)	Prospective uncontrolled before and after study (P1 Primary research using quantitative methods)
Aim of the study	To evaluate the efficacy and safety of everolimus in children and adolescents with tuberous sclerosis complex associated epilepsies.
Study dates	Initiated April 2013, unclear end date
Setting	1 clinic in Austria
Number of participants	17 patients were screened 15 patients were enrolled in the study
Population	Patients aged 18 years or younger with a confirmed diagnosis of tuberous sclerosis complex and treatment resistant TSC-associated epilepsy. The median age of patients was 6 years (range 1 to 18 years), and 40% were female. All patients had SEGA and SEN, and RML was present in 40% of patients. The median seizure frequency at baseline was 30 per month (range 1-410). The median number of AEDs used before study was 5 (range 1-11). The median number of concomitant AEDs at baseline was 2 (range 1-3). The seizure types present at baseline were 67% focal, 47% tonic clonic, 47% atypical absence, and one patient had infantile spasms. Four patients had VNS, 1 had the ketogenic diet, 1 had prior epilepsy surgery and 1 had prior SEGA surgery.
Inclusion criteria	• Ascertained diagnosis of TSC • Aged 18 years or younger • Pharmaco-resistance according to ILAE consensus proposal
Exclusion criteria	• Change of concomitant AEDs was not permitted during baseline and the first 6 months
Intervention(s)	Everolimus 5–15 ng/mL target trough range. The end of study median trough was 4.6 ng/dl (range 1.6-7.8 ng/dl). The end of study median dose was 5.8 mg/m2/day (range 2.6-9.8).
Comparator(s)	Not applicable

Length of follow-up	Median 22 months (range 6-50 months)
Outcomes	• Treatment response defined as the median reduction in seizure frequency of at least 50% at 6, 12, 18 and last observation, compared with baseline • Median number of seizure free days per 28 days • Proportion of patients seizure free
	Safety outcomes: • Frequency of adverse events
Source of funding	The European Union Seventh Framework Program EPISTOP (Grant Agreement Nr. 602391 to Martha Feucht). The Anniversary Fund of the Central Bank of the Republic of Austria (ÖNB-12036 dedicated to M. Feucht). The Austrian Science Fund FWF (J 3499 Schrödinger-Programm). The TSC research award 2015 form the German Tuberous Sclerosis Foundation 2015.

NSF-LTC

Criteria	Score	Narrative description of study quality
1. Are the research questions / aims and design clearly stated?	1/2	Aims are clear and appropriate but design not well described
2. Is the research design appropriate for the aims and objectives of the research?	1/2	Clear and appropriate for type of study. But open label are prone to bias and confounding. This study also had a small sample size
3. Are the methods clearly described?	0/2	Some details on methods provided. However, type of study prone to biases and confounding. This study also had a small sample size
4. Are the data adequate to support the authors' interpretations / conclusions?	0/2	Limitations in study methods reduce the confidence in the data, and thus the conclusions.
5. Are the results generalisable?	1/2	Inclusion criteria not as strict as EXIST-3, which should increase generalisability. However, the study included one patient aged under 2, and all patient were aged under 18
Total	3/10	
Applicability	Directly applicable	The intervention and indication are directly relevant to the decision problem

Table 13 Wiegand, 2013

Study reference	Wiegand Gert, May Theodor W, Ostertag Philipp, Boor Rainer, Stephani Ulrich, and Franz David Neal (2013) Everolimus in tuberous sclerosis patients with intractable epilepsy: a treatment option? European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society 17, 631-8
Unique identifier	Not found on clinicaltrials.gov
Study type (NSF-LTC category of research)	Prospective uncontrolled before and after (compassionate use) study (P1 Primary research using quantitative methods)
Aim of the study	To evaluate the efficacy and safety of everolimus in patients with tuberous sclerosis complex and refractory epilepsy.
Study dates	June 2010 to January 2012
Setting	1 clinic in Germany
Number of participants	7 patients were enrolled in the study 6 completed follow-up
Population	Patients with a confirmed diagnosis of tuberous sclerosis complex and treatment resistant epilepsy. All of the enrolled patients were children with a median age of 5 years (range 2 to 12 years), and 57% were female. The median number of AEDs used before study was 10 (range 4-15). Three patients had received glucocorticoid treatment, one had VNS and one had prior epilepsy surgery. Three patients had SEGA, and seven patients had renal or liver angiomyolipomas. The seizure frequency per day ranged from 0.19 to 13.9. Four patients had tonic seizures, three had complex partial seizures, three had secondary generalised seizures, two had epileptic spasms, two had myoclonic seizures and one had astatic seizures.
Inclusion criteria	• Ascertained diagnosis of TSC • Prior epilepsy surgery evaluation and judged not to candidates • Intractable epilepsy
Exclusion criteria	• Candidate for epilepsy surgery Note, changes in patient AED medications (drug or dose) for the duration of the study were not allowed, apart from 1 patient who was allowed to discontinue one AED.
Intervention(s)	Everolimus 5–10 ng/mL target trough range. At follow-up, the mean patient trough ranged from 5.5-13.4 ng/dl. At follow-up, the mean patient dose ranged from 2.9-7.0 mg/day.
Comparator(s)	Not applicable
Length of follow-up	9 months

Outcomes	• Frequency of seizures • Seizure free days Safety outcomes: • Frequency of adverse events
Source of funding	Not stated

NSF-LTC

Criteria	Score	Narrative description of study quality
1. Are the research questions / aims and design clearly stated?	1/2	Aims are clear and appropriate but design not well described
2. Is the research design appropriate for the aims and objectives of the research?	1/2	Clear and appropriate for type of study. But open label are prone to bias and confounding. This study also had a small sample size
3. Are the methods clearly described?	0/2	Some details on methods provided. However, type of study prone to biases and confounding. This study also had a small sample size
4. Are the data adequate to support the authors' interpretations / conclusions?	0/2	Limitations in study methods reduce the confidence in the data, and thus the conclusions.
5. Are the results generalisable?	1/2	Inclusion criteria not as strict as EXIST-3, which should increase generalisability. However, the study only included children.
Total	3/10	
Applicability	Directly applicable	The intervention and indication are directly relevant to the decision problem

Appendix 4 Results tables

Table 14 Franz, 2018 - data from EXIST-3 extension

	Everolimus (target trough 3-15 ng/mL) at follow up (up to 2 years) versus baseline
N	**361 (256 with ongoing treatment)**
Primary outcome	
Response rate, defined as at least 50% reduction in partial-onset seizure frequency	Response rate at week 18 (corresponding to the 12-week window of weeks 7-18 after the start of everolimus) was 31% (95% CI, 26.2-36.1; N=352) versus 46.6% (95% CI, 40.9-52.5; N=298) at 1 year (weeks 43-54) and 57.7% (95% CI, 49.7-65.4; N=163) at 2 years (weeks 91-102) of everolimus exposure. The likelihood of observing a 50% reduction in seizure frequency (calculated during a 12-week period) 1 year after start of everolimus was 45% in patients who transitioned from placebo to everolimus in the extension phase, 55% in everolimus low exposure, and 70% in the everolimus high exposure group. Fifty percent of patients experienced a persistent response and 59% of these had persistent responses lasting for ≥48 weeks.
Median percentage reduction in seizure frequency	The median percentage reduction in seizure frequency was 31.7% (95% CI, 28.5-36.1; at week 18 versus 46.7% (95% CI, 40.2-54;) at 1 year and 56.9% (95% CI, 50-68.4;) at 2 years of everolimus exposure
Median weekly seizure frequency	Baseline = 8.6 1 year = 3.6 2 year = 2.3
Secondary outcomes	
Seizure free days	The median number of additional seizure-free days (per 28-day period) increased from 2.5 days at week 18 to 4.32 at 1 year and 6.15 days at 2 years of everolimus exposure. The number of patients who were seizure-free over the previous six months remained roughly the same at 1 and 2 years although the proportion of patients increased from 5% (15/275) to 11% (13/117), respectively due to difference in denominator**.** Similarly an increase in the number of seizure-free days was observed in the low exposure and high exposure groups; however, for placebo-randomized patients, the number of seizure-free days was similar to that observed in low exposure group.
Changes to concomitant AED medication	The proportions of patients receiving 1, 2, 3 and >3 AEDs at baseline (10.8%, 41.6%, 46.8% and 0.8%) were comparable to the proportions of patients receiving the same numbers of concomitant AEDs at week 18 (10.8%, 39.5%, 47.7% and 2%), 1 year (10.7%, 36.7%, 48.3% and 4%), and 2 years (6.7%, 39.3%, 46.6% and 4.9%), respectively of everolimus exposure. Almost half of patients (47%) received the same AED regimen for ≥1 year. Half of patients (50%) received >2 concomitant AEDs from beginning to end of everolimus treatment.

Adverse effects (drug related)	The most frequent treatment-related adverse effects reported were stomatitis (33.5%), mouth ulceration (26.0%), diarrhoea (10.5%), aphthous ulcer (10.2%), and pyrexia (10.2%). Grade 3 or 4 adverse events were reported in 145 patients (40.2%) and most frequent (≥2.5%) were pneumonia (6.9%), status epilepticus (3.3%), seizures (2.8%), and stomatitis (2.5%). There was no reported increase in all grade treatment-related adverse effects over time (≤6 months, 77.8%; >6 to 12 months, 46.2%; 2nd year, 45.5%). Adverse events led to treatment discontinuation in 47 patients (13%), primarily due to pneumonia (1.7%) and stomatitis (1.4%). There were 4 deaths; 2 were thought to be treatment-related deaths (one due to pneumonia and one due to septic shock; both in children.
Adverse events of any cause	The most frequent all-grade adverse events of any cause reported (>20%) were stomatitis (35.2%), pyrexia (34.6%), diarrhoea (28.5%), mouth ulceration (27.7%), nasopharyngitis (23.8%), and upper respiratory tract infection (22.4%)). All grade treatment-related AEs did not increase over time (≤6 months, 77.8%; >6 to 12 months, 46.2%; 2nd year, 45.5%). Grade 3 or 4 adverse events were reported in 145 patients (40.2%) and most frequent (≥2.5%) were pneumonia (6.9%), status epilepticus (3.3%), seizures (2.8%), and stomatitis (2.5%). . Overall, 5.3% of patients experienced grade 4 adverse events; the most common were status epilepticus, pneumonia (3 patients each) and neutropenia (2 patients)The incidence of new or changed grade 3 or 4 adverse events during the second year (period between 12 and 24 months) of everolimus appeared to be similar to that observed within the first 6 months of treatment (≤6 months, 21.6%; >6 to 12 months, 13.8%; 2nd year, 19.9%; 3rd year, 4.7%). However, at the data cut-off date, less than 40% of patients completed a 2-year exposure to everolimus, preventing a definitive interpretation of these results. Adverse events led to treatment discontinuation in 47 patients (13%), primarily due to pneumonia (1.7%) and stomatitis (1.4%). The most common adverse events necessitating dose adjustments or interruption were stomatitis (9.4%), mouth ulceration (9.1%), pyrexia (6.1%) and pneumonia (5.3%). Two deaths occurred during the extension phase – both in paediatric patients due to pneumonia (suspected to be treatment-related) and sudden unexpected death in epilepsy (SUDEP, not suspected to be treatment-related). Two additional deaths occurred after the data cut-off date, one in a child due to septic shock (suspected to be treatment-related) and other in an adult patient due to SUDEP (not suspected to be treatment-related).
Discontinuations	105 patients out of 361 discontinued everolimus (29%) during the extension phase up to the data cut off of September 2016. 95 patients discontinued before achieving the 2 year follow up. The primary reasons for discontinuation were adverse events (12.7%), withdrawal of consent (7.2%), and lack of efficacy (5.8%).

Table 15 French, 2016

	Everolimus low trough (3-7 ng/mL)	Everolimus high trough (9-15 ng/mL)	Placebo
N	**117**	**130**	**119**
Primary outcome (ITT analysis)			
Response of at least 50% reduction in partial-onset seizure frequency from baseline through to week 12	33 patients (28.2%; 95% CI 20.3% to 37.3%) achieved a 50% or greater reduction in partial-onset seizures from baseline to week 12. This was statistically significant compared with placebo (p=0.008) The odds ratio (OR) for achieving a 50% or greater reduction in partial onset seizures with everolimus was 2.2 times higher than placebo (95% CI 1.2 to 4.2)	52 patients 40.0%; 95% CI 31.5% to 49%) achieved a 50% or greater reduction in partial-onset seizures from baseline to week 12. This was statistically significant compared with placebo (p<0.0001) The odds ratio (OR) for achieving a 50% or greater reduction in partial onset seizures with everolimus was 3.9 times higher than placebo (95% CI 2.1 to 7.3)	18 patients (15.1%; 95% CI 9.2% to 22.8%) achieved a 50% or greater reduction in partial-onset seizures from baseline to week 12
Median percentage reduction in partial onset seizure frequency from baseline through to week 12	There was a 29.3% median reduction in seizure frequency at 12 weeks compared with baseline (95% CI 18.8% to 41.9%). This was statistically significant (p=0.0028)	There was a 39.6% median reduction in seizure frequency at 12 weeks compared with baseline (95% CI 35.0% to 48.7%). This was statistically significant (p<0.0001)	14.9% (95% CI 0.1% to 21.7%)
Secondary outcomes			
Patients remaining seizure free during the maintenance phase	6 patients were seizure free at 12 weeks (5.1%; 95% CI 1.9% to 10.8%)	5 patients were seizure free at 12 weeks (3.8%; 95% CI 1.3% to 8.7%)	1 patient was seizure free at 12 weeks (0.8%; 95% CI 0% to 4.6%)
Probability of receiving treatment for 18 weeks core phase	70.1%	71.5%	75.6%

QOLCE (patients aged <11 years) and QOLE-AD-48 (patients aged 12 to 17)	No reported change – data not presented (taken from EPAR)	No reported change – data not presented (taken from EPAR)	No reported change – data not presented (taken from EPAR)
Qolie-31-P (patients aged 18 years and over)	Insufficient data – data not presented (taken from EPAR)	Insufficient data – data not presented (taken from EPAR)	Insufficient data but data reportedly favoured placebo – data not presented (taken from EPAR)
Adverse events of any cause	108 patients (92%) experienced an adverse event of any cause. 28 patients (24%) required dose modifications or interruptions. 21 patients (18%) experienced grade 3/4 adverse events. 6 patients (5%) discontinued therapy due to adverse events.	123 patients (95%) experienced an adverse event of any cause. 46 patients (35%) required dose modifications or interruptions. 31 patients (24%) experienced grade 3/4 adverse events. 4 patients (3%) discontinued therapy due to adverse events.	92 patients (77%) experienced an adverse event of any cause. 9 patients (8%) required dose modifications or interruptions. 13 patients (11%) experienced grade 3/4 adverse events. 2 patients (2%) discontinued therapy due to adverse events.

Table 16 Kilincaslan, 2017

	Everolimus (target trough 5-15 ng/mL) at follow up (median 17.5 months) versus baseline
N	**6**
Level of anti-epileptic response from baseline to endpoint	There was a 77.5% median reduction in seizure frequency 2 patients achieved a 90% or higher reduction in seizure frequency 2 patients achieved a 60-90% reduction in seizure frequency 2 patients achieved a 30-60% reduction in seizure frequency
Changes in Aberrant Behaviour Checklist (ABC) scores from baseline to endpoint	All patients were reported to achieve a reduction in scores of between 2 points and 34 points.
Changes in social interactions	3/4 patients diagnosed as autistic spectrum disorder were described by their parents as showing improvements in social interactions
Changes in attention and concentration	3/6 patients were described by their parents as showing improvements in attention and concentration.
Changes in aggression and irritability	One patient was reported by their parents as showing an increase in aggression, whilst one patient showed improvements.
Adverse effects	5/6 patients were reported as having experienced adverse effects. There were no reports of severe adverse effects. There were no changes in everolimus dose or discontinuations of everolimus.

Table 17 Krueger, 2013

	Everolimus (target trough 5-15 ng/mL) at follow up (12 weeks) versus baseline
N	**20**
Primary outcome	
Percentage of patients achieving a 50% or greater reduction in seizure frequency	12 out of 20 patients (60%) achieved a 50% or greater reduction in seizure frequency from baseline to follow-up
Secondary outcomes	
Median seizure frequency over 28 day period	There were 31 seizures at baseline versus 8.5 at follow up This equated to a statistically significant 73% median reduction in seizure frequency (p<0.001)
Change in cumulative seizure duration from baseline to follow up	There was a statistically significant 70% median cumulative reduction in seizure duration (p=0.02)
Median seizure frequency over 23 hour video EEG	There was a statistically significant reduction in median seizure frequency over 23 hours from 3.5 to 1.5 (range -33 to +3) p=0.007
Seizure free at follow-up	4 patients were reported as clinically seizure free (20%).
90% reduction in seizures	7 patients were reported as having at least a 90% reduction in seizure frequency (35%)
Nisonger child behaviour rating form (NCBRF)	There was a statistically significant reduction in the overall negative domain scores (-28.2, p=0.021*). There was a non-statistically significant increase in the positive domain scores (+1.5, p=0.083). *number in text and table do not match but both statistically significant.
Quality of life as measured by Quality of Life for Children with Epilepsy (QOLCE)	There was a statistically significant increase in the overall QOLCE score (+1.0, p<0.001), which was driven by changes in attention, behaviour, social interaction, other cognitive, stigma, physical restrictions and social activity domains.
Adverse events	All patients reported at least one adverse events (range 2-10), but all were grade 1/2. There were no grade 3/4 adverse events.
Adverse effects (treatment related)	There were 83 drug-related adverse effects. The most common were infections (29) and gastrointestinal (29).

Table 18 Krueger, 2016

	Everolimus (target trough 5-15 ng/mL) at follow up (48 months) versus baseline
N	**18**
Primary outcome	
Percentage of patients achieving a 50% or greater reduction in seizure frequency	Percentage of continuing patients achieving a 50% or greater reduction in seizure frequency from baseline were: Year 1 = 13/17 patients (76%) Year 2 = 12/16 patients (75%) Year 3 = 12/15 patients (80%) Year 4 = 13/14 patients (93%)
Secondary outcomes	
Change in median seizure frequency per month	The median number of seizures per month reduced by 72-81% throughout the extension phase.
Seizure free at follow-up points	12 months = 5 patients 24 months = 4 patients 36 months = 7 patients 48 months = 5 patients Please note it is not clearly reported how long any of the patients had sustained seizure free responses; however, graphical representations of patients' seizure response over time indicate 2 patients appeared to have achieved a close to 100% reduction in seizures consistently for over 3 years (see Figure 3, patients 13 and 16, study publication).
Changes to AED medication	One patient was weaned off daily seizure medication and maintained seizure control exclusively with everolimus. The remaining patients had at least 1 AED. Two patients reduced the number of AEDs. Three patients increased the number of AEDs.
Nisonger child behaviour rating form (NCBRF)	There was no statistically significant change in the NCBRF, although reported trends in improvements in behaviour.
Quality of Life for Children with Epilepsy (QOLCE)	The QOLCE score reportedly increased by 14%* from baseline (43.7 at baseline compared with 52.0 at 48 months) but was not statistically significant. [*52-43.7 = 8.3% not 14% (unclear which number is incorrect]
Adverse events	There were 574 adverse events over the initial phase I/II study and the extension phase up to 48 months. There were 30 grade 3 events and 5 grade 4 events. The most common adverse events were infections and gastrointestinal/oral. No patients discontinued due to an adverse event.
Adverse effects (drug related)	416 (72.5%) of all reported adverse events were thought to be treatment related. The most common treatment-related adverse effects were infection (52%) and gastrointestinal/oral (27%).
Discontinuations	4 people discontinued everolimus over the 4 years; 3 due to inefficacy (at months 10, 13 and 36), and 1 due to withdrawal of consent.

Table 19 Samueli, 2016

	Everolimus (target trough 5-15 ng/mL) at follow up (median 22 months) versus baseline
N	**15**
Patients achieving a 50% or greater reduction in seizure frequency from baseline through to follow up	Continuing patients 6 months = 13/18 patients (53%) 12 months = 10/12 patients (83%) 18 months = 8/10 patients (80%) Enrolled patients 6 months = 13/15 patients (53%) 12 months = 10/15 patients (75%) 18 months = 8/15 patients (53%)
Median number of seizure free days per 28 day period	6 months = 19.5 days (range 0-27) 12 months = 26 days (range 0-28) 18 months = 26.75 patients (range 0-28)
Patients who were seizure free	Continuing patients 6 months = 4/18 patients (27%) 12 months = 3/12 patients (25%) 18 months = 4/10 patients (40%) Enrolled patients 6 months = 4/15 patients (27%) 12 months = 3/15 patients (20%) 18 months = 4/15 patients (27%)
Changes to AED medication	The median number of AEDs was reduced from a median of 2 (range 1-3) at baseline to 1 at last observation (range 0-2). In one patient all AEDs were successfully withdrawn.
Adverse events	Grade I adverse events were seen in 14/15 patients (93%). The most commonly reported side effect was stomatitis (10/15 patients, 66%). Grade II adverse events occurred in 1 patient and no patient experienced a grade III adverse event. Four patients experienced grade IV adverse events, which required a treatment interruption (3 patients had pneumonia and one extensive impetigo).
Discontinuations	Everolimus was withdrawn in 3 patients due to pending epilepsy surgery, and in one patient due to compliance issues.

Table 20 Wiegand, 2013

	Everolimus (target trough 5-10 ng/mL) at follow up (36 weeks) versus baseline
N	**7 (6 completed follow-up)**
Change in seizure frequency per day	Of the 6 patients who completed follow up: 2 patients achieved at least a 50% reduction in seizure frequency, 2 patient achieved a 25%-49% reduction in seizure frequency, 2 patients had no change in seizure frequency The authors reported that across all patients the seizure frequency was significantly reduced from baseline at follow-up (p=0.0014)
Seizure free	One patient was reported as seizure free at follow-up. Subsequent to the end of the study, an additional patient was reported as seizure free for 8 months at long-term follow-up (34 months) and that all AED medications have been discontinued.
Seizure free days	At follow up the % seizure free days ranged from 0 to 100%.
Changes to AED medication	Subsequent to the end of the study, one patient was reported as seizure free for 8 months and that AEDs have been discontinued.
Adverse effects	All patients had adverse effects during therapy, most were grade 1 or 2. There were 5 grade 3 adverse events that led to hospitalisations.
Discontinuations	Everolimus was withdrawn in 1 patient due to adverse events. The study authors noted that this was due to facial rash and that subsequent to the study the patient re-started everolimus with a change in concomitant AEDs and has continued for 16 months without recurrence of the rash. Everolimus was withdrawn in 1 patient due to inefficacy.

Appendix 5 Grading of the evidence base

NSF-LTC Categories of research design

Primary research based evidence
P1 Primary research using quantitative approaches
P2 Primary research using qualitative approaches
P3 Primary research using mixed approaches (quantitative and qualitative)
Secondary research based evidence
S1 Meta-analysis of existing data analysis
S2 Secondary analysis of existing data
Review based evidence
R1 Systematic reviews of existing research

NSF-LTC scoring notes

1. Are the research questions/aims and design clearly stated?	Yes = 2 In part = 1 No = 0
2. Is the research design appropriate for the aims and objectives of the research?	Yes = 2 In part = 1 No = 0
3. Are the methods clearly described?	Yes = 2 In part = 1 No = 0
4. Are the data adequate to support the authors' interpretations / conclusions?	Yes = 2 In part = 1 No = 0
5. Are the results generalisable?	Yes = 2 In part = 1 No = 0

Overall grading by outcome

For each key outcome, studies were then grouped and the following NSF-LTC criteria were applied to achieve an overall grade of evidence by outcome.

Grade	Criteria
Grade A	• more than one study of high quality score (≥7/10); AND • at least one of these has direct applicability
Grade B	• one study of high quality score (≥7/10) which is of direct applicability. OR • more than one study of high quality score (≥7/10) which are of indirect applicability OR • more than one study of medium quality score (4–6/10); AND • at least one of these has direct applicability. OR • one study of medium quality score (4–6/10) which is of direct applicability; AND • one study of high quality score (≥7/10) which is of indirect applicability.
Grade C	• 1 study of medium quality score (4–6/10) which is of direct applicability OR • studies of low quality score (2–3/10) only OR • studies of indirect applicability only; AND • no more than one is of high quality score (≥7/10).

Applicability should be classified as:

- Direct - studies that focus on people with the indication and characteristics of interest
- Indirect - studies based on evidence extrapolated from populations with other conditions and characteristics