Canada's Drug and
Health Technology Agency

## CADTH Reimbursement Review

# Everolimus

**Nonsponsored Review**

**Therapeutic area:** Renal angiomyolipoma associated with tuberous sclerosis complex

Clinical and Pharmacoeconomic Report

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## Abbreviations

| | |
|---|---|
| **AE** | adverse event |
| **CI** | confidence interval |
| **CKD** | chronic kidney disease |
| **GFR** | glomerular filtration rate |
| **HR** | hazard ratio |
| **HRQoL** | health-related quality of life |
| **ITT** | intention-to-treat |
| **LAM** | lymphangioleiomyomatosis |
| **mTOR** | mammalian target of rapamycin |
| **OR** | odds ratio |
| **PgP** | p-glycoprotein |
| **RCT** | randomized controlled trial |
| **SAE** | serious adverse event |
| **SD** | standard deviation |
| **SEGA** | subependymal giant-cell astrocytoma |
| **SEN** | subependymal nodule |
| **TSC** | tuberous sclerosis complex |

# Executive Summary

An overview of the drug under review is provided in Table 1.

## Table 1: Submitted for Review

| Item | Description |
|---|---|
| **Drug product** | Everolimus 2.5 mg, 5 mg, and 10 mg oral tablets |
| **Health Canada indication** | For the treatment of adult patients (≥ 18 years of age) with renal angiomyolipoma associated with tuberous sclerosis complex who do not require immediate surgery |
| **Indication under consideration for reimbursement** | For patients (children and adults) with renal angiomyolipoma associated with tuberous sclerosis complex who do not require immediate surgery |
| **Health Canada approval status** | NOC[1] |
| **NOC date** | January 25, 2013 (with conditions); September 27, 2016 (without conditions) |
| **Requester** | Formulary Working Group |

NOC = Notice of Compliance.

Note: NOC is for the adult population only.

## Introduction

Tuberous sclerosis complex (TSC) is a rare genetic disorder with a birth incidence of 1 in 6,000 that results in growth of noncancerous tumours or hamartomas in several organs, including the brain, kidneys, skin, lungs, eyes, and heart.[1,2] Angiomyolipomas are the most common renal lesions associated with TSC, occurring in up to 80% of patients.[3,4] Angiomyolipomas are usually asymptomatic, but as tumours exceed 3 cm to 4 cm, they may become symptomatic and are at increasing risk for aneurysms that can lead to hemorrhage.[5,6] Renal angiomyolipomas may lead to chronic kidney disease (CKD) and eventually renal failure;[5,7] despite their noncancerous nature, renal angiomyolipomas are the most common cause of TSC-related death due to the risk of hemorrhage and resulting renal failure.[5,8]

The key goal of treatment in patients with renal angiomyolipomas is prevention of bleeding and preservation of renal function. The current practice guidelines recommend mammalian target of rapamycin (mTOR) inhibitors, such as sirolimus and everolimus, as the first-line therapy for TSC-associated renal angiomyoilipomas.[9] However, while everolimus can be accessed through compassionate access or exceptional access drug programs, the process is labour-intensive, involving extensive imaging, applications, and reviews. Currently in Canada, surgery and embolization remain the first line of therapy, which is primarily due to limited access to medications and a general lack of familiarity with the needs of this special patient population. According to the clinical expert consulted by CADTH, many patients have significant renal angiomyolipomas in both kidneys that progress over time, making surgery or embolization unsuitable. These procedures carry important risks (e.g., due to anesthesia) and are associated with high rates of treatment failure or need for re-treatment with surgical and interventional radiology therapies.

In 2013, CADTH completed a Reimbursement Review for everolimus in renal angiomyolipoma in adult patients with TSC, and the Canadian Drug Expert Committee (CDEC) recommended that everolimus not be

listed. The Formulary Working Group (FWG) requested that CADTH rereview everolimus for the treatment of renal angiomyolipomas in patients (adults and children) with TSC who do not require immediate surgery, and provide a reimbursement recommendation in light of new long-term data from the pivotal trial of everolimus in TSC-related renal angiomyolipomas that were not available at the time of the last CADTH Reimbursement Review of everolimus.

The clinical and pharmacoeconomic evidence for the review was provided through the CADTH Nonsponsored Reimbursement Review process. The review includes an appraisal of the clinical evidence and a comparison between the treatment costs associated with everolimus and comparators deemed to be appropriate based on feedback from clinical experts and public drug programs for patients with renal angiomyolipoma associated with TSC.

## Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from clinical expert(s) consulted by CADTH for the purpose of this review. No input was received from clinician groups.

### Patient Input

This section was prepared by CADTH staff based on the input provided by patient groups.

One patient advocacy group, TSC Canada, submitted the patient input for this review. The respondents indicated that TSC profoundly impacts both patients and caregivers with medical, behavioural, and psychosocial implications. Respondents indicated that the severity and incidence of TSC manifestations vary widely among individuals and severely impact the quality of life of patients. They noted that the currently available treatments for TSC-associated renal angiomyolipoma — surgery and embolization — are invasive and do not prevent the recurrence of angiomyolipomas, and are also painful and challenging for patients, especially those with developmental and intellectual disabilities.

Patients and caregivers value treatments that prevent the development of new renal angiomyolipomas, preserve kidney tissue, and reduce the risk of angiomyolipoma hemorrhage. Being noninvasive, accessible, and easy to administer were noted as key advantages of everolimus. Respondents indicated challenges in accessing everolimus, including limited expertise in TSC among medical professionals and lack of reimbursement and insurance coverage of everolimus.

### Clinician Input

#### *Input From Clinical Experts Consulted by CADTH*

One clinical specialist with expertise in the diagnosis and management of TSC provided the input.

The clinical expert noted that renal angiomyolipomas in TSC pose various complications, including hemorrhage, renal tissue destruction, hypertension, and an increased risk of renal failure, especially when angiomyolipomas exceed 3 cm and are considered extremely high-risk when they grow beyond 8 cm. Despite current practice guidelines recommending treatment with an mTOR inhibitor as the first-line therapy for TSC-associated renal angiomyolipomas, surgery and embolization remain the current primary treatments in

Canada due to limited access to mTOR inhibitors and medical professionals familiar with treating this rare disease. More treatment options that are easier to administer are needed to prevent hemorrhage and end-stage kidney disease, and to minimize pain and trauma associated with invasive procedures.

The clinical expert indicated that, compared to noncurative surgery or interventional radiology, TSC manifestations result from mTOR pathway dysregulation, making everolimus a comprehensive treatment addressing underlying disease pathways. Patients with bilateral large angiomyolipomas, and those with impending or active hemorrhage who require emergency intervention with embolization, may be suitable for adjunctive medical management with everolimus to treat remaining angiomyolipomas and/or prevent recurrence. While everolimus can be accessed through provincial drug plans' compassionate or exceptional access programs, the process is cumbersome and involves extensive imaging and reviews for extension of funding. The clinical expert emphasized a need for harmonization of criteria and conditions to access everolimus across public drug plans to ensure equitable access to care for patients with TSC in Canada.

### Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's Reimbursement Review processes by identifying issues that may affect their ability to implement a recommendation. The drug plans noted that the age restrictions in the pivotal EXIST-2 trial and Health Canada's approval are for patients aged 18 years and older. However, everolimus is approved for pediatric use (in patients aged > 1 year) in other TSC-related conditions, which will potentially lead to reimbursement requests for TSC-associated renal angiomyolipoma in pediatric patients. The drug plans highlighted the absence of a suitable comparator, as sirolimus does not have Health Canada's specific indication for this condition, and the off-label use of sirolimus is not funded. Timely access to crucial diagnostic imaging like renal CT or MRI, which is limited in some regions, was identified as a potential challenge for treatment monitoring. The drug plans also noted the budget impact of everolimus as first-line therapy, and the availability of generics for everolimus but not for sirolimus.

## Clinical Evidence

### Protocol-Selected Study

#### *Description of the Study*

The main evidence base for this review was the EXIST-2 trial, a randomized, double-blind, placebo-controlled, phase III trial of oral everolimus (n = 79) versus placebo (n = 39) in adult patients (aged 18 years and older) with renal angiomyolipoma associated with TSC or lymphangioleiomyomatosis (LAM). The core (double-blind) phase of the trial lasted until the last randomized patient had been treated for 6 months, after which a preplanned, open-label extension phase was launched and continued until 4 years after the last patient was randomly assigned. The primary end point was confirmed angiomyolipoma response, and the key secondary end point was time to angiomyolipoma progression. The median age was 31 years (range, 18 years to 61 years); 66% of patients were female and 34% of patients were male. The median duration of blinded study treatment was 48.1 weeks (range, 2 weeks to 115 weeks) for patients receiving everolimus and 45.0 weeks (range, 9 weeks to 115 weeks) for those receiving placebo.

As the EXIST-2 trial included only adult patients, the report was supplemented with data from the EXIST-1 trial, a phase III, randomized, double-blind, placebo-controlled trial of patients of any age with a diagnosis of TSC and subependymal giant-cell astrocytoma (SEGA), that included an analysis of the effect of everolimus on renal angiomyolipoma in a single-arm subset of pediatric patients with TSC being treated for SEGA (n = 33). The median age of these patients was 11.5 years (range, 5.4 years to 17.5 years), with 39.4% aged between 3 years and 10 years.

### *Critical Appraisal*

Patients were randomized 2:1, but the method used for randomization and to conceal allocation until group assignment was not described. Randomization appeared successful, as the baseline characteristics were generally balanced between treatment arms; however, due to the small sample size, there remained the potential for prognostic imbalances between treatment arms. The primary end point of angiomyolipoma response was reasonable in this setting and outcome assessment was by central radiology review, reducing assessment bias.

The trial inclusion and exclusion criteria were clinically relevant and the administration of everolimus in the EXIST-2 trial was consistent with common practice, with dosing adjustments done based on tolerability. With respect to outcomes, angiomyolipoma response — as defined in the EXIST-2 trial — while an objective measure and clinically relevant, is not a validated surrogate marker for some important clinical outcomes that are of interest to patients with TSC-related angiomyolipoma, such as renal hemorrhage, renal function, pain, and HRQoL.

### *Efficacy Results*

Three patients (4%) in the everolimus arm and 8 patients (21%) in the placebo arm experienced angiomyolipoma progression. Estimated progression-free probabilities were 98% (95% confidence interval [CI], 89% to 100%) in the everolimus arm and 83% (95% CI, 65% to 93%) in the placebo arm at 6 months, and 92% (95% CI, 65% to 98%) in the everolimus arm and 25% (95% CI, 1% to 64%) in the placebo arm at 12 months. No patient with an angiomyolipoma response had progressed at the date of data cut-off. The median time to angiomyolipoma progression was 11.4 months for placebo and was not reached for everolimus.

Angiomyolipoma response rate was 42% in the everolimus arm and 0% in the placebo arm (difference = 42%; 95% CI, 24% to 58%; P < 0.0001). The median time to angiomyolipoma response for everolimus was 2.9 months. All angiomyolipoma responses were ongoing for 10 weeks to 85 weeks at the time of the data cut-off. Detailed results on duration of response were not provided in the trial publication.

Median time to angiomyolipoma progression was not reached in the everolimus arm and was 11.4 months in the placebo arm (hazard ratio [HR] = 0.08; 95% CI, 0.02 to 0.37; P < 0.0001).

Pain and HRQoL were not end points in the trial.

### *Harms Results*

All patients in the everolimus arm and 97% of the patients in the placebo arm experienced at least 1 adverse event (AE). The most common AEs in the everolimus arm were stomatitis (48%), nasopharyngitis (24%), acne-like skin lesions (22%), headache (22%), cough (20%), and hypercholesterolaemia (20%). Serious adverse events (SAEs) were reported for 19% of patients in the everolimus arm and 18% of patients in the placebo arm.

AEs leading to discontinuation occurred in 3 patients (4%) in the everolimus arm and 4 patients (10%) in the placebo arm. One death (due to status epilepticus) was reported in the everolimus arm, in a 28-year-old patient with a history of intractable seizures.

## Table 2: Summary of Key Results From the EXIST-2 Trial

| Outcome | Everolimus (N = 79) | Placebo (N = 39) |
|---|---|---|
| **Efficacy** | | |
| **Angiomyolipoma progression** | | |
| Patients with progression, n (%) | 3 (4) | 8 (21) |
| HR (95% CI) | 0.08 (0.02 to 0.37)<br>P < 0.0001 | |
| Median time to progression, months | Not reached | 11.4 |
| KM estimates of progression-free probability, % (95% CI) | | |
| At 6 months | 98 (89 to 100) | 83 (65 to 93) |
| At 12 months | 92 (65 to 98) | 25 (1 to 64) |
| **Angiomyolipoma response, n (%)** | 33 (42) | 0 (0) |
| Difference, % (95% CI) | 42% (24 to 58)<br>P < 0.0001 | |
| **Harms** | | |
| Patients with ≥ 1 AE, n (%) | 79 (100) | 38 (97) |
| Patients with ≥ 1 SAE, n (%) | 15 (19) | 7 (18) |
| Discontinuation due to AEs, n (%) | 3 (4) | 4 (10) |
| Deaths, n (%) | 1 (1.3) | 0 (0) |

AE = adverse event; CI = confidence interval; HR = hazard ratio; KM = Kaplan-Meier; SAE = serious adverse event.

**Source**: Bissler et al. (2013).[10]

## Other Relevant Evidence

### *Description of the Study*

Two additional publications of the EXIST-2 trial presenting long-term follow-up were reviewed. The first publication reports early results of the open-label extension phase and the second presents a 4-year update

of the results of the end of the open-label extension phase of the trial (final analysis). Findings related to the open-label extension were not available at the time of the original CADTH Reimbursement Review.

Because the primary analysis of the EXIST-2 trial favoured everolimus over placebo, the study was unblinded, and a preplanned, open-label extension phase was launched during which all patients still receiving double-blind study treatment or undergoing posttreatment evaluation could receive open-label everolimus. The extension phase of the EXIST-2 trial continued until 4 years after the last patient was randomly assigned.

### *Critical Appraisal*

The extension phase of the study lacked a placebo arm and, as such, these long-term analyses are noncomparative.

### *Efficacy Results*

Compared with an angiomyolipoma response rate of 42% (95% CI, 31% to 53%) in patients treated with everolimus in the primary analysis (with at least 6 months of follow-up), the response rate during the open-label period was 54% (95% CI, 44% to 63%). At the final analysis, of the 112 patients with at least 1 target renal angiomyolipoma at baseline, 65 patients (58.0%) had a confirmed response at any time.

Overall, the median time to angiomyolipoma progression was not reached, because 94.6% of patients (106 of 112) did not have angiomyolipoma progression. By the final analysis, 14.3% of patients (n = 16) experienced angiomyolipoma progression at some point in the study. Reasons for progression were increased angiomyolipoma size (6 patients) and kidney enlargement (10 patients); 9 patients continued the treatment despite disease progression because of a perceived clinical benefit.

Most patients (93.8%) had a glomerular filtration rate (GFR) of at least 30 mL/min/1.73 $m^2$ or normal serum creatinine levels (86.6%) while receiving everolimus. By the final analysis, most patients had a GFR of 30 mL/min/1.73 $m^2$ (92.9%) or normal serum creatinine values (83.9%) while on treatment with everolimus. Median GFR and serum creatinine values remained stable during the everolimus treatment. Severe renal impairment (postbaseline GFR < 30 mL/min/1.73 $m^2$) was observed in 8 patients (7.1%); all patients had a GFR of < 60 mL/min/1.73 $m^2$ at baseline, including 3 patients with a GFR below 30 mL/min/1.73 $m^2$ before everolimus initiation.

### *Harms Results*

For the 112 patients in who received everolimus, the most frequently reported AEs were nasopharyngitis (42.9%), stomatitis (42.9%), headache (30.4%), acne (29.5%), hypercholesterolemia (29.5%), urinary tract infection (27.7%), and aphthous stomatitis (25.9%). Most AEs were grade 1 or 2 in severity. Overall, 42% of patients experienced grade 3 or 4 AEs; 27% were suspected to be drug related.

At the final analysis, the most common AEs (reported in > 20% of the patients) suspected to be related to everolimus were stomatitis (42%), hypercholesterolemia (30.4%), acne (25.9%), aphthous stomatitis (21.4%), and nasopharyngitis (21.4%). Serious AEs were observed in 37.5% of the patients, most frequently epilepsy (5.4%) and pneumonia (2.7%). Infections were noted in 91.1% of patients, most involving the upper

respiratory tract. Dose interruptions and adjustment were needed for 36.6% of patients who experienced infections.

One death resulting from status epilepticus was reported and was not suspected by the investigator to be related to treatment.

### Pediatric Population

#### *Description of the Study*

As the EXIST-2 trial did not include patients younger than 18 years, data from the EXIST-1 trial (a phase III, randomized, double-blind, placebo-controlled trial that included patients of any age with a diagnosis of TSC and serial SEGA growth, who were randomly assigned to receive everolimus or placebo) were considered. Similar to the EXIST-2 trial, the EXIST-1 trial included a 6-month double-blind phase, followed by an open-label phase where all patients received everolimus, lasting until 4 years after the last patient was randomized. CADTH identified a noncomparative (i.e., patients treated with everolimus only) post hoc analysis of the effect of everolimus on renal angiomyolipoma in pediatric patients with TSC being treated for SEGA in the EXIST-1 trial. Angiomyolipoma response rates were analyzed in the subset of 33 patients younger than 18 years with at least 1 target angiomyolipoma lesion at baseline, with a longest lesion diameter of at least 1.0 cm.

#### *Critical Appraisal*

The open-label design of the long-term extension phase and the lack of a comparator arm limit conclusions on the long-term use of everolimus. In addition, this analysis was based on a small subset of pediatric patients with renal angiomyolipoma from the EXIST-1 trial and was not adequately powered to assess this subgroup.

#### *Efficacy Results*

Among the 33 patients with angiomyolipoma at baseline, an angiomyolipoma response was reported in 25 patients (75.8%; 95% CI, 57.7% to 88.9%) and stable disease was reported as a best response in 4 patients (12.1%).

In general, the patients had primarily normal GFRs, with some patients having hyperfiltration. None of the patients had a renal bleeding episode while on everolimus. Most patients (n = 26; 78.8%) also had negative protein results on urinalysis at baseline.

#### *Harms Results*

All patients experienced at least 1 AE during the study, with most (90.9%) experiencing an AE that was suspected to be related to everolimus. The most commonly reported AEs of any grade occurring in more than 25% of patients included convulsion (45.5%), mouth ulceration (45.5%), stomatitis (42.4%), and cough (27.3%). Eighteen patients (54.5%) experienced 1 grade 3 or 4 AE; 30.3% of patients experienced a grade 3 or 4 AE that was suspected to be related to everolimus.

All patients required additional therapy (pharmacological or nonpharmacological) to treat an AE at some point in the study. Three patients (9.1%) discontinued everolimus because of an AE (grade 3 neutropenia, grade 3 neurosurgery for epilepsy, grade 2 aggression following grade 3 convulsion).

### Cost Information

In adult and adolescent patients, the annual cost of everolimus (5 mg or 10 mg daily, regular tablets) is $62,873 per patient in jurisdictions with more expensive wholesale pricing (Alberta, British Columbia, Nunavut, Northwest Territories, Ontario, Saskatchewan, Yukon), and $18,492 per patient in jurisdictions with less expensive wholesale pricing (Manitoba, New Brunswick, Newfoundland and Labrador, Nova Scotia, Prince Edward Island). For patients requiring a dose of 7.5 mg daily, the annual cost is expected to be $125,747 and $36,984 in jurisdictions with higher and lower pricing, respectively. The annual cost of sirolimus is $6,658 to $9,986 per adult or adolescent patient, depending on dose. As such, the use of everolimus for adult and adolescent patients with renal angiomyolipoma associated with TSC is more costly than sirolimus: in jurisdictions with more expensive wholesale pricing for everolimus, the incremental cost ranges from $52,887 to $119,089 per patient annually; in jurisdictions with less expensive wholesale pricing, the incremental cost ranges from $8,506 to $30,327 per patient annually. CADTH notes that sirolimus is not indicated for the treatment of renal angiomyolipoma associated with TSC and is not reimbursed for this indication by most public drug plans.

In younger pediatric patients, the annual cost of treatment with everolimus regular tablets (assuming 1 or 2 tablets daily) ranges from $62,873 to $125,747 per patient in jurisdictions with higher wholesale pricing and from $18,492 to $36,984 per patient in jurisdictions with lower wholesale pricing. In younger pediatric patients requiring everolimus oral suspension tablets, the annual cost of treatment ranges from $70,627 to $141,254 per patient. The annual cost of sirolimus is $1,664 to $9,986 per younger pediatric patient, depending on dose. As such, the use of everolimus regular tablets in younger pediatric patients with renal angiomyolipoma associated with TSC is more costly than sirolimus: in jurisdictions with more expensive wholesale pricing for everolimus, the incremental cost ranges from $52,887 to $124,082 per patient annually; in jurisdictions with less expensive wholesale pricing, the incremental cost ranges from $8,506 to $35,320 per patient annually. CADTH notes that the cost-comparison results pertaining to the younger pediatric population should be interpreted in light of the following caveats: sirolimus is not indicated for the treatment of renal angiomyolipoma associated with TSC or for pediatric patients younger than 13 years for any condition; sirolimus is rarely funded by public drug plans for the treatment of renal angiomyolipoma associated with TSC in pediatric patients; and the dose range of sirolimus for the pediatric population used in this review is based on initial pediatric doses reported in the literature, and assumes later dosing will not exceed the usual dose of sirolimus used in adults with renal angiomyolipoma.

Costs are based on publicly available wholesale prices and may not reflect actual prices paid by Canadian public drug plans.

## Conclusions

Evidence from 1 trial (the EXIST-2 trial, N = 118) and its long-term, single-arm, open-label extension suggests a benefit of everolimus for achieving renal angiomyolipoma response and delaying angiomyolipoma

progression in patients with TSC not requiring immediate surgery. The long-term analysis of the core phase and open-label extension phase of the trial show that angiomyolipoma response may be sustained over time with no additional or late-emerging toxicities. There was no comparative evidence available for the pediatric population, although the response rate appeared to mirror that of adults in a single-arm, post hoc analysis of a small subset of pediatric patients with renal angiomyolipoma who were being treated for TSC-related SEGA. There is an unmet clinical need for systemic treatments for angiomyolipoma to address the multifocal nature of renal involvement and the multisystem nature of the disease itself. Current treatment strategies — embolization and surgical therapies — are often used in emergency situations, carry important risks, and do not prevent recurrence of renal angiomyolipomas or organ damage. Everolimus appears to meet a key treatment goal in patients with renal angiomyolipomas, which is the prevention of renal bleeding and need for renal intervention. However, the limitations of the evidence considered in the previous CADTH Reimbursement Review — including reliance on surrogate end points and the absence of important outcomes such as pain and HRQoL — are not fully addressed by the new long-term evidence, which is based on noncomparative data.

No literature was identified comparing everolimus with sirolimus; therefore, the comparative clinical efficacy of these treatments is unknown. To effectively consider drug acquisition costs, health care resource implications, and comparative clinical benefits, a cost-effectiveness analysis of everolimus compared with sirolimus would be required. As a cost-effectiveness analysis was not available, the cost-effectiveness of everolimus in comparison with sirolimus for the treatment of renal angiomyolipoma associated with TSC could not be determined.

Results of the cost comparison of drug acquisition costs demonstrate that everolimus is more costly than sirolimus for the treatment of renal angiomyolipoma associated with TSC. The incremental cost is dependent on the wholesale price of everolimus, and the population treated (adults and adolescents, or younger pediatric patients). For adult and adolescent patients with renal angiomyolipoma associated with TSC: in jurisdictions with more expensive wholesale pricing, the incremental cost of everolimus ranges from $52,887 to $119,089 per patient annually compared with sirolimus; in jurisdictions with less expensive wholesale pricing, the incremental cost of everolimus ranges from $8,506 to $30,327 per patient annually compared with sirolimus. For younger pediatric patients: in jurisdictions with higher wholesale pricing, the incremental cost ranges from $52,887 to $124,082 per patient annually; in jurisdictions with lower wholesale pricing, the incremental cost ranges from $8,506 to $35,320 per patient annually compared to sirolimus. A price reduction of 84% to 89% would be required for the drug acquisition cost of everolimus to be equal to sirolimus in jurisdictions with higher everolimus pricing, while a price reduction of 46% to 64% would be required in jurisdictions with lower everolimus pricing.

# Introduction

## Disease Background

TSC is a rare, autosomal-dominant genetic disorder caused by decreased or absent expression of the *TSC1* (hamartin) or *TSC2* (tuberin) genes, with a birth incidence of 1 in 6,000.[11] TSC affects approximately 3,500 individuals in Canada.[11] The disease is characterized by pleomorphic features involving many organ systems, including multiple benign hamartomas of the brain, eyes, heart, lung, liver, kidney, and skin.[1,5,12] The disease is highly variable in its expression, age of onset, severity of disease, and different signs and symptoms that result from a specific genotype.[1] TSC presents most often with neurologic manifestations, in up to 90% of patients.[5,8] Neurologic manifestations of TSC include subependymal nodules (SENs), malformations of the cerebral cortex (tubers), SEGA, epilepsy, and TSC-associated neuropsychiatric disorders (e.g., autism spectrum disorder, cognitive disability).[5,8] Renal manifestations are the second most common, with angiomyolipomas occurring in 80% of patients.[3,4] Pulmonary manifestations are the third most common cause of TSC-associated morbidity and include lymphangioleiomyomatosis (LAM), a rare lung disease that occurs in 35% to 40% of patients with TSC.[5] The diagnosis of TSC can be made clinically or through genetic testing, but genetic testing is recommended, where available, to support a clinical diagnosis. Although the majority of tumours resulting from TSC are noncancerous, they may lead to severe complications or death.

Angiomyolipomas usually manifest as multifocal, bilateral, asymptomatic disease. Patients with TSC-related renal angiomyolipomas are at risk from hemorrhage of their angiomyolipomas.[5] Larger angiomyolipomas often develop microaneurysms and macroaneurysms that can rupture and hemorrhage.[5,13] The risk of hemorrhage is proportional to the size of the aneurysm, and aneurysms larger than 5 mm carry the greatest risk of rupture.[5,6] Renal angiomyolipomas also encroach on normal renal tissue leading to CKD and eventually renal failure.[5,7] Patients with angiomyolipomas frequently develop new lesions and recurrence of treated lesions.[10,14] Despite their noncancerous nature, renal angiomyolipomas are the most common cause of TSC-related death due to the risk of hemorrhage and resulting renal failure.[5,8] Consequently, renal angiomyolipoma management is an important area of focus for clinical management of patients with TSC.

## Standards of Therapy

The clinical expert consulted by CADTH indicated that currently in Canada, surgery and embolization remain the first line of therapy. The expert noted that current practice guidelines recommend mTOR inhibitors, such as sirolimus and everolimus, as the first-line therapy for TSC-associated renal angiomyoilipomas.[9] However, while everolimus can be accessed through compassionate access or exceptional access drug programs, the process is labour-intensive, involving extensive imaging, applications, and reviews. Consequently, in Canada, the primary approach to treatment is still surgical intervention and embolization, which is primarily due to limited access to medications and a general lack of familiarity with the needs of this special patient population. Many patients have significant renal angiomyolipomas in both kidneys, which progress over time, making surgery or embolization unsuitable. As the ongoing treatment is closely monitored, funding extension requires evidence of efficacy through repeated imaging. In the case of patients with autism who are nonverbal, this necessitates general anesthesia and MRI scans, making it burdensome for patients and

caregivers. Surgery or embolization also require travel to a specialized hospital centre and time off work for caregivers, with associated risks related to anesthesia. Furthermore, there is a high rate of treatment failure or need for re-treatment with surgical and interventional radiology therapies.

### Drug

Everolimus is a rapamycin derivative that inhibits the mTOR pathway by acting on the mTOR complex 1 (mTORC1). Everolimus currently has a Health Canada NOC for the treatment of adult patients (aged ≥ 18 years) with renal angiomyolipoma associated with TSC who do not require immediate surgery. Everolimus is also approved for the treatment of patients with SEGA who are not suitable for surgery.[15] Everolimus is not indicated for use in pediatric patients with renal angiomyolipoma associated with TSC in the absence of everolimus treatment for SEGA.[16]

In 2013, CADTH completed a Reimbursement Review for everolimus in renal angiomyolipoma in adult patients with TSC, and CDEC recommended that everolimus not be listed. In 2023, CADTH received a request from patients with TSC and their caregivers to conduct a new review of everolimus for the treatment of TSC-related renal angiomyolipomas, in light of new long-term data from the pivotal trial of everolimus in TSC-related renal angiomyolipomas that were not available at the time of the last CADTH Reimbursement Review of everolimus in 2013.[17] This request was supported by FWG. CADTH evaluated the need to re-review everolimus for TSC given the availability of new evidence, recently updated international TSC consensus guidelines, and unmet needs expressed by patients with TSC. FWG requested that CADTH also consider evidence of the efficacy and safety of everolimus in the pediatric population with renal angiomyolipoma with other earlier emerging TSC manifestations (e.g., SEGA), given past requests for this population. The patients and caregivers also requested that pediatric patients be included in this review. The current CADTH nonsponsored reimbursement request for everolimus is for all patients (children and adults) with renal angiomyolipoma associated with TSC who do not require immediate surgery. Everolimus is available in 2.5 mg, 5 mg, and 10 mg oral tablets. The recommended dose for adults with renal angiomyolipoma associated with TSC is 10 mg once daily. The product monograph states that the optimal duration of treatment with everolimus is not known.

## Stakeholder Perspectives

### Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups. The full patient group input is posted online.

One patient advocacy group, TSC Canada, submitted the patient input for this review. TSC Canada is a national, voluntary, nonprofit, charitable organization dedicated to raising public awareness of TSC, encouraging mutual support between individuals with TSC and their families, and promoting research and education. The submission was based on perspectives gathered through a variety of sources, including

patient and caregiver lived experiences, survey results, and families who contacted TSC Canada seeking help in accessing everolimus. The information was gathered over the previous 10 years.

The respondents highlighted that the currently available treatments for TSC-associated renal angiomyolipoma — surgery and embolization — are invasive, painful, and challenging procedures, and are burdensome to patients (requiring travel for those who do not live near major hospitals in Canada). Patients and caregivers value treatments that are noninvasive, easily accessible, and simple to administer, and those that preserve healthy kidney tissue and reduce the risk of angiomyolipoma hemorrhage. The advantages of everolimus include its noninvasiveness, ease of administration, preservation of healthy kidney tissue, and prevention of complications associated with angiomyolipoma development. Furthermore, the treatment eliminates the need for hospital stays, which can be particularly challenging for patients with developmental and intellectual disabilities and those who live far from hospital centres.

Challenges in accessing everolimus included limited access to specialists with expertise in treating TSC and lack of public funding and insurance coverage. The respondents noted that some patients and caregivers have accessed everolimus through compassionate access programs, provincial publicly funded plans, and private insurers, but various obstacles remain. Many provincial drug plans do not fund everolimus for TSC-associated renal angiomyolipoma. Further, due to the previous negative reimbursement recommendation for everolimus, medical professionals (particularly those with limited expertise in TSC treatment) do not use the drug, and private insurance plans do not fund everolimus for TSC-associated renal angiomyolipoma.

## Clinician Input

### Input From Clinical Experts Consulted by CADTH

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol; assisting in the critical appraisal of clinical evidence; interpreting the clinical relevance of the results; and providing guidance on the potential place in therapy). The following input was provided by 1 clinical specialist with expertise in the diagnosis and management of TSC.

#### *Unmet Needs*

The clinical expert highlighted that renal angiomyolipomas can lead to various complications due to mass effect, including hemorrhage or rupture of blood vessels feeding the lesion, destruction of adjacent renal tissue, risk of hypertension, and renal failure. The risk of hemorrhage begins to rise for angiomyolipomas larger than 3 cm; angiomyolipomas larger than 8 cm are considered very high risk. Surgery and embolization both carry a risk of hemorrhage, off-target embolization (i.e., damage to healthy tissues), and loss of remaining kidney function or renal failure.

The goals of treatment include prevention of hemorrhage and the resulting morbidity and mortality, as well as prevention of end-stage kidney disease, need for dialysis, and/or transplant. Further, minimizing pain, disability, and trauma associated with invasive procedures such as surgery and embolization is particularly important in adults with developmental and intellectual disabilities. The clinical expert also emphasized that

there is a high rate of treatment failure or need for re-treatment with surgical and interventional radiology therapies. There is an important unmet need for medications that can be easily administered and can ease the burden of treatment of patients with TSC-related angiomyolipomas. TSC can affect virtually any organ in the body and all of the clinical manifestations are related to dysregulation of the mTOR pathway. Everolimus treats the underlying metabolic and cellular pathways to treat the entire patient, while the alternatives of surgery and interventional radiology treat the symptoms rather than the disease.

### *Place in Therapy*

The clinical expert emphasized that the TSC manifestations are linked to mTOR pathway dysregulation. Therefore, everolimus offers a comprehensive treatment addressing the underlying metabolic and cellular pathways, rather than merely alleviating symptoms, unlike surgery or interventional radiology. According to the clinical expert, while everolimus may be used to treat renal angiomyolipomas, patients may also experience stability in SENS or SEGA progression and improvement in seizure severity or frequency. Based on experience in clinical practice, the clinical expert noted that patients on everolimus experience reduced angiomyolipoma size, decreased hemorrhage risk, and often avoid surgical or embolization procedures. Although side effects may occur, these are manageable in most cases. While a few patients may not tolerate everolimus, it may still be ideal to opt for other medical options rather than rely on surgery or embolization.

### *Patient Population*

The clinical expert noted that patients with bilateral large angiomyolipomas are suitable for medical management with everolimus. While those with impending or active hemorrhage require emergency intervention with embolization, the clinical expert indicated that everolimus should still be used in this patient population, as they will be at high risk of requiring recurrent embolization or surgery and have other disease features that can be treated or modified by addressing mTOR dysregulation.

### *Assessing Response to Treatment*

The clinical expert noted that even a small reduction in the diameter of an angiomyolipoma results in significant reduction in its volume. Everolimus “stabilizes” the fragile vasculature inherent in the aneurysmal angiomyolipoma. Therefore, even if the angiomyolipomas do not continue to shrink, the risk of hemorrhage continues to fall.

The following side effects are monitored during therapy with everolimus: mouth sores, urinary protein excretion, respiratory complications, dyslipidemia and abnormalities of blood counts, liver enzymes, and menstrual and ovulatory abnormalities.

### *Discontinuing Treatment*

Reasons for discontinuation include intolerable side effects and desire to pursue pregnancy, as well as loss of insurance coverage. However, the clinical expert noted that discontinuation with everolimus is infrequent.

### *Prescribing Conditions*

Specialty clinics associated with a hospital would be most appropriate for treating TSC-associated renal angiomyolipoma. Experienced nephrologists, urologists, and oncologists would be appropriate clinicians to prescribe and monitor response to therapy and side effects.

### Clinician Group Input
No input from clinician groups was received.

### Drug Program Input
The drug programs provide input on each drug being reviewed through CADTH's Nonsponsored Reimbursement Review processes by identifying issues that may impact their ability to implement a recommendation.

The drug plans highlighted that the age restriction in the EXIST-2 trial (pivotal trial) and Health Canada's indication is for patients aged 18 years and older. However, everolimus is approved for pediatric use in other conditions associated with TSC, raising the possibility of reimbursement requests for pediatric patients with TSC-associated renal angiomyolipoma. The drug plans also noted that mTOR inhibitors including everolimus are used in other TSC-related conditions, such as SEGA, seizures, skin lesions, and ophthalmic manifestations associated with TSC and lymphangioleiomyomatosis. The drug plans also noted the lack of a suitable comparator for the review, as sirolimus — while a potential treatment option — lacks a Health Canada–specific indication for treating renal angiomyolipoma associated with TSC, and it is not reimbursed consistently across drug plans for the indication. Drug plans raised concerns around timely access to essential diagnostic imaging, such as renal CT or MRI, which may be limited in some regions, affecting treatment monitoring. Lastly, the budget impact and sustainability of covering everolimus as a first-line therapy were noted, as well as the availability of generics for everolimus but not for sirolimus.

The implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in the Drug Plan Input.

### Industry Input
No input was provided to CADTH from the industry.

## Clinical Evidence
The clinical evidence included in the review of everolimus is presented in 3 sections. The first section, the Systematic Review, includes studies that were selected according to an a priori protocol. The second section would have included indirect evidence selected from the literature that met the selection criteria specified in the review; however, no indirect evidence was considered relevant for inclusion in the review. The third section includes long-term extension studies and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review.

### Systematic Review (Pivotal and Protocol-Selected Studies)
#### Objectives
The objective was to perform a systematic review of the efficacy and safety of everolimus for the treatment of patients with renal angiomyolipoma associated with TSC who do not require immediate surgery.

## Methods

Studies selected for inclusion in the systematic review included those meeting the selection criteria presented in Table 3. Outcomes included in the CADTH review protocol reflect outcomes considered to be important to patients, clinicians, and drug plans.

### Table 3: Inclusion Criteria for the Systematic Review

| Criteria | Description |
|---|---|
| **Patient population** | Patients with renal angiomyolipoma associated with TSC who do not require immediate surgery |
| **Intervention** | Oral everolimus, 10 mg once daily (supplied as 2.5 mg, 5 mg, and 10 mg oral tablets) |
| **Comparators** | • Placebo<br>• Oral sirolimus (rapamycin) |
| **Outcomes** | **Efficacy outcomes:**<br>• angiomyolipoma progression<br>• angiomyolipoma response (confirmed)<br>• duration of response<br>• pain<br>• avoidance of renal bleeding<br>• avoidance of surgery or embolization<br>• renal function<br>• health-related quality of life<br>**Harms outcomes:**<br>• AEs, SAEs, WDAEs, mortality<br>**Harms of special interest:**<br>• angiomyolipoma hemorrhage<br>• infection<br>• noninfectious pneumonitis<br>• renal failure |
| **Study design** | Phase III and IV RCTs |

AE = adverse effect; AML = angiomyolipoma; RCT = randomized controlled trial; SAE = severe adverse event; TSC = tuberous sclerosis complex; WDAE; withdrawal due to adverse event.

An information specialist performed the literature search for clinical studies, using a peer-reviewed search strategy according to CADTH's Peer Review of Electronic Search Strategies (PRESS) checklist.[18]

Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. All Ovid searches were run simultaneously as a multifile search. Duplicates were removed using Ovid deduplication for multifile searches, followed by manual deduplication in EndNote. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the PICOS framework and research questions. The main search concepts were everolimus, renal angiomyolipoma, and tuberous sclerosis complex. The following clinical trials registries were searched: the US National Institutes

of Health's ClinicalTrials.gov, WHO's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, the European Union Clinical Trials Register, and the European Union Clinical Trials Information System (CTIS).

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. Refer to Appendix 1 for the detailed search strategies. The initial search was completed on August 01, 2023. Regular alerts updated the search until the meeting of the Formulary Management Expert Committee (FMEC) on February 01, 2024.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from CADTH's Grey Matters: A Practical Tool For Searching Health-Related Grey Literature. Included in this search were the websites of regulatory agencies (FDA and European Medicines Agency). Google was used to search for additional internet-based materials. Refer to Appendix 1 for more information on the grey literature search strategy.

These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

A focused literature search for indirect treatment comparisons (ITCs) dealing with everolimus, renal angiomyolipoma, and tuberous sclerosis complex was run in MEDLINE on July 31, 2023. No limits were applied to the search; conference abstracts were excluded.

Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least 1 reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

## Protocol-Selected Study

One publication of 1 study (the EXIST-2 trial) met the selection criteria and was included in the systematic review (Figure 6 in Appendix 2). Of note, the previous CADTH Reimbursement Review of everolimus for the indication under review was based on this evidence (i.e., the core phase of the EXIST-2 trial). This evidence is revisited in the current review, as the full sponsor-initiated CADTH Reimbursement Review published in 2013 is not publicly available.

Two publications reporting long-term and extension phase results of the EXIST-2 trial were identified from the literature search. Because these reports did not meet the systematic review protocol selection criteria (e.g., they did not have a comparator arm), they are included in the third section of this review (Other Relevant Evidence). Of note, this evidence was not available at the time of the previous CADTH Reimbursement Review and forms new evidence included in the current review.

### Characteristics of Included Study

The protocol-selected study, the EXIST-2 trial, is summarized in Table 4.

### *Study Design*

The EXIST-2 trial was a multicentre, double-blind, placebo-controlled, phase III trial that assessed the efficacy and safety of everolimus in adult patients with angiomyolipoma associated with TSC or sporadic lymphangioleiomyomatosis. The trial was conducted in 24 centres across 11 countries. Patients (N = 118) were randomly assigned in a 2:1 fashion to receive either oral everolimus 10 mg daily or placebo, stratified by enzyme-inducing antiepileptic drug use at randomization and by the presence of sporadic lymphangioleiomyomatosis. Patient enrolment was from May 8, 2009, to December 30, 2010. The cut-off date for the core (blinded) phase of the trial, which lasted until the last randomized patient had been treated for 6 months, was June 30, 2011. An independent data-monitoring committee conducted safety reviews every 6 months. The trial was sponsored by Novartis Pharmaceuticals.

### *Inclusion and Exclusion Criteria*

Eligible patients were those aged 18 years or older who had at least 1 angiomyolipoma 3 cm or larger in its longest diameter, and a definite diagnosis of TSC per consensus criteria[19,20] or sporadic lymphangioleiomyomatosis (biopsy-proven or chest CT scan).[19,20] Patients whose angiomyolipoma required surgery at randomization, or who had angiomyolipoma-related bleeding or embolization during the 6 months before randomization, were excluded.

### *Interventions*

Patients in the treatment arm received everolimus 10 mg per day administered orally, with dose modifications allowed based on safety findings. Patients received blinded study treatment until angiomyolipoma progression, occurrence of unacceptable toxicity, or patient withdrawal for any other reason. Patients with angiomyolipoma progression were unblinded and patients in the placebo arm were offered open-label everolimus at progression.

### *Concomitant Medications*

Concomitant use of strong inhibitors or inducers of cytochrome P450 3A4 or p-glycoprotein (PgP) was to be avoided during the study. Use of antiproliferative agents other than the study drug was not allowed.

### *Subsequent Therapy*

At progression, patients in the placebo arm were offered open-label everolimus.

### *Outcomes*

The efficacy end points identified in the CADTH review protocol that were assessed in the EXIST-2 trial are summarized below. Pain and HRQoL were not assessed.

The primary efficacy end point of the EXIST-2 trial was angiomyolipoma response rate, defined as the proportion of patients with a reduction in angiomyolipoma volume (sum of volumes of all target angiomyolipomas identified at baseline) of 50% or more relative to baseline and absence of angiomyolipoma progression. Initial response required confirmation by another scan performed no sooner than 8 weeks from the initial scan. The key secondary end point related to angiomyolipomas was time to angiomyolipoma progression. Time to angiomyolipoma progression was defined as the time from the date of randomization

to 1 or more of: increase from the nadir of 25% or more in angiomyolipoma volume (sum of volumes of all target angiomyolipomas identified at baseline) to greater than baseline; appearance of a new angiomyolipoma at least 1 cm in longest diameter; increase from nadir of 20% or more volume of either kidney to greater than baseline; or angiomyolipoma-related bleeding grade 2 or more as defined by the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.[21]Another secondary end point was the proportion of patients with renal impairment from day 1 to 28 days after the end of treatment. Renal function was assessed using the lowest postbaseline GFR.[17]

Other angiomyolipoma specific end points included time to angiomyolipoma response (measured only in patients with a response), and duration of angiomyolipoma response, defined as the date of randomization until angiomyolipoma progression or further antiangiomyolipoma mediation or surgery. Exploratory end points included time to angiomyolipoma progression and incidence of angiomyolipoma-related surgery. Censoring rules for the time-to-event outcomes were not provided. Patients who could not be assessed (due to drop-out or other reasons) were considered nonresponders. Handling of missing data for other end points was not described.

Response and progression outcomes were informed by kidney CT or MRI performed at baseline, 12 weeks, 24 weeks, 48 weeks, and annually after the start of study treatment, and assessed with a blinded central radiology review.

AEs were assessed continuously throughout the study and graded according to CTCAE version 3.0 via patient-reported or caregiver-reported responses as well as investigator assessment.[21] Any patient who discontinued everolimus had a follow-up visit 28 days after the last dose to assess safety.

### Table 4: Details of the EXIST-2 Trial

| Detail | EXIST-2 trial |
|---|---|
| **Designs and populations** | |
| **Study design** | Phase III, double-blind, randomized, placebo-controlled trial |
| **Locations** | 24 centres across 11 countries |
| **Patient enrolment dates** | May 8, 2009, to December 30, 2010 |
| **Randomized (N)** | 118 patients (everolimus arm, n = 79; placebo, n = 39) |
| **Inclusion criteria** | • Aged 18 years or older<br>• At least 1 angiomyolipoma 3 cm or larger in its longest diameter<br>• A definite diagnosis of tuberous sclerosis per consensus criteria[19,20] or sporadic lymphangioleiomyomatosis (biopsy-proven or chest CT scan) |
| **Exclusion criteria** | • Angiomyolipoma requiring surgery at randomization<br>• Angiomyolipoma-related bleeding or embolization during the 6 months before randomization |
| **Drugs** | |
| **Intervention** | Everolimus 10 mg per day (two 5 mg tablets), administered orally |
| **Comparator(s)** | Placebo |

| Detail | EXIST-2 trial |
|---|---|
| **Duration** | |
| **Follow-up** | Ongoing at time of data cut off. Cut-off date: June 30, 2011 (efficacy, 6 months after last patient randomized); October 14, 2011 (safety) |
| **Outcomes** | |
| **Primary end point** | • Confirmed angiomyolipoma response (defined as a reduction in angiomyolipoma volume of at least 50% relative to baseline and absence of angiomyolipoma progression) |
| **Secondary end points** | • Time to angiomyolipoma progression<br>• Skin lesion response rate |
| **Additional end points** | • Time to angiomyolipoma response<br>• Duration of angiomyolipoma response<br>• Duration of skin lesion response<br>• Pharmacokinetics of everolimus<br>• Change from baseline in pulmonary function in lymphangioleiomyomatosis and sporadic lymphangioleiomyomatosis patients<br>• Safety |
| **Notes** | |
| **Publications included** | Bissler et al., 2013[10] |
| **Sources of support** | Novartis Pharmaceuticals |

Source: Bissler et al. (2013).[10]

### *Statistical Analysis*

The planned sample size of 99 patients provided 93% power to detect a 20% difference in angiomyolipoma response rates between treatments. Efficacy analyses included all randomized patients (intention-to-treat population), and safety analyses included all patients who received at least 1 dose of study drug and had at least 1 postbaseline assessment.

Treatment groups were compared using an exact stratified Cochran-Mantel-Haenszel test for angiomyolipoma response rates, and a 1-sided stratified log-rank test for time to angiomyolipoma progression (all at the 1-sided 2.5% significance level). Stratification was modified for statistical testing because only five patients had sporadic lymphangioleiomyomatosis; these patients were grouped with patients with TSC not using an enzyme-inducing antiepileptic drug (use versus non-use of an enzyme-inducing antiepileptic drug). Multiplicity was controlled for the primary and key secondary end points using a predefined fixed sequence testing procedure with a hierarchy of angiomyolipoma response rate, followed by time to angiomyolipoma progression, and skin lesion response rate (not relevant to this report).

The core phase of the trial, which lasted until the last randomized patient had been treated for 6 months, was analyzed and only data until the database lock on June 30, 2011 (before the start of the open-label phase), were considered in the main analysis.

## Critical Appraisal

### Internal Validity

#### *Study Design, Intervention, and Comparators*

The EXIST-2 trial was powered to detect a 20% difference in angiomyolipoma response rates between the intervention and placebo arms. As TSC is a rare condition, the EXIST-2 study was a relatively small trial that may have been underpowered to detect differences for some important efficacy outcomes of interest to this review. The trial was quadruple blind with patients, caregivers, study personnel, and outcome assessors unaware of treatment arm. The primary outcome was based on central blinded radiology review. Patients were unblinded on progression and those in the placebo arm were offered open-label everolimus. This may bias any assessment of outcomes after progression including reporting of AEs. However, the primary end point of angiomyolipoma response is not affected by the unblinding of a few patients at progression or subsequent everolimus treatment in the placebo group.

#### *Selection, Allocation, and Disposition of Patients*

Patients were randomized 2:1 to achieve prognostic balance but the method used for randomization and to conceal allocation until group assignment was not described. Randomization appeared successful, as the baseline characteristics were generally balanced between treatment arms, although the possibility of prognostic imbalance remains due to the small sample size. Details of patient disposition were reported and reasons for discontinuation from the study were provided, and there is no evidence of selective attrition. There was 1 patient in the everolimus arm with a protocol deviation, but the nature of the protocol deviation was not described and unlikely to impact results, as this represented a small proportion of all included patients.

#### *Outcome Measures*

The primary end point of angiomyolipoma response was reasonable in this setting and outcome assessment was by central radiology review. Duration of angiomyolipoma response was listed as an outcome but results were not described in detail in the trial publication; there is a potential for selective nonreporting of this result. AEs were reported in both treatment arms by grade. All notable harms of interest except angiomyolipoma hemorrhage were reported. However, angiomyolipoma-related bleeding (grade 2 and higher) was part of the outcome definition of angiomyolipoma progression and would be captured in this efficacy end point.

#### *Statistical Analysis*

The statistical analyses of the primary end point were appropriate. Multiplicity was controlled using a prespecified fixed sequence testing procedure with a hierarchy of the primary and secondary outcomes. However, no details on censoring nor methods for missing data handling and the number of patients with missing assessments were reported. The rate of treatment discontinuation was imbalanced across groups (9% in the everolimus arm versus 33% in the placebo arm), and it is unclear whether assessments continued for these patients.

### External Validity

#### *Patient Selection*

The trial inclusion and exclusion criteria were clinically relevant. Patients with at least 1 angiomyolipoma 3 cm or larger in diameter were included. Angiomyolipomas smaller than 4 cm are commonly observed with no medical interventions if they remain asymptomatic. Angiomyolipomas larger than 4 cm may be more actively monitored and assessed by imaging for potential growth, but these also are unlikely to receive an intervention if they are not at risk of bleeding.

#### *Treatment Regimen and Length of Follow-Up*

The administration of everolimus in the EXIST-2 trial was consistent with common practice. The clinical expert noted that, as in the trial, dosing adjustments are often made based on tolerability. The core (double-blind) phase of the trial lasted until the last randomized patient had been treated for 6 months and the main analyses were based on the core phase of the trial. This duration of follow-up is not sufficiently long, particularly considering that everolimus treatment will continue for many years. The 4-year update to the analyses provides long-term data regarding the efficacy and harms of everolimus and, although important, these are based on the open-label extension phase.

#### *Outcome Measures*

Angiomyolipoma response, as defined in the EXIST-2 trial, while an objective measure and clinically relevant, is not a validated surrogate marker for some important clinical outcomes that are of interest to patients with TSC-related angiomyolipoma, such as avoidance of surgery, pain, and HRQoL. These important clinical outcomes were not assessed in the trial.

## Results of the Included Study

### Baseline Characteristics

Baseline demographic and disease characteristics were generally balanced between treatment arms (Table 5). The median age was 32 years (range, 18 to 61 years) in the everolimus arm and 29 years (range, 18 to 58 years) in the placebo arm. The proportion of patients with SEGA was 54% in the everolimus arm and 36% in the placebo arm. Overall, 78% of patients had angiomyolipomas in both kidneys, and 29% of patients had an angiomyolipoma at least 8 cm in longest diameter. Almost 40% of patients had a previous intervention, including 19% with prior nephrectomy.

### Patient Disposition

Between May 8, 2009, and December 30, 2010, 118 patients were randomly assigned to receive everolimus (n = 79) or placebo (n = 39). At the data cut-off (June 30, 2011), 83% of patients (98 of 118) were receiving double-blind study treatment, and 17% (20 of 118) had discontinued from the study, mainly because of disease progression. Of the 26 patients in the placebo arm with ongoing participation in the double-blind period, 13 patients (50%) discontinued interventions, of which 9 discontinuations were due to disease progression (4 due to AEs). Of the 72 patients in the everolimus arm with ongoing participation in double-

blind period, 7 patients (10%) discontinued intervention (2 due to AEs, 1 due to abnormal laboratory value, 1 withdrew consent, 1 due to administrative problem, 1 death, and 1 due to a protocol deviation).

### Treatment Exposure

The median dose intensity was 10 mg per day for both treatment arms; mean dose intensity was 8.6 mg per day in the everolimus arm and 9.6 mg per day in the placebo arm. The median exposure duration was 38 weeks for everolimus and 34 weeks for placebo.

### Concomitant Therapy

Coadministration of strong and moderate cytochrome 3A inhibitors, PgP inhibitors, *CYP3A* inducers, and PgP inducers was reported for 47 patients (59%) in the everolimus arm and 23 patients (59%) in the placebo arm.

## Table 5: Baseline Patient Characteristics – EXIST-2 Trial

| Characteristic | Everolimus (N = 79) | Placebo (N = 39) |
|---|---|---|
| Age in years, median (range) | 32 (18 to 61) | 29 (18 to 58) |
| Age, n (%) | | |
| < 30 years | 35 (44) | 20 (51) |
| ≥ 30 years | 44 (56) | 19 (49) |
| Sex, n (%) | | |
| Male | 27 (34) | 13 (33) |
| Female | 52 (66) | 26 (67) |
| Race, n (%) | | |
| White | 71 (90) | 34 (87) |
| Asian | 7 (9) | 4 (10) |
| Other | 1 (1) | 1 (3) |
| Diagnosis of tuberous sclerosis complex, n (%)[a] | 77 (97) | 36 (92) |
| Diagnosis of sporadic lymphangioleiomyomatosis, n (%) | 2 (3) | 3 (8) |
| Diagnosis of lymphangioleiomyomatosis, n (%) | 22 (28) | 7 (18) |
| ≥ 1 skin lesion, n (%)[b] | 77 (97) | 37 (95) |
| Presence of subependymal giant-cell astrocytoma, n (%)[c] | 43 (54) | 14 (36) |
| Previous angiomyolipoma therapy, n (%) | | |
| Surgery or invasive procedure | 31 (39) | 15 (38) |
| Renal embolization | 19 (24) | 9 (23) |
| Nephrectomy | 14 (18) | 8 (21) |
| Medication | 0 | 0 |
| Longest diameter of largest angiomyolipoma lesion, n (%) | | |

| Characteristic | Everolimus (N = 79) | Placebo (N = 39) |
|---|---|---|
| ≥ 8 cm | 22 (28) | 12 (31) |
| ≥ 4 cm and < 8 cm | 45 (57) | 19 (49) |
| ≥ 3 cm and < 4 cm | 6 (8) | 4 (10) |
| < 3 cm | 5 (6) | 2 (5) |
| Unknown[d] | 0 | 1 (3) |
| Not applicable[e] | 1 (1) | 1 (3) |
| Bilateral angiomyolipoma, n (%) | 65 (83) | 27 (71) |
| Number of target angiomyolipoma lesions, n (%) | | |
| 0[f] | 1 (1) | 1 (3) |
| 1 to 5 | 32 (41) | 15 (38) |
| 6 to 10 | 46 (58) | 23 (59) |
| Sum of volumes of target angiomyolipoma lesions | | |
| Number of patients with one or more target angiomyolipoma, n | 78 | 37 |
| Median (range), $cm^3$ | 85 (9 to 1,612) | 120 (3 to 4,520) |

[a]All patients diagnosed with tuberous sclerosis complex had 2 or more major features.

[b]Based on patients having skin lesion photos at baseline or assessment postbaseline, not based on the modified Gomez criteria.

[c]Based on the major feature of subependymal giant-cell astrocytoma in the modified Gomez criteria being ticked yes.

[d]Longest diameter of the largest angiomyolipoma lesion is unknown when at least 1 target lesion larger than 1 cm is confirmed but no precise diameter could be measured.

[e]Lesions marked as not applicable are those where there is not at least 1 target lesion.

[f]Lesions identified as not meeting target status were determined by central radiology, whereas eligibility criteria were based on the local radiologist.

Source: Bissler et al. (2013).[10] Reprinted from The Lancet, Vol. 381, number 9869, Bissler JJ, Kingswood JC, Radzikowska E, et al., Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomized, double-blind, placebo-controlled trial, pages 817 to 824, Copyright 2013, with permission from Elsevier.

## Efficacy Results

Only those efficacy outcomes identified as relevant in the review protocol are reported below.

### *Angiomyolipoma Response*

Angiomyolipoma response rate was 42% (95% CI, 31% to 53%) (33 of 79 patients) in the everolimus arm, compared with 0% (95% CI, 0% to 9%) (0 of 39 patients) in the placebo arm (difference = 42%; 95% CI, 24% to 58%; P < 0.0001). The median time to angiomyolipoma response for everolimus was 2.9 months.

At week 24, 39 of 71 patients (55%) in the everolimus arm had at least a 50% reduction from baseline in sum of volumes of target angiomyolipoma lesions compared with 0% of patients in the placebo arm, and 57 of 71 patients (80%) of patients in the everolimus arm had at least a 30% reduction compared with 3% (1 of 33) of patients in the placebo arm.

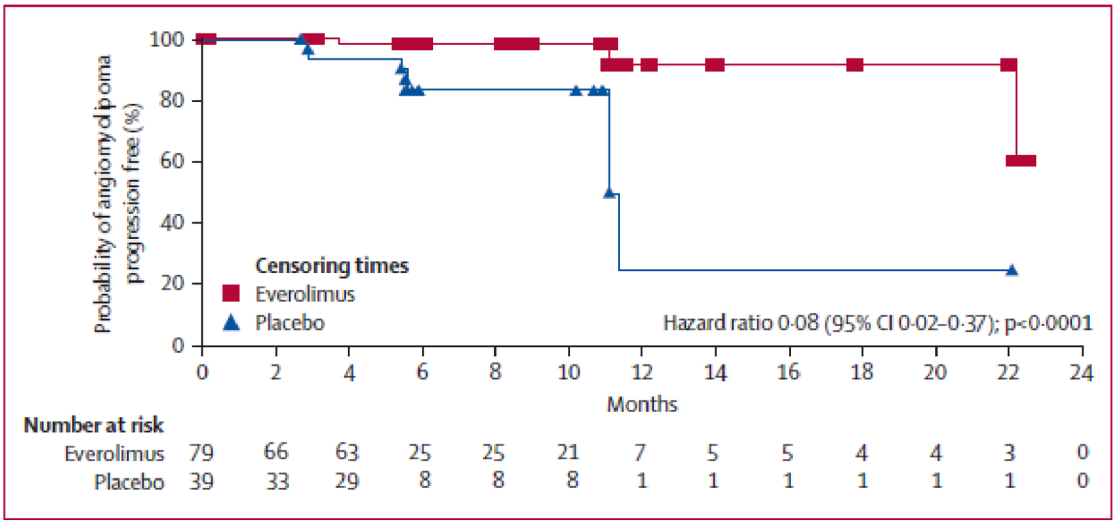
### *Duration of Angiomyolipoma Response*

All angiomyolipoma responses in the everolimus arm were ongoing for periods between 10 weeks and 85 weeks at the time of the data cut-off. Detailed results on duration of response were not provided in the trial publication.

### *Time to Angiomyolipoma Progression*

Three patients (4%) in the everolimus arm and 8 patients (21%) in the placebo arm experienced angiomyolipoma progression (stratified HR = 0.08; 95% CI, 0.02 to 0.37; P < 0.0001) (Figure 1). Estimated progression-free probability was 98% (95% CI, 89% to 100%) in the everolimus arm, and 83% (95% CI, 65% to 93%) in the placebo arm at 6 months, and 92% (95% CI, 65% to 98%) in the everolimus arm and 25% (95% CI, 1% to 64%) in the placebo arm at 12 months. The median time to angiomyolipoma progression was 11.4 months for placebo and was not reached for everolimus.

## Figure 1: Kaplan-Meier Plot Showing Time to Angiomyolipoma Progression as Assessed by Central Review




CI = confidence interval.

Notes: The hazard ratio and 95% CI were obtained from the Cox model, stratified by the modified stratification factor (use versus non-use of enzyme-inducing antiepileptic drug). The P value was obtained from the 1-sided log-rank test, stratified by use versus non-use of enzyme-inducing antiepileptic drug.

Source: Bissler et al. (2013)[10] Reprinted from The Lancet, Vol. 381, number 9869, Bissler JJ, Kingswood JC, Radzikowska E, et al., Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomized, double-blind, placebo-controlled trial, pages 817 to 824, Copyright 2013, with permission from Elsevier.

### *Pain*

Pain was not an end point in the trial.

### *Avoidance of Renal Bleeding*

Avoidance of renal bleeding was not an end point in the trial. However, some renal bleeding events would have been captured in the definition of angiomyolipoma response (i.e., reduction in angiomyolipoma volume and no angiomyolipoma bleeding of grade 2 or higher).

### *Kidney Function*

Kidney function was not reported in the trial publication. The previous CADTH Reimbursement Review reported that the proportion of patients with a decrease in GFR below 30 mL/min was 3% in the everolimus group and 8% in the placebo group; however, this difference was not statistically significant.[17]

### *Health-Related Quality of Life*

HRQoL was not an end point in the trial.

## Harms Results

Only those harms identified in the review protocol are reported below.

### *Adverse Events*

All patients in the everolimus arm and 97% of the patients in the placebo arm experienced at least 1 AE. The most common AEs (reported in 20% of patients or more) in the everolimus arm were stomatitis (48%), nasopharyngitis (24%), acne-like skin lesions (22%), headache (22%), cough (20%), and hypercholesterolaemia (20%). These AEs were primarily grade 1 and 2 (Table 6).

### *Serious Adverse Events*

SAEs were reported for 19% of patients in the everolimus arm and 18% of patients in the placebo arm.

Grade 3 events in the everolimus arm included stomatitis (n = 1), aphthous stomatitis (n = 2), fatigue (n = 1), and mouth ulceration (n = 2). Grade 3 AEs in the placebo arm included headache (n = 1) and abdominal pain (n = 1) (Table 6).

### Table 6: AEs of Any Cause Experienced by at Least 10% of Patients in the Everolimus Treatment Arm, by Grade

| | Everolimus (N = 79) | | | Placebo (N = 39) | | |
|---|---|---|---|---|---|---|
| AE | All grades | Grade 3 | Grade 4 | All grades | Grade 3 | Grade 4 |
| Stomatitis | 38 (48) | 1 (1) | 0 | 3 (8) | 0 | 0 |
| Nasopharyngitis | 19 (24) | 0 | 0 | 12 (31) | 0 | 0 |
| Acne-like skin lesions | 17 (22) | 0 | 0 | 2 (5) | 0 | 0 |
| Headache | 17 (22) | 0 | 0 | 7 (18) | 1 (3) | 0 |
| Cough | 16 (20) | 0 | 0 | 5 (13) | 0 | 0 |
| Hypercholesterolaemia | 16 (20) | 0 | 0 | 1 (3) | 0 | 0 |
| Aphthous stomatitis | 15 (19) | 2 (3) | 0 | 4 (10) | 0 | 0 |
| Fatigue | 14 (18) | 1 (1) | 0 | 7 (18) | 0 | 0 |
| Mouth ulceration | 13 (16) | 2 (3) | 0 | 2 (5) | 0 | 0 |
| Nausea | 13 (16) | 0 | 0 | 5 (13) | 0 | 0 |
| Urinary tract infection | 12 (15) | 0 | 0 | 6 (15) | 0 | 0 |

| AE | Everolimus (N = 79) | | | Placebo (N = 39) | | |
|---|---|---|---|---|---|---|
| | All grades | Grade 3 | Grade 4 | All grades | Grade 3 | Grade 4 |
| Vomiting | 12 (15) | 0 | 0 | 2 (5) | 0 | 0 |
| Anemia | 10 (13) | 0 | 0 | 1 (3) | 0 | 0 |
| Arthralgia | 10 (13) | 0 | 0 | 2 (5) | 0 | 0 |
| Diarrhea | 10 (13) | 0 | 0 | 2 (5) | 0 | 0 |
| Abdominal pain | 9 (11) | 0 | 0 | 3 (8) | 1 (3) | 0 |
| Increased blood lactate dehydrogenase | 9 (11) | 0 | 0 | 2 (5) | 0 | 0 |
| Hypophosphatemia | 9 (11) | 0 | 0 | 0 | 0 | 0 |
| Eczema | 8 (10) | 0 | 0 | 3 (8) | 0 | 0 |
| Leucopenia | 8 (10) | 0 | 0 | 3 (8) | 0 | 0 |
| Oropharyngeal pain | 8 (10) | 0 | 0 | 4 (10) | 0 | 0 |
| Upper respiratory tract infection | 8 (10) | 0 | 0 | 2 (5) | 0 | 0 |

AE = adverse event.

Source: Bissler et al. (2013)[10] Reprinted from The Lancet, Vol. 381, number 9869, Bissler JJ, Kingswood JC, Radzikowska E, et al., Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomized, double-blind, placebo-controlled trial, pages 817 to 824, Copyright 2013, with permission from Elsevier.

### *Withdrawals Due to Adverse Events*

AEs leading to discontinuation occurred in 3 patients (4%) in the everolimus arm and 4 patients (10%) in the placebo arm. In the everolimus arm, these AEs included grade 2 blood phosphorous decrease, and 1 patient with concurrent grade 3 hypersensitivity, grade 3 angioedema, grade 3 bronchospasm, and convulsion deemed not related to study drug, which resulted in death due to status epilepticus.

### *Mortality*

One death was reported in the everolimus arm as a result of intractable seizures, which the investigator did not consider related to study treatment.

### *Harms of Special Interest*

#### Angiomyolipoma Hemorrhage

Angiomyolipoma hemorrhage was not reported.

#### Infection

Infections (most frequently urinary tract and upper respiratory tract infections) occurred in 65% of patients on everolimus and 72% on placebo; there were no grade 4 infections.

#### Noninfectious Pneumonitis

Grade 2 noninfectious pneumonitis was reported in 1 patient in the everolimus arm, which resolved within 14 days after dose reduction.

### Renal Failure

Renal events were reported in 5% of patients in the everolimus arm and 15% of patients in the placebo arm. Renal events included proteinuria (everolimus 4% [3 of 79] versus placebo 8% [3 of 39]), increased blood creatinine (everolimus 1% [1 of 79] versus placebo 8% [3 of 39]), and transient acute renal failure (everolimus 2.5% [2 of 79] versus placebo 0% [0 of 39]); all were grade 1 or 2.

## Indirect Evidence

A total of 155 references were identified from the ITC search. After title and abstract screening, none met the selection criteria to be included for full-text review. No ITCs were included in this review.

## Other Relevant Evidence

Two additional publications of the EXIST-2 trial presenting long-term follow-up are included in this review. The first publication reported early results of the open-label extension phase (data cut-off date: May 1, 2013),[22] and the second presented a 4-year update of the results of the end of the open-label extension phase of the trial (data cut-off date: February 4, 2015).[23] Findings related to the open-label extension were not available at the time of the original CADTH Reimbursement Review.

Because the primary analysis of the EXIST-2 trial, conducted 6 months after the last participant was randomly assigned (data cut-off: June 30, 2011), favoured everolimus over placebo, the study was unblinded on September 9, 2011, and a preplanned open-label extension phase was launched. Given the magnitude of effect with everolimus in the primary analysis, maintenance of an untreated arm was deemed unethical, thus justifying the omission of the placebo arm in the extension phase. During this phase, all patients still receiving double-blind study treatment or undergoing posttreatment evaluation could receive open-label everolimus. Patients initially randomized to everolimus continued to receive the same dose they were taking at the conclusion of the double-blind phase; those switching from placebo received everolimus 10 mg once daily. The extension phase of the EXIST-2 trial continued until 4 years after the last patient was randomly assigned, ensuring patient follow-up of 4 to 5 years. Patients switching from placebo to everolimus received 10 mg per day as a starting dose. The dose could be reduced to 5 mg each day or every other day, based on tolerability. For patients requiring concomitant treatment with strong cytochrome P450 3A4 or PgP inducers, the dose could be increased in 5 mg increments up to twice the currently used dose. Reported outcomes were angiolipoma response, time to angiolipoma progression, renal function, and harms (definitions aligned with the core phase). Descriptive summary statistics were provided for all patients receiving at least 1 dose of everolimus.

By the cut-off date of May 1, 2013, 112 patients had received everolimus at any time during the study, including the 79 patients originally randomized to everolimus and 33 patients who switched to open-label everolimus from placebo. Of the 112 patients receiving everolimus at any time during the study, 95 (87.5%) continued to receive everolimus and 14 (12.5%) had discontinued treatment at the cut-off date of May 1, 2013. The most common reason for everolimus discontinuation was AEs (including abnormal laboratory values), reported in 9 patients (8%). The median duration of everolimus exposure was 28.9 months (range, 0.5 to 46.2 months) and the median dose intensity was 8.91 mg/day (range, 2.3 to 19.0 mg/day).

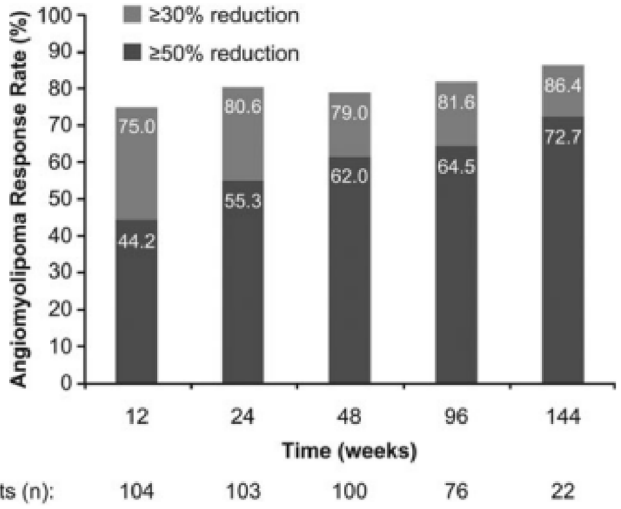
The 4-year update of the EXIST-2 trial (final analysis) combined all data from patients who had received everolimus during either the core phase or extension phase of the study, up to the data cut-off date of February 4, 2015. The median time on study was 47.2 months (range, 0.9 to 65.3 months) and the median duration of everolimus exposure was 46.9 months (range, 0.5 to 63.9 months). The median dose intensity was 8.7 (range, 1.9 to 19.3 mg/day); 82.1% of patients were exposed to everolimus for 2.8 years, and 12.5% had exposure for 4.5 years.

### Angiomyolipoma Response

Compared with an angiomyolipoma response rate of 42% (95% CI, 31% to 53%) in patients treated with everolimus in the primary analysis (with at least 6 months of follow-up), the response rate during the open-label period was 54% (95% CI, 44% to 63%); 38 patients (33.9%) had stable disease and 1 (0.9%) had disease progression as the best overall response.

The proportion of patients who had at least a 50% reduction from baseline in the sum of volumes of target lesions was 44.2% after 12 weeks of treatment and 64.5% at Week 96, and the proportion of patients who had at least a 30% reduction was 75.0% after 12 weeks and 81.6% after 96 weeks of treatment (Figure 2). Among the patients with angiomyolipoma response at any time, the median time to response was 2.83 months.

## Figure 2: Effect of Everolimus on Renal Angiomyolipoma Volume Over Time




ERA-EDTA = European Renal Association – European Dialysis and Transplantation Association.

Source: Bissler et al. (2016)[22] Bissler JJ, Kingswood JC, Radzikowska E, et al. Everolimus for renal angiomyolipoma in patients with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis: extension of a randomized controlled trial. Nephrol Dial Transplant. 2016;31(1):111 to 119, Copyright 2015, by permission of Oxford University Press on behalf of ERA-EDTA.

At the final analysis, of the 112 patients with at least 1 target renal angiomyolipoma at baseline, 65 patients (58.0%) had a confirmed response at any time. The median time to angiomyolipoma response was 2.89 months (95% CI, 2.79 to 3.19). The proportion of patients with at least 50% reductions in angiomyolipoma

volume increased over time until month 44 of treatment; 68.9% of patients had at least a 50% reduction in angiomyolipoma volume compared to 44.2% at month 3 and 55.3% at month 24 (Figure 3).

### Time to Angiomyolipoma Progression

Overall, the median time to angiomyolipoma progression was not reached, because 94.6% of patients (106 of 112) did not have angiomyolipoma progression. The estimated progression-free probability was 98.0% (95% CI, 92.1% to 99.5%) at 6 months, 95.7% (95% CI, 89.0% to 98.4%) at 12 months, 94.1% (95% CI, 86.1% to 97.5%) at 24 months, and 89.4% (95% CI, 73.2% to 96.0%) at 36 months. Among the 6 patients (5.4%) with angiomyolipoma progression at any time during the study, 2 had increased size of target lesions and 4 had increased kidney size. Four of these patients with progression had intermittent dose reductions or temporary dose interruptions within 6 months before progression. At the last follow-up, 2 patients had increased angiomyolipoma volume and 3 had decreased angiomyolipoma volume after progression (1 patient did not have a follow-up assessment).

By the final analysis, 14.3% of patients (n = 16) experienced angiomyolipoma progression at some point during the study. Reasons for progression were increased angiomyolipoma size (6 patients) and kidney enlargement (10 patients); 9 continued the treatment despite disease progression because of a perceived clinical benefit. Progressive disease was preceded by dose reduction or interruption in 13 of the 16 patients (81.3%). The time from first response to progression or last radiologic assessment ranged from 3.0 months to 55.5 months.

### Renal Function

Most patients (93.8%) had a GFR of at least 30 mL/min/1.73 $m^2$ or normal serum creatinine levels (86.6%) while receiving everolimus. Median GFR at baseline was 85 mL/min/1.73 $m^2$, and overall, GFR remained stable over time (median GFR at week 120 was 84 mL/min/1.73 $m^2$). Severe renal impairment (GFR < 30 mL/min/1.73 $m^2$) was observed in 7 patients (6.3%) at least once postbaseline. All of these patients had compromised renal function (GFR < 60 mL/min/1.73 $m^2$) before everolimus initiation. No patients had grade 3 or 4 elevated serum creatinine, but 15 patients (13.4%) had grade 1 or 2 elevations, which were temporary in 7 patients; 8 patients (7.1%) experienced grade 3 hypophosphatemia.

By the final analysis, most patients had a GFR of at least 30 mL/min/1.73 $m^2$ (92.9%) or normal serum creatinine values (83.9%) while on treatment with everolimus. Median GFR and serum creatinine values remained stable during the everolimus treatment. Severe renal impairment (postbaseline GFR < 30 mL/min/1.73 $m^2$) was observed in 8 patients (7.1%); all patients had GFRs below 60 mL/min/1.73 $m^2$ at baseline, including 3 patients with GFRs below 30 mL/min/1.73 $m^2$ before everolimus initiation.

Grade 1 or 2 elevations in serum creatinine were observed in 15.2% of patients, and 1 patient (0.9%) had a grade 3 elevation in serum creatinine. Among the 18 patients with grade 1 elevations in serum creatinine, half reported normal creatinine levels at baseline and half reported grade 1 or 2 serum creatinine increases before starting everolimus.

Renal events occurred in 20.5% of the 112 patients treated with everolimus for this final analysis (treatment duration = 46.9 months), compared to 5% of patients (4 of 79) treated with everolimus and 15% of patients

(6 of 39) receiving placebo during the double-blind period (median treatment duration = 8.8 months and 7.8 months, respectively).

### Angiomyolipoma-Related Interventions

Among the 112 patients who received everolimus, 2 patients underwent angiomyolipoma-related interventions. One patient receiving everolimus for 1.5 years who was experiencing worsening pain in the right flank underwent embolization (for progressive disease). Another patient underwent elective left partial nephrectomy 3 years after everolimus discontinuation.

#### *Harms*

For the 112 patients who received everolimus, the most frequently reported AEs were nasopharyngitis (42.9%), stomatitis (42.9%), headache (30.4%), acne (29.5%), hypercholesterolemia (29.5%), urinary tract infection (27.7%), and aphthous stomatitis (25.9%). Most AEs were grade 1 or 2 in severity. Overall, 42% of patients experienced grade 3 or 4 AEs; 27% were suspected to be drug related. The most frequent grade 3 AEs regardless of relationship to study drug were amenorrhea (4.2% of female patients aged 18 to 55 years) and decreased blood phosphorus (3.6%). Grade 4 AEs were increased blood uric acid (1.8%) and convulsion, hydrocephalus, hypertensive crisis, neutropenia, pancreatic carcinoma, and rhabdomyolysis (0.9% each). No patients treated with everolimus experienced renal bleeding.

Rates of new AEs while on treatment with everolimus decreased over time. Most AEs except nasopharyngitis reduced to incidences less than 10% in year 2 and further declined in year 3. Nasopharyngitis had an incidence of 32.1% in the first year, 18.8% in the second year, and 18.2% in the third year. The incidence of SAEs also decreased, from 19.6% in year 1 to 7.9% in year 2 and 7.8% in year 3.

Overall, 71.4% of patients (n = 80) required dose interruptions or reductions, with AEs being the most common reason (50% and 58.9% for dose reductions and dose interruptions, respectively).

At the final analysis, the most common AEs suspected to be related to everolimus (in > 20% of the patients) were stomatitis (42%), hypercholesterolemia (30.4%), acne (25.9%), aphthous stomatitis (21.4%), and nasopharyngitis (21.4%). Serious AEs were observed in 37.5% of the patients, most frequently epilepsy (5.4%) and pneumonia (2.7%). Infections were noted in 91.1% of patients, most involving the upper respiratory tract. Dose interruptions and adjustment were needed for 36.6% of patients who experienced infections.

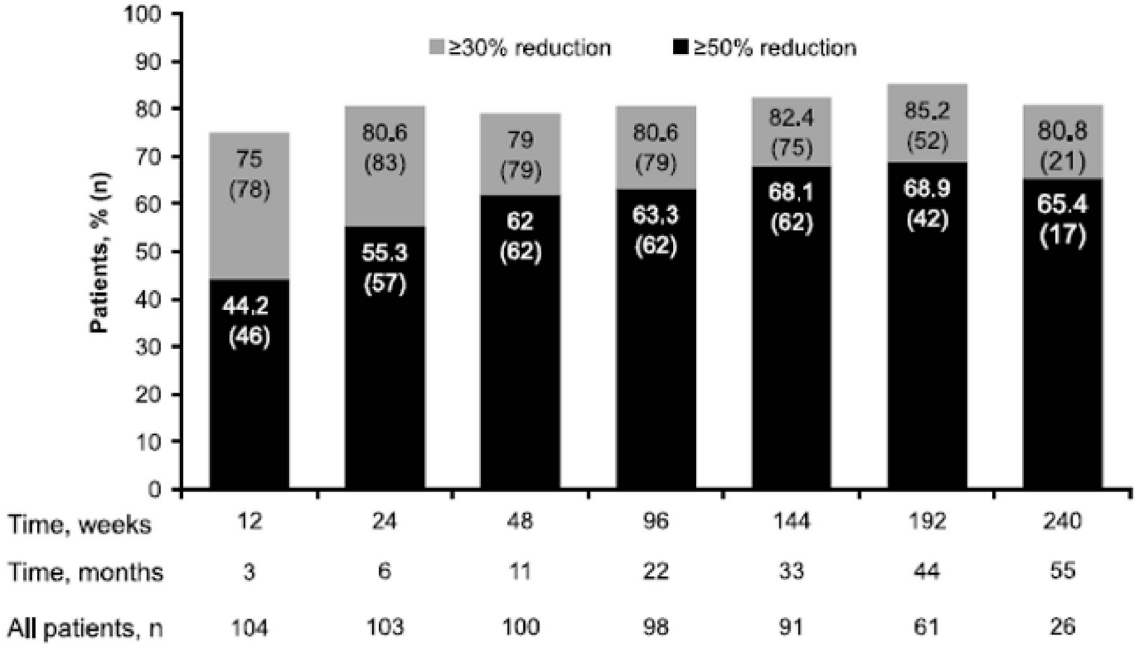
No angiomyolipoma-related bleeding or nephrectomies were reported.

Renal events occurred in 20.5% of the 112 patients treated with everolimus for this final analysis.

Overall, 8.9% of patients (n = 10) withdrew from the study because of an AE. Approximately 80% of patients required 1 dose interruption and/or reduction; AEs were the most common reason (66.1% for dose interruptions and 59.8% for dose reductions).

One death resulting from status epilepticus was reported and was not suspected by the investigator to be related to treatment.

## Figure 3: Renal Angiomyolipoma Response Rate With Everolimus Over Time




Source: Bissler et al. (2017)[23] Reprinted from Bissler JJ, Kingswood JC, Radzikowska E, et al. Everolimus long-term use in patients with tuberous sclerosis complex: Four-year update of the EXIST-2 study. PLoS ONE. 2017;12(8):e0180939. Copyright 2017 Bissler et al. Creative Commons CC BY 4.0: https://creativecommons.org/licenses/by/4.0/.

## Pediatric Population

The EXIST-2 trial, which formed the evidence base for this CADTH review of the efficacy and AEs of everolimus in the treatment of TSC-related angiomyolipoma, did not include patients younger than 18 years. To fill this gap in evidence, the review is supplemented with data from the EXIST-1 trial, which preceded the EXIST-2 trial. The phase III, randomized, double-blind, placebo-controlled EXIST-1 trial included patients of any age with a diagnosis of TSC and serial SEGA growth who were randomly assigned to receive everolimus or placebo. Similar to EXIST-2, the trial included a 6-month double-blind phase, followed by an open-label phase during which all patients received everolimus, lasting until 4 years after the last patient was randomized. Patients received oral everolimus at an initial dose of 4.5 mg/m$^2$ body surface area (BSA), which was then titrated via blood trough levels to 5 ng/mL to 15 ng/mL according to tolerability. Use of strong inhibitors of cytochrome P450 3A4 and PgP inhibitors, strong inducers of *CYP3A4*, and antiproliferative drugs was prohibited.

CADTH identified a noncomparative (i.e., including patients treated with everolimus only) post hoc analysis of the effect of everolimus on renal angiomyolipoma in pediatric patients with TSC being treated for SEGA in the EXIST-1 trial.[24] Angiomyolipoma response rates were analyzed in the subset of 33 patients younger than 18 years with 1 or more target angiomyolipoma lesions at baseline with a longest lesion diameter of at least 1.0 cm. Response was defined as the proportion of patients with at least a 50% reduction in the sum volume of target renal angiomyolipomata from baseline, in the absence of new target angiomyolipomata, a

greater than 20% increase in kidney volume from nadir, and angiomyolipoma-related bleeding of grade 2 or higher. Renal function was assessed via change from baseline in eGFR and protein urinalysis. Analyses were performed including patients who had received at least 1 dose of everolimus, and findings were presented descriptively.

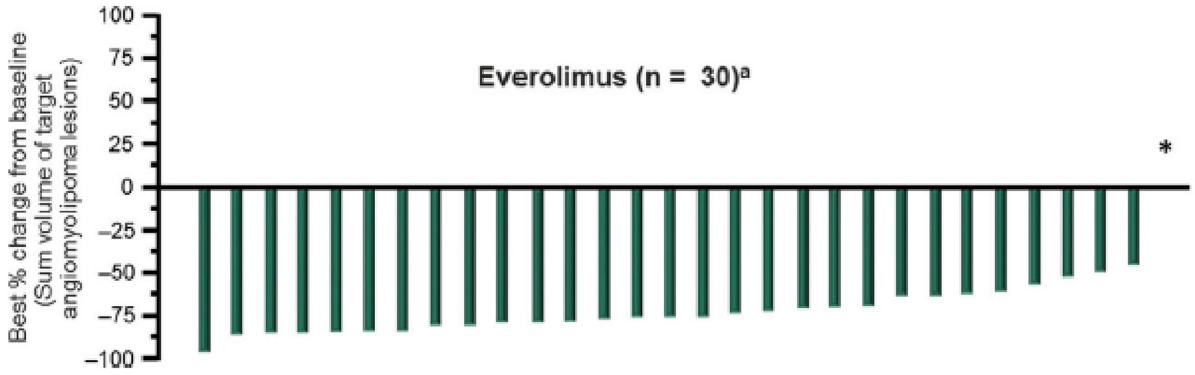
Of the 33 patients in the original study with renal angiomyolipoma, 23 (70%) completed the study per protocol, while the remaining patients discontinued early. More than half (54.5%) of the patients in this subgroup were male, and 91% were white. The median age of these patients was 11.5 years (range, 5.4 to 17.5 years), with 39.4% aged between 3 years and less than 10 years. Most patients (81.8%) had a lesion smaller than 3 cm at baseline. At the time of study completion (on October 2, 2014), the median duration of everolimus exposure in these patients was 44.8 months (range, 1.9 months to 57.9 months).

### Efficacy Results

#### *Angiomyolipoma Response*

Among the 33 patients with angiomyolipoma at baseline, an angiomyolipoma response was reported in 25 patients (75.8%; 95% CI, 57.7% to 88.9%) and stable disease was reported as a best response in 4 patients (12.1%). Of the 30 patients for whom best percentage change from baseline could be determined, 29 (96.7%) had a reduction in their renal angiomyolipoma volume relative to baseline as their best response (Figure 4). The mean percentage reduction of renal angiomyolipoma volume increased from 47% at week 12 to 70.7% at week 96, and then stabilized for the duration of the study, remaining above 67% through week 240.

## Figure 4: Best Percentage Change in Renal Angiomyolipoma Volume on Treatment




[a] Patients for whom best the percent change in target angiomyolipoma lesion volume was not available or with an overall response of "not evaluable" were excluded from the graph.

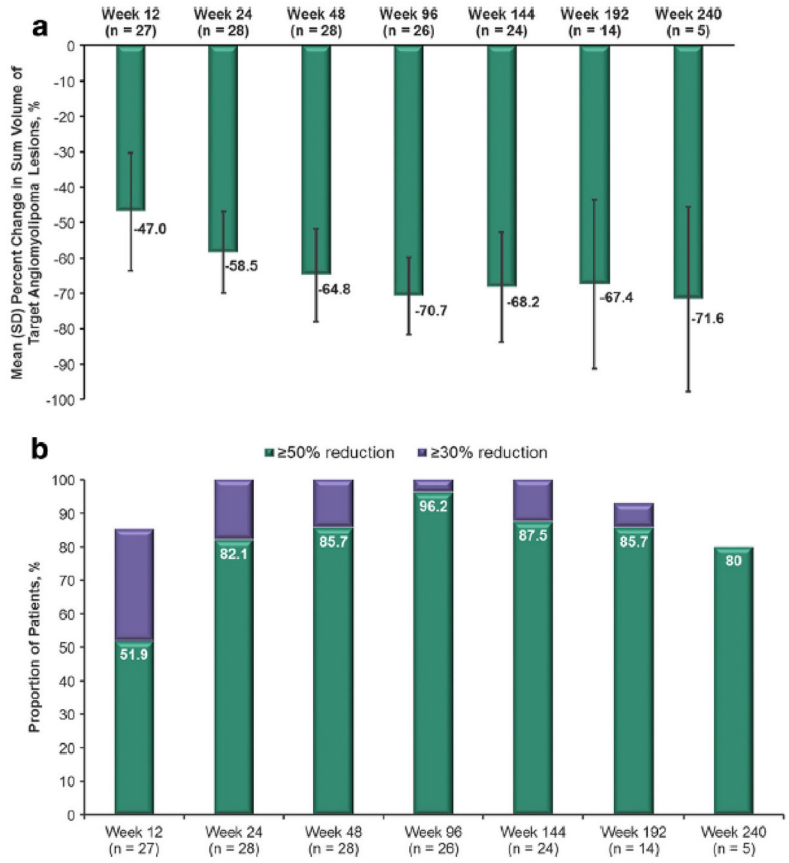
Note: The asterisk denotes the percent change in sum of volumes of target angiomyolipoma lesion available for one patient but contradicted by overall angiomyolipoma response equalling progressive disease.

Source: Bissler et al. (2018).[24] Reprinted from Bissler JJ, Franz DN, Frost MD, et al. The effect of everolimus on renal angiomyolipoma in pediatric patients with tuberous sclerosis being treated for subependymal giant-cell astrocytoma. Pediatr Nephrol. 2018;33(1):101 to 109. Copyright 2017 Bissler et al. Creative Commons CC BY 4.0: https://creativecommons.org/licenses/by/4.0/.

More than 80% of patients experienced at least a 50% reduction in angiomyolipoma volume from week 24 through the remainder of the study. At week 192 (n = 14), 92.9% had at least a 30% reduction in renal angiomyolipoma volume, and 85.7% had at least a 50% reduction in volume (Figure 5).

Nine patients in this subgroup were randomly assigned to receive placebo during the double-blind, primary core phase of the study and went on to receive everolimus in the long term, open-label extension phase. During the placebo phase, no clear trend in angiomyolipoma volume changes from baseline was observed in these patients; however, angiomyolipoma volume decreased in all 9 patients after everolimus initiation.

## Figure 5: Mean Reductions in the Sum of Volume of Target Angiomyolipoma Lesions Over Time and the Proportion of Patients Achieving an Angiomyolipoma Volume Reduction of at Least 50% or 30% Over Time




**Source**: Bissler et al. (2018)[24] Reprinted from Bissler JJ, Franz DN, Frost MD, et al. The effect of everolimus on renal angiomyolipoma in pediatric patients with tuberous sclerosis being treated for subependymal giant-cell astrocytoma. Pediatr Nephrol. 2018;33(1):101 to 109. Copyright 2017 Bissler et al. Creative Commons CC BY 4.0: https://creativecommons.org/licenses/by/4.0/.

### *Renal Function*

In general, the patients had primarily normal GFRs, with some patients having hyperfiltration. Mean GFR remained stable over the course of the study (data not reported). None of the patients had a renal bleeding episode while on everolimus. Most patients (n = 26; 78.8%) also had negative protein results on urinalysis at baseline.

Intermittent proteinuria occurs in TSC-related renal disease, and the level of proteinuria was exacerbated in 9 patients (27.3%) who had a protein urinalysis value of 2 or higher at least once during the study. Proteinuria was reported as an AE in 2 patients. No renal aneurysms were reported.

### Harms Results

All patients experienced at least 1 AE during the study, with most (90.9%) experiencing an AE that was suspected to be related to everolimus (Table 7). The most commonly reported AEs of any grade (occurring in more than 25% of patients) included convulsion and mouth ulceration (45.5% each), stomatitis (42.4%), and cough (27.3%). Approximately half of the patients (n = 18; 54.5%) experienced 1 grade 3 or 4 AE; 30.3% of patients experienced a grade 3 or 4 AE that was suspected to be related to everolimus. The most common grade 3 AEs (regardless of the study drug relationship) included pneumonia, convulsion, stomatitis (n = 3 each; 9.1%), and amenorrhea (n = 2 out of 10 at-risk female patients aged 10 to < 18 years; 20%). Of the 2 cases of grade 3 amenorrhea, 1 resolved after 296 days with treatment, and 1 was ongoing at the time of the data cut-off. Grade 4 AEs (all-cause) included pyrexia, pneumonia, gastroenteritis, and hyperkalemia (n = 1 each; 3.0%). No cases of noninfectious pneumonitis were reported.

All patients required additional therapy (pharmacological or nonpharmacological) to treat an AE at some point in the study. Three patients (9.1%) discontinued everolimus because of an AE (grade 3 neutropenia, grade 3 neurosurgery for epilepsy, grade 2 aggression following grade 3 convulsion).

### Table 7: AEs of any Grade Occurring in at Least 15% of Patients

| AE | Everolimus (N = 33)<br>n (%) |
|---|---|
| Any | 33 (100) |
| Convulsion | 15 (45.5) |
| Mouth ulceration | 15 (45.5) |
| Stomatitis | 14 (42.4) |
| Cough | 9 (27.3) |
| Nasopharyngitis | 8 (24.2) |
| Headache | 7 (21.2) |
| Sinusitis | 7 (21.2) |
| Upper respiratory tract infection | 7 (21.2) |
| Blood cholesterol increase | 6 (18.2) |
| Otitis media | 6 (18.2) |
| Pyrexia | 6 (18.2) |
| Vomiting | 6 (18.2) |
| Acne | 5 (15.2) |
| Aggression | 5 (15.2) |
| Bronchitis | 5 (15.2) |

| AE | Everolimus (N = 33)<br>n (%) |
|---|---|
| Diarrhea | 5 (15.2) |
| Fatigue | 5 (15.2) |
| Pneumonia | 5 (15.2) |
| Rash | 5 (15.2) |
| Streptococcal pharyngitis | 5 (15.2) |
| Viral gastroenteritis | 5 (15.2) |

AE = adverse event.

Source: Bissler et al. (2018)[24] Reprinted from Bissler JJ, Franz DN, Frost MD, et al. The effect of everolimus on renal angiomyolipoma in pediatric patients with tuberous sclerosis being treated for subependymal giant-cell astrocytoma. Pediatr Nephrol. 2018;33(1):101 to 109. Copyright 2017 Bissler et al. Creative Commons CC BY 4.0: https://creativecommons.org/licenses/by/4.0/.

# Economic Evidence

Because this review is part of the CADTH Nonsponsored Reimbursement Review program, in which an application filed by a sponsor is absent, CADTH does not have access to an economic model for everolimus in renal angiomyolipoma associated with TSC. As a result, the economic review consists of a cost comparison between everolimus and sirolimus for the treatment of renal angiomyolipoma associated with TSC.

## CADTH Analyses

### Adults and Older Adolescents

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical experts and drug plans. Recommended doses were based on the product monograph of each product, where applicable, and validated by clinical experts. If discrepancies in dosing between the product monograph and Canadian clinical practice were present, the dose specified by clinical experts was used. Everolimus tablets are not indicated for the treatment of renal angiomyolipoma associated with TSC in patients younger than 18 years, and everolimus oral suspension tablets are not indicated for the treatment of renal angiomyolipoma associated with TSC at any age. Based on wholesale prices reported in the IQVIA DeltaPA database (accessed on November 19, 2023), 2.5 mg, 5 mg, and 10 mg oral tablets of everolimus are all priced at $172.26 per tablet in Alberta, British Columbia, Ontario, Saskatchewan, and the 3 territories,[25] and at $50.66 per tablet in Manitoba, New Brunswick, Newfoundland and Labrador, Nova Scotia, and Prince Edward Island. Pricing for comparator products was based on publicly available list prices.

When used at doses of 5 mg to 10 mg daily, the cost of everolimus was $62,873 to $125,747 per patient per year for adult or older adolescent patients who can use oral tablets, in jurisdictions with more expensive wholesale pricing (Alberta, British Columbia, Nunavut, Northwest Territories, Ontario, Saskatchewan, Yukon), or $18,492 to $36,985 in jurisdictions with less expensive wholesale pricing (Manitoba, New Brunswick, Newfoundland and Labrador, Nova Scotia, Prince Edward Island). The annual cost of treatment was $70,627

to $141,254 per patient per year for patients requiring everolimus oral suspension tablets in all jurisdictions. The cost of treatment with sirolimus is $6,658 to $9,986 per patient per year. As such, the incremental cost of everolimus regular tablets for adult and older adolescent patients in jurisdictions with more expensive wholesale pricing ranges from $52,887 to $119,089 per patient per year compared to sirolimus, while in jurisdictions with less expensive wholesale pricing, the incremental cost ranges from $8,506 to $30,327 per patient per year. Note that results may differ by jurisdiction if there are differences in their list prices for the drugs under review compared to those presented in Table 8.

## Table 8: CADTH Cost-Comparison Table for Adults and Older Adolescents With Renal AML Associated With TSC

| Treatment | Strength or concentration | Form | Price ($) | Recommended dosage[a] | Daily cost ($) | Annual cost ($) |
|---|---|---|---|---|---|---|
| Everolimus (generics) | 2.5 mg<br>5 mg<br>10 mg | Tablet | 50.6637 or 172.2559 per tablet[b] | 5 to 10 mg once daily[c] | 50.66 to 101.33 or 172.26 to 344.51[b,d] | 18,492 to 36,985 or 62,873 to 125,747[b,d] |
| Everolimus (Afinitor Disperz) | 2 mg<br>3 mg<br>5 mg | Tablets for oral suspension | 193.4990[e] | 5 mg to 10 mg once daily[f] | 193.50 to 387.00 | 70,627 to 141,254 |
| **Other mTOR inhibitor** | | | | | | |
| Sirolimus (Rapamune) | 1 mg<br>1 mg/mL | Tablet<br>Oral solution | 9.1200[e] | 2 to 3 mg once daily[g] | 18.24 to 27.36 | 6,658 to 9,986 |

AML = angiomyolipoma; mTOR = mechanistic target of rapamycin; SEGA = subependymal giant-cell astrocytoma; TSC = tuberous sclerosis complex.

[a]According to clinical expert opinion obtained by CADTH, pediatric patients requiring mTOR inhibitor treatment primarily for renal AML associated with TSC typically begin to require it after adolescence, due to the time it takes renal AML to grow to symptomatic size, and are therefore usually of adult or near-adult size and receive adult doses. According to this clinical expert input, younger pediatric patients with TSC who would benefit from an mTOR inhibitor for renal AML are generally already receiving it for SEGA and/or seizures and therefore are not primarily receiving the mTOR for renal AML.

[b]Wholesale price according to IQVIA DeltaPA (November 2023) for generic everolimus in Alberta, British Columbia, Ontario, Saskatchewan, and the 3 territories is $172.2559 per tablet.[25] The wholesale price reported by DeltaPA for Manitoba, New Brunswick, Nova Scotia, Prince Edward Island, and Newfoundland and Labrador is $50.6637 per tablet.

[c]According to clinical expert opinion obtained by CADTH, while the product monograph–recommended and Ontario Exceptional Access Program dose of everolimus for the treatment of renal AML associated with TSC is 10 mg daily,[26,27] patients are often started at 5 mg daily, with some later increased to 7.5 mg or 10 mg daily depending on individual response and tolerance.

[d]According to clinical expert opinion obtained by CADTH, when considering both individual AML volume response and the patient's tolerance to side effects, some patients have an optimal everolimus dose of 7.5 mg daily. Due to flat pricing across tablet strengths, a 7.5 mg daily dose is double the daily and annual cost of a 5 mg or 10 mg dose, as it requires a 2.5 mg tablet and a 5 mg tablet daily.

[e]Wholesale price according to IQVIA DeltaPA (November 2023) per tablet or per mL.[25]

[f]According to clinical expert opinion obtained by CADTH, a small proportion of adult patients with renal AML associated with TSC may have health statuses or developmental conditions which prevent them from being able to swallow regular tablets and may instead receive oral suspension tablets. Everolimus oral suspension tablets (Afinitor Disperz) are indicated only for the treatment of patients with SEGA associated with TSC or as adjunctive treatment of seizures associated with TSC,[27] and thus their use for the treatment of renal AML associated with TSC is off-label. Oral suspension tablets were not available in generic form at the time of this review.

[g]Sirolimus is not indicated for the treatment of renal AML associated with TSC.[28] Dosing was based on clinical expert opinion obtained by CADTH as to the typical use of sirolimus for renal AML associated with TSC in current Canadian practice. Alternate dosing has been used in a phase II nonrandomized trial of the effect of sirolimus on renal AML and other kidney tumours, where adult patients with TSC received 6 mg of sirolimus on day 1, followed by 2 mg daily, followed by dose adjustments to maintain a target blood level of 3 to 9 ng/mL for the first 16 weeks, then to maintain a target level of 9 to 15 ng/mL unless there was evidence for a partial or complete response. Mean daily dose in this study at week 52 was 6.7 mg,[29] which would correspond to a mean daily cost of $61.10 per patient.

### Younger Pediatric Patients

Everolimus is not indicated in Canada for the treatment of angiomyolipoma associated with TSC in pediatric patients and, according to clinical expert input obtained by CADTH, most preadolescent patients requiring

mTOR inhibitor treatment for renal angiomyolipoma associated with TSC already require it for the treatment of SEGA and/or seizures. A post hoc analysis of the EXIST-1 SEGA trial demonstrated angiomyolipoma response in pediatric patients with at least 1 angiomyolipoma (largest lesion size ≥ 1 cm diameter) at baseline.[24] For further detail on this analysis, refer to the Pediatric Population section of the Clinical Evidence presented within this report.

The median baseline BSA reported for the post hoc analysis of pediatric patients with angiomyolipoma within the EXIST-1 trial was 1.28 $m^2$ (range, 0.8 $m^2$ to 2.2 $m^2$).[24] The final everolimus dose for this subset of patients was not reported; however, the median final dose intensity reported for all patients in the EXIST-1 trial was 5.89 mg/$m^2$/day (range, 1.0 to 13.8 mg/$m^2$/day).[30] Assuming this median BSA and dose, the median final daily dose for pediatric patients with SEGA and angiomyolipoma associated with TSC was approximately 7.5 mg/day. However, given the ranges reported for both BSA and final dose within the EXIST-1 trial, as well as nonsplitable nature of the regular tablets,[27,31] it is likely that most pediatric patients will receive 1 to 2 tablets per day, corresponding to doses of 2.5 to 20 mg daily. Similarly, while more graduated doses are possible with everolimus oral suspension tablets, administration instructions stipulate that the tablets should not be split before suspension and that any suspension not administered to the patient should be discarded within 60 minutes of preparation.[27] Thus, most pediatric patients receiving the oral suspension tablets will also use a full 1 to 2 tablets per day. As such, the daily and annual cost of treatment with everolimus for younger pediatric patients with angiomyolipoma associated with TSC who are receiving doses consistent with those recommended for SEGA is the same as the daily and annual costs for adult patients with angiomyolipoma associated with TSC (Table 9).

The cost of treatment with sirolimus for younger pediatric patients is $1,664 to $9,986, if used at 0.5 mg to 3 mg per day and if relevant to public plans. As such, the incremental cost of everolimus regular tablets for younger pediatric patients in jurisdictions with more expensive wholesale pricing of everolimus regular tablets would range from $52,887 to $124,082 per patient per year compared to sirolimus, depending on dose, while in jurisdictions with less expensive wholesale pricing, the incremental cost would range from $8,506 to $35,320 per patient per year. The incremental cost of everolimus oral suspension tablets would be $60,641 to $139,590 per patient per year compared to sirolimus, depending on dose. Note that results may differ by jurisdiction if there are differences in their list prices for the drugs under review compared to those presented in Table 9.

## Table 9: CADTH Cost Comparison Table for Younger Pediatric Patients With Renal AML Associated With TSC

| Treatment | Strength or concentration | Form | Price ($) | Recommended dosage | Daily cost ($) | Annual cost ($) |
|---|---|---|---|---|---|---|
| Everolimus (generics) | 2.5 mg<br>5 mg<br>10 mg | Tablet | 50.6637 or 172.2559 per tablet[a] | Starting dose: 4.5 mg/m$^2$ BSA daily, followed by titration to attain trough concentrations of 5 to 15 ng/mL[b]<br>Median final dose from EXIST-1 trial: 5.89 mg/m$^2$/day[c] | 50.66 to 101.33 or 172.26 to 344.51[ad] | 18,492 to 36,985 or 62,873 to 125,747[ad] |
| Everolimus (Afinitor Disperz) | 2 mg<br>3 mg<br>5 mg | Tablets for oral suspension | 193.4990[e] | | 193.50 to 387.00[d] | 70,627 to 141,254[d] |
| **Other mTOR inhibitor** | | | | | | |
| Sirolimus (Rapamune) | 1 mg<br>1 mg/mL | Tablet<br>Oral solution | 9.1200[e] | Initially 0.5 mg/m$^2$/day, up 2 mg to 3 mg daily[f] | 4.56 to 27.36 | 1,664 to 9,986 |

AML = angiomyolipoma; BSA = body surface area; mTOR = mechanistic target of rapamycin; NHS = National Health Service; SEGA = subependymal giant-cell astrocytoma; TSC = tuberous sclerosis complex.

[a]Wholesale price according to IQVIA DeltaPA (November 2023) for generic everolimus in Alberta, British Columbia, Ontario, Saskatchewan, and the 3 territories.[25] The wholesale price reported by DeltaPA for Manitoba, New Brunswick, Nova Scotia, Prince Edward Island, and Newfoundland and Labrador is $50.6637 per tablet.

[b]As everolimus is not indicated for TSC-associated AMLs, this dose is recommended for the treatment of SEGA associated with TSC, based on BSA. This is the dose regimen used in the EXIST-1 trial, and thus the regimen used in the post hoc analysis of AML response in pediatric patients with SEGA who also had renal AML.[24,30] This dose is also consistent with that funded by the NHS (UK) for the treatment of pediatric renal AML associated with TSC[32,33] which is also the approved pediatric SEGA dose in Canada.[27]

[c]The final dose was not reported for the subset of pediatric patients within the post hoc AML response analysis from EXIST-1. This is the median final dose reported for all patients within the EXIST-1 trial.

[d]Assumes the use of 1 to 2 tablets daily. While the dispersion tablets for oral suspension can be administered in more graduated doses, the recommended administration includes the suspension of full tablets and the discarding of excess medication, and thus the daily and annual costs assume the use of a full 1 or 2 tablets per day regardless of the dose administered to the patient.[27]

[e]Wholesale price according to IQVIA DeltaPA (November 2023) per tablet or per mL.[25]

[f]Sirolimus is not indicated in Canada for any condition for patients younger than 13 years.[28] Initial doses of 0.5 mg/m$^2$/day when used for young children with TSC have been reported in the literature,[34,35] with subsequent dosing targeting a blood level of 3 to 4 ng/mL[35] or 5 to 15 ng/mL.[34] Dosing in this table assumes that pediatric doses will not exceed the opinions of the clinical experts consulted by CADTH about typical adult dosing.

## Price Reduction Analyses

In jurisdictions that reimburse sirolimus for the treatment of renal angiomyolipoma associated with TSC, the price of everolimus, assuming a 2.5 mg, 5 mg, or 10 mg daily dose, would need to be reduced by 84% to 89% in jurisdictions with higher wholesale prices for everolimus, or 46% to 64% in jurisdictions with lower wholesale prices for everolimus, to result in cost parity compared to sirolimus (Table 10). According to feedback received from jurisdictional drug plans, sirolimus is a full benefit in New Brunswick and in the Non-Insured Health Benefits (NIHB) program.

## Table 10: CADTH Price Reduction Analyses

| Scenario | Wholesale price ($) | Reduction needed | Reduced price ($) | Savings relative to list price[a] ($) |
|---|---|---|---|---|
| Price reduction required to equal sirolimus (jurisdictions with higher everolimus wholesale list prices) | 172.26 per tablet | 84% to 89%[b,c] | 18.24 to 27.36[b,c] | 52,887 to 56,216 |
| Price reduction required to equal sirolimus (jurisdictions with lower everolimus wholesale list prices) | 50.66 per tablet | 46% to 64%[b,c] | 18.24 to 27.36[b,c] | 8,506 to 11,835 |
| Price reduction required to equal sirolimus (when considering everolimus oral suspension tablets and younger pediatric dosing) | 193.50 | 86% to 98% | 4.56 to 27.36[d] | 60,641 to 68,963 |

[a]Savings from the sponsor list price per patient per year.

[b]Reductions in this table assume patients are using a single 2.5 mg, 5 mg, or 10 mg tablet of everolimus per day. For patients requiring 7.5 mg daily, the price of everolimus would need to be reduced by 92% to 95% in jurisdictions with higher everolimus list prices, and 73% to 82% in jurisdictions with lower everolimus list prices to equal the cost of treatment with sirolimus.

[c]Relative to publicly available list price of sirolimus, assuming the use of 2 mg to 3 mg daily.

[d]Assuming the use of 1 oral suspension tablet and relative to the publicly available price of sirolimus oral liquid, assuming the use of 0.5 mg to 3 mg daily.

## Issues for Consideration

According to clinical expert opinion received by CADTH, the use of mTOR inhibitor therapy typically eliminates the need for renal embolization, debulking, and/or nephrectomy for most patients receiving it, due to the reduction in angiomyolipoma volume and reduction in vascular fragility and thus hemorrhage risk. As such, treatment with everolimus (or sirolimus) is likely to reduce the number and thus the resource use of such procedures in the renal angiomyolipoma population. The long-term follow-up to the EXIST-2 trial reported no angiomyolipoma -related bleeding events, while 1 embolization was reported during the study period (i.e., while still using everolimus) and 1 nephrectomy was reported after treatment discontinuation.[23] Additionally, unlike local surgical procedures, mTOR inhibitor therapy is systemic and therefore is likely to also impact other regions with TSC-associated tumour growth beyond those in the kidneys, such as those in the brain or lungs.

Currently, sirolimus is only available under the brand name Rapamune.[28] A generic brand of sirolimus received authorization from Health Canada in 2011 but is not marketed in Canada.[36] Should this or another generic brand of sirolimus become available in future, the incremental cost of everolimus compared to sirolimus could increase.

No cost-effectiveness studies were identified based on a literature search conducted on August 4, 2023.

# Discussion

## Summary of Available Evidence

The main evidence base for this review was the EXIST-2 trial, a randomized, double-blind, placebo-controlled, phase III trial of oral everolimus (n = 79) versus placebo (n = 39) in patients with renal angiomyolipoma associated with TSC or LAM. Patients were treated until they experienced angiomyolipoma progression or toxicity. The mean treatment duration was 45 weeks with everolimus and 40 weeks with placebo. The core (double-blind) phase of the trial lasted until the last randomized patient had been treated for 6 months (data cut-off date: June 30, 2011), after which a preplanned, single-arm, open-label extension phase was launched, in which all patients still receiving double-blind study treatment or undergoing posttreatment evaluation could receive open-label everolimus. The extension phase of the EXIST-2 trial continued until 4 years after the last patient was randomly assigned, ensuring patient follow-up of 4 to 5 years. The primary end point for the core phase was confirmed angiomyolipoma response, and the key secondary end point was time to angiomyolipoma progression. The median age was 31 years, and 66% were female. The cumulative median duration of exposure to everolimus (112 patients who took at least 1 dose of everolimus) was 46.9 months (range, 0.5 to 63.9).[10,17,22,23]

As the EXIST-2 trial included only adult patients (aged 18 years and older), data from the EXIST-1 trial — a phase III, randomized, double-blind, placebo-controlled trial that recruited patients of any age with a diagnosis of TSC and SEGA — were included to provide information on the efficacy and harms of everolimus treatment in the pediatric population.[24] The secondary analysis of the effect of everolimus on renal angiomyolipoma in pediatric patients with TSC being treated for SEGA in the EXIST-1 trial was based on a descriptive analysis of the subset of 33 patients younger than 18 years with 1 or more target angiomyolipoma lesions of at least 1.0 cm in diameter at baseline. The median age of these patients was 11.5 years (range, 5.4 years to 17.5 years), with 39.4% aged between 3 years and 10 years; 54.5% of the patients in this subgroup were male. Most patients (81.8%) had a lesion size smaller than 3 cm at baseline. The median duration of everolimus exposure was 44.8 months (range, 1.9 months to 57.9 months).

No evidence regarding the efficacy and harms of everolimus compared to another mTOR inhibitor (sirolimus, which was the main comparator of interest) was identified in the CADTH systematic review.

## Interpretation of Results

### Efficacy

In the EXIST-2 core phase, a larger proportion of patients treated with everolimus had an objective response compared to patients receiving placebo (42% versus 0%; $P < 0.0001$). Everolimus was favoured over placebo for prolonging the time to angiomyolipoma progression. The median time to angiomyolipoma progression was 11.4 months with placebo and was not reached with everolimus. The long-term analysis of the core phase and open-label extension phase of the EXIST-2 trial support the long-term efficacy of everolimus, showing that angiomyolipoma response seems to be sustained over time; however, there was no comparison group for this phase. Renal angiomyolipoma response continued to improve from 42% in the core phase, after a median exposure of 8.8 months, to 58% in the single-arm, open-label extension

phase, after a median exposure of 46.9 months. Few angiomyolipoma-related complications or procedural interventions were reported over the 4-year duration of everolimus treatment, and no patient treated with everolimus experienced an angiomyolipoma-associated hemorrhage. There was 1 patient who needed embolization while on everolimus over a median exposure of approximately 4 years, which suggests that longer-term mTOR inhibition may reduce the need for future surgical interventions or embolization by preventing or slowing down tumour regrowth.

In the initial CADTH review of everolimus, CDEC noted that response, as defined in the EXIST-2 trial, is not a validated surrogate marker for the clinical outcomes of greatest interest to patients with renal angiomyolipoma associated with TSC, including hemorrhage, renal function, and pain, and that despite clinical opinion suggesting that an increase in angiomyolipoma size results in an increased risk of complications, there is insufficient evidence to suggest that a subsequent reduction in angiomyolipoma size will result in a reduction in bleeding complications, avoidance of surgery, or long-term preservation of renal function. At the time of the initial CADTH review, long-term efficacy and safety outcomes were unknown. Some limitations remain and are not addressed in the long term analysis of the extension phase of the EXIST-2 trial (e.g., absence of HRQoL and pain outcomes). The open-label extension provides supportive noncomparative evidence regarding the long-term efficacy and harms associated with everolimus, including angiomyolipoma-related clinical events such as bleeding, and a need for procedural interventions such as embolization.

Given that the extension study did not have a comparator, the clinical significance of angiomyolipoma reduction as a surrogate for renal bleeding may be inferred by observational data of the natural progressions of disease without active treatment. Risk of spontaneous rupture in renal angiomyolipomas is influenced by several factors, most importantly tumour size and aneurysm size. There is evidence to suggest that tumour size of at least 4 cm and aneurysm size of at least 5 mm are important predictors of rupture.[5,6] Although several studies have concluded that larger lesions are more susceptible to bleeding, raising the need for prophylactic management, there is no consensus on what size should be used as cut-off for prophylaxis.[37] The clinical expert noted that physicians do not wait for hemorrhage to occur, and patients get embolization (and recurrent embolization) before the occurrence of renal bleeding. The clinical expert further noted that while in clinical practice response related to renal angiomyolipoma is measured, it is important to consider that, in their opinion, the drug has other systemic benefits in terms of treating the other manifestations of TSC. Indeed, the EXIST-2 trial also demonstrated benefit on other manifestations of TSC, including skin lesions and SEGA, among patients being treated for renal angiomyolipomas.

For the pediatric population, the analysis of the subpopulation of pediatric patients with renal angiomyolipoma treated for SEGA in the EXIST-1 trial was based on a small number of patients (n = 33) with small angiomyolipoma lesions. More than 80% of the patients had a lesion size smaller than 3 cm. A higher angiomyolipoma response rate was reported in the pediatric analysis (76% versus 54% for adult patients in the EXIST-2 trial). This difference in response rates may be due to disease severity and length of follow-up. Patients in the EXIST-2 trial had more severe disease (i.e., target angiomyolipoma > 3 cm in the longest diameter in the EXIST-2 trial versus > 1 cm in the EXIST-1 trial) and outcomes were reported after a shorter duration of time (median = 28.9 months versus 44.8 months).[24]

Important limitations regarding the evidence presented on the efficacy and harms of everolimus in the pediatric population should be noted when interpreting the results. The findings are based on a post hoc analysis of a small subset of pediatric patients with renal angiomyolipomas who were being treated primarily for SEGA in the EXIST-1 trial, and the analyses were not adequately powered to assess this subgroup. In addition, these patients were selected into the trial based on serial SEGA growth and not based on the need for treatment of angiomyolipoma lesions; more than 80% of patients had angiomyolipomas smaller than 3 cm, which in some cases may not receive any intervention in clinical practice. Finally, the open-label design of the long-term extension phase and the lack of a comparator further limit conclusions regarding the long-term use of everolimus for treating renal angiomyolipomas in the pediatric population.

Treatment with everolimus is continuous. Until there is a tolerability issue, patients are continued on the systemic treatment with mTOR inhibitors. There were insufficient data from the trial to indicate if treatment with everolimus should be discontinued if angiomyolipoma size is reduced below a particular threshold or if treatment should be continuous. There was also uncertainty regarding the timing of initiating treatment with everolimus. The trial recruited patients with angiomyolipomas 3 cm or larger. However, as noted by the clinical expert for this review, the goal of systemic treatment with a mTOR inhibitor is to slow down angiomyolipoma growth and prevent or delay the need for surgical intervention and embolization.

**Harms**

All of the patients treated with everolimus and 97% of the patients receiving placebo experienced at least 1 AE, most of which were grade 1 or 2 and reversible. The longer-term safety profile of everolimus was consistent with what was previously reported, although it is difficult to distinguish between true everolimus side effects and AEs due to TSC after the placebo arm was discontinued. The most common AEs that occurred more frequently with everolimus than placebo were stomatitis, acne, and hypercholesterolemia. AEs were consistent with the mechanism of action of everolimus. Mouth ulcerations, for example, can be attributed to the downregulation of cellular turnover and are a known effect of mTOR inhibition. SAEs were reported for 19% of patients in the everolimus arm and 18% of patients in the placebo arm. Although infection is an identified risk in patients treated with everolimus, they occurred with similar frequency and severity in both treatment arms, most commonly upper respiratory infections. There were fewer withdrawals due to AEs with everolimus than with placebo (3% versus 10% of patients).

Renal events occurred in 20.5% of the 112 patients treated with everolimus for the 4-year update final analysis (median treatment duration = 46.9 months), compared to 5% of patients treated with everolimus and 15% of patients receiving placebo during the double-blind core phase of the trial (median treatment duration = 8.8 months and 7.8 months, respectively). The clinical expert consulted indicated that this could reflect longer duration of treatment, and the fact that this patient population are prone to CKD, and the worsening GFR for other reasons may have been included as events.

The AE profile in the subgroup of pediatric patients in the EXIST-1 trial was generally consistent with those in the adult population of the EXIST-2 trial. Although all patients had at least 1 AE, with convulsion, mouth ulceration, stomatitis, and cough being the most frequently reported events, grade 3 or 4 events occurred in no more than 4 patients (12.1%) each. Discontinuation due to an everolimus-related AE was reported in

2 patients (6%). Convulsions were frequently reported in this pediatric subpopulation (45.5%). This may be partly because all of these patients had SEGA with related neurologic symptoms; similar proportions of patients had convulsions in the everolimus and placebo arms during the primary core phase of the EXIST-1 trial (23% versus 26%).

**Cost**

In adult and adolescent patients, the annual cost of everolimus (5 mg or 10 mg daily, regular tablets) is $62,873 per patient in jurisdictions with more expensive wholesale pricing (Alberta, British Columbia, Nunavut, Northwest Territories, Ontario, Saskatchewan, Yukon), and $18,492 per patient in jurisdictions with less expensive wholesale pricing (Manitoba, New Brunswick, Newfoundland and Labrador, Nova Scotia, Prince Edward Island). For patients requiring a dose of 7.5 mg daily, the annual cost is expected to be $125,747 and $36,984 in jurisdictions with higher and lower pricing, respectively. The annual cost of sirolimus is $6,658 to $9,986 per adult or adolescent patient, depending on dose. As such, the use of everolimus for adult and adolescent patients with renal angiomyolipoma associated with TSC is more costly than sirolimus: in jurisdictions with more expensive wholesale pricing for everolimus, the incremental cost ranges from $52,887 to $119,089 per patient annually; in jurisdictions with less expensive wholesale pricing, the incremental cost ranges from $8,506 to $30,327 per patient annually. CADTH notes that sirolimus is not indicated for the treatment of renal angiomyolipoma associated with TSC and is not reimbursed for this indication by most public drug plans.

In younger pediatric patients, the annual cost of treatment with everolimus regular tablets (assuming 1 or 2 tablets daily) ranges from $62,873 to $125,747 per patient in jurisdictions with higher wholesale pricing and from $18,492 to $36,984 per patient in jurisdictions with lower wholesale pricing. In younger pediatric patients requiring everolimus oral suspension tablets, the annual cost of treatment ranges from $70,627 to $141,254 per patient. The annual cost of sirolimus is $1,664 to $9,986 per younger pediatric patient, depending on dose. As such, the use of everolimus regular tablets for younger pediatric patients with renal angiomyolipoma associated with TSC is more costly than sirolimus: in jurisdictions with more expensive wholesale pricing for everolimus, the incremental cost ranges from $52,887 to $124,082 per patient annually; in jurisdictions with less expensive wholesale pricing, the incremental cost ranges from $8,506 to $35,320 per patient annually. CADTH notes that the cost-comparison results pertaining to the younger pediatric population should be interpreted in light of the following caveats: sirolimus is not indicated for the treatment of renal angiomyolipoma associated with TSC or for pediatric patients younger than 13 years for any condition; sirolimus is rarely funded by public drug plans for the treatment of renal angiomyolipoma associated with TSC in pediatric patients; and the dose range of sirolimus for the pediatric population used in this review is based on initial pediatric doses reported in the literature and assumes later dosing will not exceed the usual dose of sirolimus used in adults with renal angiomyolipoma.

Costs are based on publicly available wholesale prices and may not reflect actual prices paid by Canadian public drug plans.

## Conclusions

Evidence from 1 trial (the EXIST-2 trial, n = 118) and its long-term, single-arm, open-label extension suggests a benefit of everolimus for achieving renal angiomyolipoma response and delaying angiomyolipoma progression in patients with TSC not requiring immediate surgery. The long-term analysis of the core phase and open-label extension phase of the trial show that angiomyolipoma response may be sustained over time with no additional or late-emerging toxicities. There was no comparative evidence available for the pediatric population, though the response rate appeared to mirror that of adults in a single-arm post hoc analysis of a small subset of pediatric patients with renal angiomyolipoma who were being treated for TSC-related SEGA. There is an unmet clinical need for systemic treatments for angiomyolipoma to address the multifocal nature of renal involvement and the multisystem nature of the disease itself. Current treatment strategies — embolization and surgical therapies — are often used in emergency situations, carry important risks, and do not prevent recurrence of renal angiomyolipomas or organ damage. Everolimus appears to meet a key treatment goal in patients with renal angiomyolipomas, which is prevention of renal bleeding and the need for renal intervention. However, the limitations of evidence considered in the previous CADTH Reimbursement Review — including reliance on surrogate end points and absence of important outcomes such as pain and HRQoL — are not fully addressed by the new long-term evidence, which is based on noncomparative data.

No literature was identified comparing everolimus with sirolimus; therefore, the comparative efficacy of these treatments is unknown. To effectively consider drug acquisition costs, health care resource implications, and comparative clinical benefits, a cost-effectiveness analysis of everolimus compared with sirolimus would be required. As a cost-effectiveness analysis was not available, the cost-effectiveness of everolimus in comparison with sirolimus for the treatment of renal angiomyolipoma associated with TSC could not be determined. Results of the cost comparison of drug acquisition costs demonstrate that everolimus is more costly than sirolimus for the treatment of renal angiomyolipoma associated with TSC. The incremental cost is dependent on the wholesale price of everolimus and the population treated (adults and adolescents or younger pediatric patients). For adult and adolescent patients with renal angiomyolipoma associated with TSC: in jurisdictions with more expensive wholesale pricing, the incremental cost of everolimus ranges from $52,887 to $119,089 per patient annually compared with sirolimus; in jurisdictions with less expensive wholesale pricing, the incremental cost of everolimus ranges from $8,506 to $30,327 per patient annually, compared with sirolimus. For younger pediatric patients: in jurisdictions with higher wholesale pricing, the incremental cost of everolimus ranges from $52,887 to $124,082 per patient annually; in jurisdictions with lower wholesale pricing, the incremental cost ranges from $8,506 to $35,320 per patient annually, compared to sirolimus. A price reduction of 84% to 89% would be required for the drug acquisition cost of everolimus to be equal to sirolimus in jurisdictions with higher everolimus pricing, while a price reduction of 46% to 64% would be required in jurisdictions with lower everolimus pricing.

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# Appendix 1: Literature Search Strategy

Note that this appendix has not been copy-edited.

## Clinical Literature Search

### Overview

**Interface**: Ovid

**Databases**:

- MEDLINE All (1946-present)
- Embase (1974-present)
- Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

**Date of search**: August 01, 2023

**Alerts**: Bi-weekly search updates until project completion

**Search filters applied**: No filters were applied to limit the retrieval by study type.

**Limits**:

- Publication date limit: none
- Language limit: none
- Conference abstracts: excluded

### Table 11: Syntax Guide

| Syntax | Description |
|---|---|
| / | At the end of a phrase, searches the phrase as a subject heading |
| MeSH | Medical Subject Heading |
| * | Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings |
| .ti | Title |
| .ot | Original title |
| .ab | Abstract |
| .hw | Heading word; usually includes subject headings and controlled vocabulary |
| .kf | Author keyword heading word (MEDLINE) |
| .dq | Candidate term word (Embase) |
| .pt | Publication type |

| Syntax | Description |
|---|---|
| .rn | Registry number |
| .nm | Name of substance word (MEDLINE) |

### MEDLINE Strategy

1. Everolimus/
2. (everolim* or afinitor* or affinitor* or aderolio* or advacan* or boletraaz* or certican* or certirobell* or ersteine* or evercan* or evergraf* or evermil* or everocan* or everofin* or evertor* or evrilus* or exher* or osys* or rocas* or rolimus* or sumirol* or verimmus* or votubia* or xilcator* or zortress* or "RAD 001" or RAD001 or RAD 001a or RAD001a or "nvp rad 001" or nvp rad001 or nvprad001 or rad 666 or rad666 or SDZ RAD or SDZRAD or 9HW64Q8G6G).ti,ab,kf,ot,hw,rn,nm.
3. or/1-2
4. Angiomyolipoma/
5. (angiomyolipoma* or angiomyo lipoma* or angio myolipoma* or AML or hemangiomyolipoma*).ti,ab,kf.
6. ((benign* or noncancerous* or non-cancerous*) and (renal* or kidney*) and (tumour* or tumor* or mass or masses or growth* or neoplasm*)).ti,ab,kf.
7. Tuberous Sclerosis/
8. (tuber* adj5 (sclerosis* or scleroses* or complex*)).ti,ab,kf.
9. ((sclerosis* or scleroses*) adj5 (complex* or cerebral*)).ti,ab,kf.
10. (Bourneville-Pringle* or Pringle-Bourneville* or epiloia* or TSC or hamartin*).ti,ab,kf.
11. ((Bourneville* or Pringle*) adj5 (disease* or syndrome* or disorder* or phakomatosis* or phacomatosis*)).ti,ab,kf.
12. ((tuberin* or TSC1 or TSC-1 or TSC2 or TSC-2) adj5 protein).ti,ab,kf.
13. (adenoma adj5 sebaceum*).ti,ab,kf.
14. or/4-13
15. 3 and 14

### Embase Strategy

1. *everolimus/
2. (everolim* or afinitor* or affinitor* or aderolio* or advacan* or boletraaz* or certican* or certirobell* or ersteine* or evercan* or evergraf* or evermil* or everocan* or everofin* or evertor* or evrilus* or exher* or osys* or rocas* or rolimus* or sumirol* or verimmus* or votubia* or xilcator* or zortress* or "RAD 001" or RAD001 or RAD 001a or RAD001a or "nvp rad 001" or nvp rad001 or nvprad001 or rad 666 or rad666 or SDZ RAD or SDZRAD).ti,ab,kf,dq.
3. or/1-2

4. angiomyolipoma/ or renal angiomyolipoma/ or angiomyolipoma cell line/ or renal epithelioid angiomyolipoma/ or benign renal tumor/
5. (angiomyolipoma* or angiomyo lipoma* or angio myolipoma* or AML or hemangiomyolipoma*).ti,ab,kf,dq.
6. ((benign* or noncancerous* or non-cancerous*) and (renal* or kidney*) and (tumour* or tumor* or mass or masses or growth* or neoplasm*)).ti,ab,kf,dq.
7. exp tuberous sclerosis/
8. (tuber* adj5 (sclerosis* or scleroses* or complex*)).ti,ab,kf,dq.
9. ((sclerosis* or scleroses*) adj5 (complex* or cerebral*)).ti,ab,kf,dq.
10. (Bourneville-Pringle* or Pringle-Bourneville* or epiloia* or TSC or hamartin*).ti,ab,kf,dq.
11. ((Bourneville* or Pringle*) adj5 (disease* or syndrome* or disorder* or phakomatosis* or phacomatosis*)).ti,ab,kf,dq.
12. ((tuberin* or TSC1 or TSC-1 or TSC2 or TSC-2) adj5 protein).ti,ab,kf,dq.
13. (adenoma adj5 sebaceum*).ti,ab,kf,dq.
14. or/4-13
15. 3 and 14
16. 15 not (conference abstract or conference review).pt.

### Clinical Trials Registries

#### *ClinicalTrials.gov*

Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials.

[Search -- Studies with results | (everolimus AND angiomyolipoma) OR (everolimus AND tuberous sclerosis)]

#### *WHO ICTRP*

International Clinical Trials Registry Platform, produced by the WHO. Targeted search used to capture registered clinical trials.

[Search terms -- (everolimus or afinitor or certican OR votubia) AND (angiomyolipoma OR tuberous sclerosis)]

#### *Health Canada's Clinical Trials Database*

Produced by Health Canada. Targeted search used to capture registered clinical trials.

[Search terms -- everolimus]

#### *EU Clinical Trials Register*

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms -- everolimus AND tuberous sclerosis]

### *EU Clinical Trials Information System (CTIS)*

European Union Clinical Trials Information System, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms -- everolimus AND tuberous sclerosis]

## Grey Literature

**Search dates**: July 19, 2023 – August 01, 2023

**Keywords**: [everolimus, afinitor, certican, votubia, angiomyolipoma, tuberous sclerosis, TSC]

**Limits**: Publication years: none

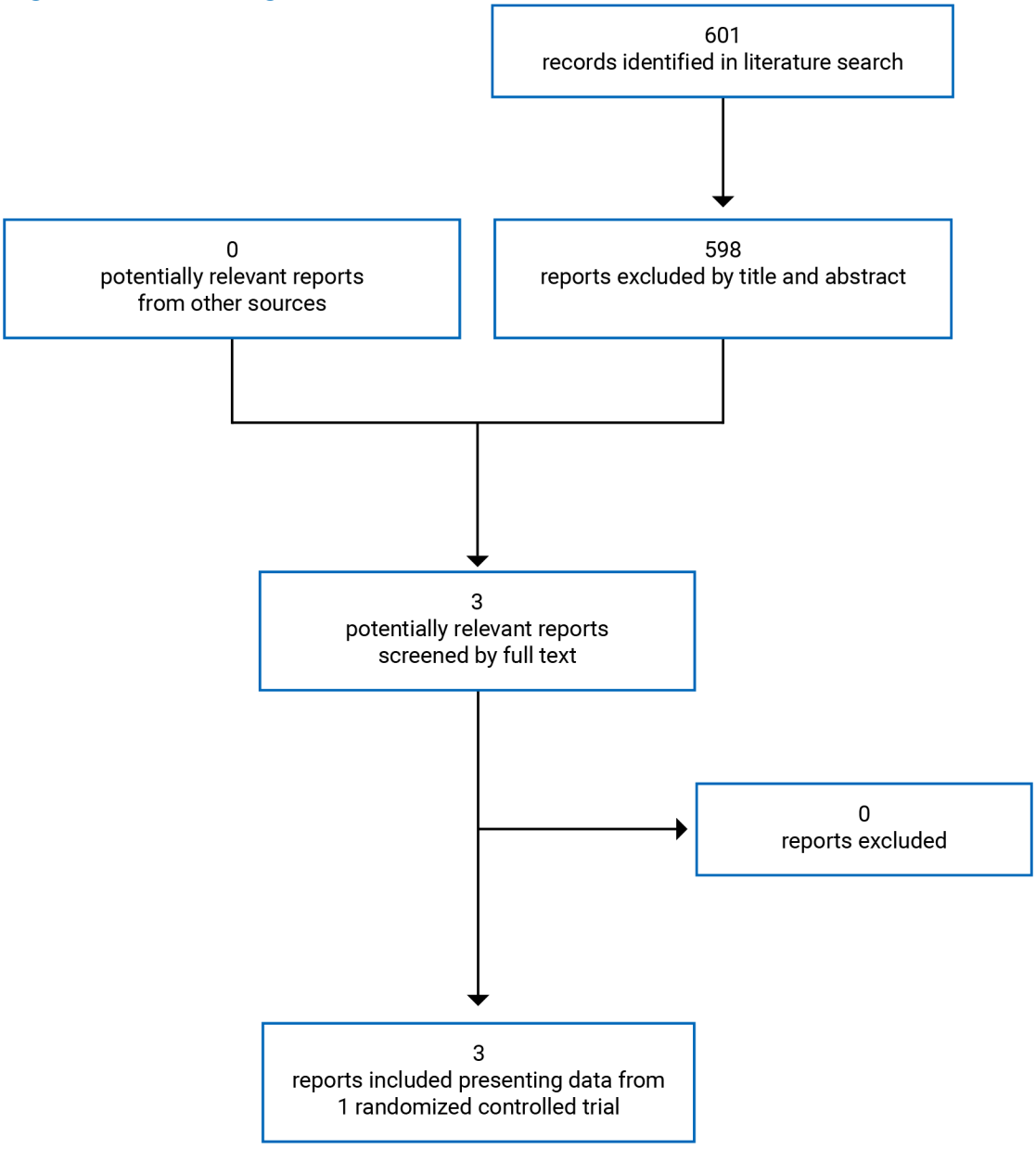
**Updated**: Search updated before FMEC

Relevant websites from the following sections of the CADTH grey literature checklist Grey Matters: A Practical Tool for Searching Health-Related Grey Literature were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Databases (free)
- Internet Search

# Appendix 2: Study Selection

## Figure 6: Flow Diagram for Inclusion and Exclusion of Studies



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