CDA-AMC
Canada's Drug Agency
L'Agence des médicaments du Canada

Drugs Health Technologies Health Systems

Reimbursement Review

Everolimus

(Nonsponsored Review)
Therapeutic area: Tuberous sclerosis complex

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Abbreviations

AE	adverse event
BSA	body surface area
CDA-AMC	Canada's Drug Agency
CDEC	Canadian Drug Expert Committee
CI	confidence interval
FMEC	Formulary Management Expert Committee
IQR	interquartile range
ITC	indirect treatment comparison
mTOR	mammalian target of rapamycin
SAE	serious adverse event
SEGA	subependymal giant cell astrocytoma
SEN	subependymal nodule
TAND	TSC-associated neuropsychiatric disorders
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 patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) that have demonstrated serial growth, who are not candidates for surgical resection and for whom immediate surgical intervention is not required
Indication under consideration for reimbursement	Same as indication
Health Canada approval status	NOC
NOC date	November 3, 2014
Requester	Formulary Working Group

NOC = Notice of Compliance.

Introduction

Tuberous sclerosis complex (TSC) is a rare, autosomal-dominant, genetic disorder with an incidence of 1 in 6,000 to 1 in 10,000.[1-3] TSC affects 3,500 individuals in Canada.[4] The disease is characterized by the development of nonmalignant tumours across multiple organ systems. The most common manifestations of TSC are neurologic, followed by renal and pulmonary symptoms.[5] Neurologic manifestations are present in up to 90% of patients and include subependymal nodules (SENs), malformations of the cerebral cortex (tubers), subependymal giant cell astrocytomas (SEGAs), epilepsy, and TSC-associated neuropsychiatric disorders (TAND), which include hyperactivity, aggression, intellectual disability, and autism spectrum disorder.[5] SEGAs, which are benign glioneural brain tumours, are observed in up to 20% of patients with TSC, almost exclusively in the first 2 decades of life,[6-9] and are identified by serial growth or association with hydrocephalus on neuroimaging studies.[10,11] Although often asymptomatic and slow-growing, SEGAs can reach sufficient size to cause symptoms from ventricular obstruction and hydrocephalus, and they may require surgery. Although minimally invasive surgical techniques have led to better outcomes, these procedures are associated with considerable risks as well as postoperative complications.[12] An important goal of treatment in patients with TSC-related tumours, including SEGAs, is to stop or ytumour growth to eliminate the need for surgical intervention.

The management of TSC-related SEGAs depends on the clinical signs and symptoms of the individual. Patients with a SEGA presenting with acute deterioration due to obstructive hydrocephalus, or tumoural hemorrhage, undergo urgent surgical treatment.[13] Treatment with mammalian target of rapamycin (mTOR) inhibitors, such as sirolimus and everolimus, is recommended for individuals with asymptomatic growing or large SEGAs, as well as for those who are not surgical candidates or prefer medical treatment over surgery.[13] The clinical experts consulted by Canada's Drug Agency (CDA-AMC) indicated that, currently in Canada, the

standard of care for patients with TSC-related SEGA that does not require immediate surgery is treatment with an mTOR inhibitor.

In 2015, we completed a reimbursement review of everolimus for the treatment of SEGA associated with TSC, and the Canadian Drug Expert Committee (CDEC) recommended that everolimus not be reimbursed for this indication, noting insufficient evidence regarding the benefit of everolimus for improving quality of life and other clinical outcomes, including seizure frequency, hydrocephalus, and need for neurosurgery, as well as lack of data on long-term safety and uncertain cost-effectiveness.[14] Everolimus for TSC-related renal angiomyolipomas was also initially reviewed by CDA-AMC in 2013 with a similar recommendation not to reimburse.[15] In 2023, we received requests from caregivers of patients with TSC-related renal angiomyolipomas to conduct a new review of everolimus for the treatment of renal angiomyolipomas in light of new data not available at the time of the original reimbursement review. We conducted a new review of the evidence, and the Formulary Management Expert Committee (FMEC) recommended that everolimus be reimbursed for the treatment of TSC-related angiomyolipomas.[16] Subsequently, the Formulary Working Group requested that we also review everolimus for the treatment of TSC-related SEGA, identify new evidence since the original review, and provide a reimbursement recommendation for this indication.

The clinical and pharmacoeconomic evidence for the review is based on the CDA-AMC Nonsponsored Reimbursement Review process. The review includes an appraisal of the clinical evidence and a comparison of 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 SEGA associated with TSC.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to our call for patient input, clinical experts consulted by CDA-AMC for the purpose of this review, and the drug programs. No input was received from clinician groups or from industry for the purpose of this review.

Patient Input

One patient group, Tuberous Sclerosis Canada Sclérose Tubéreuse, provided input for this review. Information was gathered from patients and caregivers in Canada via a survey in September 2023. There were 11 respondents to the survey, of whom 4 had children living with SEGAs. All respondents commented on the stress of not knowing when or how much a SEGA would grow or what the outcomes would be. Although SEGA is typically slow-growing, it can grow and become potentially life-threatening between MRI scans and doctor visits. The respondents said that having a SEGA is like living with a time bomb — you do not know when it will cause an emergency. Parents whose child has a SEGA live with this fear every day. The respondents also mentioned the burden of repeated MRI scans, especially with sedation, and the constant fear they feel about their children needing brain surgery, either an initial operation or repeated operations.

Clinician Input

Input From Clinical Experts We Consulted

Two clinical specialists with expertise in the diagnosis and management of TSC provided input. No input was received from clinician groups.

The clinical experts consulted for this review indicated that the goals of treatment for patients with TSC-related SEGA are prevention and elimination of symptoms of hydrocephalus and of secondary permanent disability due to hydrocephalus, as well as prevention of further growth of SEGA, progression of disease, and need for neurosurgery in emergency situations. Maintaining health with noninvasive treatment is an important goal in this patient population, who may already be affected by several other features of the disease. These treatment goals are not met by surgical intervention, which is invasive, often risky, stressful to families, and traumatizing for children. Moreover, no treatments are available to reverse the course of the disease and interact with the underlying pathological mechanism of the disease. mTOR inhibitors are currently the only noninvasive treatment that can target the underlying disease mechanism of TSC and SEGA. They also have a secondary benefit for other disease manifestations, such as renal angiomyolipomas.

Patients most likely to benefit from everolimus are those with multiple lesions (SEGAs), large SEGAs not accessible to minimally invasive surgery, SEGAs with difficult attachment (which pose a high risk for morbidity from surgery), small lesions that do not yet require surgery but have potential to grow and cause future damage (to prevent disease progression), and patients with prior incomplete resection (to prevent regrowth). Treatment response is typically assessed via MRI to assess SEGA size. Evaluating response to treatment also involves evaluating indirect effects, including seizure control and progression of disease in other organs, including the kidneys, lungs, and skin. The standard of practice for screening and follow-up is MRI (every 1 to 3 years) for screening after TSC diagnosis and more intense follow-up (every 6 months) when small SEGAs are suspected.

Drug Program Input

The drug plans highlighted that the EXIST-1 trial was placebo-controlled, as there are no pharmacological therapies other than mTOR inhibitors for SEGA. The drug plans also asked questions about outcomes and appropriate assessments to determine drug efficacy in clinical practice and whether everolimus may be discontinued in patients who have no disease progression. The implementation questions and corresponding responses from the clinical experts we consulted is available online.

Clinical Evidence

Protocol Selected Studies

Description of Studies

The main evidence base for this review was the EXIST-1 trial, a randomized, double-blind, placebo-controlled, phase III trial of oral everolimus (n = 78) versus placebo (n = 39) in patients with SEGA associated with TSC. Patients were treated for 6 months in the double-blind phase and up to 5 years in the open-label extension phase. The primary outcome was the proportion of patients with a SEGA response, defined as a reduction of 50% of target SEGA volume, in the absence of worsening nontarget SEGAs, new

lesions of at least 1 cm in diameter, and new or worsening hydrocephalus. Five studies reporting results of the EXIST-1 trial were included. This included 1 report of the core double-blind phase and 2 reports of the extension phase, with 2-year interim and 5-year final analyses. Two additional reports on subgroups of patients aged younger than 3 years in the EXIST-1 trial, 1 reporting on the effects of everolimus on epilepsy and growth and the other reporting on harms of everolimus in this pediatric population, were also included.

Efficacy Results

Tumour Response

In the double-blind core phase of the EXIST-1 trial, 27 of 78 patients (35%) in the everolimus arm and none of the 39 patients in the placebo arm had a SEGA response (difference = 35%; 95% confidence interval [CI], 15% to 52%; 1-sided exact Cochran-Mantel-Haenszel test, $P < 0.0001$). At the 2-year interim analysis, 54 of 111 patients treated with everolimus (49%; 95% CI, 39% to 58%), which included patients originally randomized to the everolimus group and patients who were randomized to placebo who crossed over to receive everolimus, showed a SEGA response. At the 5-year final analysis, 57.7% of patients (95% CI, 47.9% to 67.0%) showed a SEGA response.

Tumour Progression

In the double-blind core phase, 6 patients, all in the placebo arm, had progression of SEGAs. At the 2-year interim analysis 9 patients (8%), all of whom had been treated with everolimus, had SEGA progression. At the 5-year final analysis, 13 patients (11.7%) had SEGA progression at any time during the study.

Time to Tumour Progression

In the double-blind core phase, the median time to tumour progression was not reached in either treatment arm, but the estimated progression-free rates at 6 months were 100% for everolimus and 86% for placebo ($P = 0.0002$). At the 5-year final analysis, because of the low number of SEGA progressions, median time to SEGA progression could not be determined. The progression-free survival rate at 3 years after treatment initiation was 88.8% (95% CI, 80.6% to 93.6%).

Episodes of Acute Hydrocephalus

Episodes of hydrocephalus were not reported. Although the absence of new or worsening hydrocephalus was required for classifying patients as SEGA responders, episodes of hydrocephalus were not reported separately. At the time of the 2-year open-label extension analysis, 1 patient developed hydrocephalus in the absence of SEGA growth (this patient had a SEGA volume reduction larger than 70%), and the hydrocephalus resolved with continued everolimus treatment.

Need for Neurosurgery

No patient required surgery for SEGA progression during the double-blind core phase of the study. One patient required neurosurgery during the open-label extension phase.

Pediatric Patients Aged Under 3 Years

Eight children (2 girls and 6 boys) aged under 3 years from a participating centre of the EXIST-1 trial who received everolimus were included in this analysis. In all of the children, everolimus treatment was introduced before 3 years of age (range, 12 to 35 months; mean 24.1 months). In 6 out of 8 children, a reduction in SEGA volume of at least 50% was observed. In 1 child with drug-resistant epilepsy, everolimus treatment resulted in cessation of seizures, and, in 2 other children, reduction in the number of seizures of at least 50% was noted.

Harms Results

During the double-blind core phase of the EXIST-1 trial, 96% of patients in the everolimus arm and 90% of patients in the placebo arm had at least 1 adverse event (AE). The most common AEs were mouth ulceration, stomatitis, convulsion, and pyrexia. Forty-nine percent of patients in the everolimus arm and 10% in the placebo arm had AEs requiring dose reduction or temporary interruption of treatment; the most common were stomatitis (17% of patients in the everolimus arm and 3% in the placebo arm), mouth ulceration (8% versus 0), pyrexia (6% versus 3%), and pneumonia (5% versus 0). No AEs led to discontinuation from the study, and no patients died during the study.

At the 2-year interim analysis, mouth ulceration (30% of patients) and stomatitis (43% of patients) were the 2 most frequently reported AEs. Six patients (5%) discontinued the study drug as a result of a total of 8 AEs (1 case each of *Acinetobacter* bacteremia, aggression, anemia, increased blood alkaline phosphatase concentrations, neutropenia, pneumonia, sinusitis, and viral infection).

At the long-term final analysis, all but 1 patient (99.1%) experienced an AE during the long-term phase of the study. The most common AEs (by preferred term) suspected to be treatment-related in more than 10% of patients were stomatitis (43.2%), mouth ulceration (32.4%), pneumonia (13.5%), blood cholesterol level increase (11.7%), hypercholesterolemia (11.7%), nasopharyngitis (10.8%), and pyrexia (10.8%). Among all patients, 36.0% experienced a grade 3 treatment-related AE. The most common grade 3 AEs, experienced by at least 5% of patients, were stomatitis (10.8%), pneumonia (8.1%), and neutropenia (5.4%). Five patients (4.5%) experienced grade 4 AEs, which included neutropenia (2 patients, 1.8%), pneumonia, febrile infection, gastroenteritis, and pneumothorax (1 patient each, 0.9%); febrile infection and gastroenteritis occurred in the same patient. Most patients (91.0%) required at least 1 dose interruption or reduction during the study, mainly due to AEs (72.1%).

No deaths were reported at the 2-year interim analysis. One death (accidental asphyxiation) was reported at the time of the final analysis, and it was not suspected by the investigator to be related to treatment.

Pediatric Patients Aged Under 3 Years

In the analysis of long-term safety of everolimus in 18 patients aged younger than 3 years (median age 1.82 years) from the EXIST-1 trial, AEs were reported in all 18 patients (100%). Most AEs were considered by the investigator to be grade 1 or grade 2 in severity. The most common AEs, regardless of relationship to study medication, were stomatitis, cough, pharyngitis, and pyrexia. Fourteen patients (77.8%) experienced grade 3 or 4 AEs, which were suspected to be related to everolimus in 11 patients (61.1%). Serious adverse events

(SAEs) were reported in 50.0% of the patients and consisted of pneumonia in 16.7%, and pyrexia, bronchitis, upper respiratory tract infection, and convulsion in 11.1% of patients each. Infections and infestations occurred in all patients, followed by stomatitis and related events in 12 patients (66.7%), and cytopenia in 5 patients (27.8%). The dose was reduced or interrupted for 17 patients (94.4%), and all patients (100.0%) required additional therapy because of AEs.

There were no deaths.

Other Relevant Evidence

Description of Studies

Two studies, both nonrandomized, single-arm trials, were included in this section. These are studies that did not meet the prespecified literature search protocol (because they were noncomparative) but were deemed important, as they reported additional data on long-term safety outcomes. Study 2485 was a single-centre, phase I and II, single-arm study conducted at 1 hospital in the US that recruited 28 patients aged 3 years and older treated with everolimus. The trial had an initial 6-month treatment phase and an extension phase that followed patients for up to 5 years. The primary outcome was change from baseline in volume of the primary SEGA lesion after 6 months of treatment with the study drug. The second study, EFFECTS, was an open-label, phase IIIb, single-arm, multicentre, expanded-access study of everolimus for the treatment of 120 patients aged 3 years and older with SEGA associated with TSC who should not have participated in the EXIST-1 study.

Efficacy Results

Study 2485

Tumour Response

During the core 6-month treatment phase, 9 patients (32%) had reductions of 50% or more in SEGA volume relative to baseline; 21 patients (75%) had at least a 30% reduction in tumour volume. At the 3-year analysis, primary SEGA volume was reduced by at least 30% from baseline in 79.2%, 64.7%, and 77.8% of patients at 24, 30, and 36 months, respectively, and by at least 50% from baseline in 50.0%, 41.2%, and 55.6% of patients, respectively. Nine patients had between 30% and 50% reduction in primary SEGA volume within 6 months. In the 5-year long-term follow-up, 82.1% of patients were noted to have a 50% or greater reduction in primary SEGA volume relative to baseline at some point during the treatment period.

Tumour Progression

Tumour progression was not reported.

Time to Tumour Progression

At the final long-term analysis, among the 23 patients with at least a 50% reduction in primary SEGA volume at any time, 95.7% were progression-free at their last radiological assessment before the data cut-off date, initiation of further systemic anti-SEGA therapy, or study discontinuation.

Episodes of Acute Hydrocephalus

No patient had worsening hydrocephalus or worsening symptoms attributable to increased intracranial pressure as a result of the reduction in volume of the SEGA. No new lesions developed, and no patient needed to undergo surgical resection or other therapy for the tumour.

Need for Neurosurgery

No patients required surgery for a SEGA during the treatment period.

EFFECTS

Efficacy was not the primary objective of this study. The primary objective of the study was to evaluate the safety of everolimus in patients with SEGA associated with TSC.

Harms Results

Study 2485

All patients had at least 1 AE during the core phase of the trial. Stomatitis and upper respiratory tract infections were the most common (79% of patients each). Grade 3 AEs were reported in 10 patients, and 1 grade 4 event (convulsion) occurred in 1 patient. Four patients had SAEs. No new safety signals were noted during the extension phase of the trial; all patients reported at least 1 AE, and all patients experienced at least 1 AE that was suspected to be related to treatment. The type, incidence, and severity of AEs reported by the new cut-off date were similar to those reported in the primary treatment phase. Six patients experienced 9 SAEs, 3 of which were suspected to be related to everolimus: 1 patient with pneumonia, 1 patient with viral bronchitis, and 1 patient with an abscess of the right leg (all grade 3 reactions). The SAEs were managed by hospitalization, concomitant drug therapy, and interruption of everolimus therapy or dose reduction. There was no treatment discontinuation due to AEs. There was 1 death reported for the 5-year analysis.

EFFECTS

In the EFFECTS study, 74.2% of patients had at least 1 AE. The most common AEs were aphthous stomatitis (18%), pyrexia (18%), bronchitis (9.2%), and stomatitis (8.3%). Grade 3 and 4 AEs were reported in 20.8% and 2.5% of patients, respectively. The most frequent grade 3 AE was stomatitis (3.3%). Grade 4 AEs included acute respiratory failure, gastroenteritis, increased gamma-glutamyltransferase, near drowning, and aspiration pneumonia. SAEs were reported in 26.7% of patients. The most common SAEs were pyrexia (4.2%) and bronchitis (2.5%). A total of 29 patients (24.2%) had AEs leading to hospitalization or prolonged hospitalization. Of these, 23 were pediatric patients. The most frequent AEs were pyrexia (4 patients) and bronchitis (3 patients), followed by gastroenteritis, viral gastroenteritis, pneumonia, sinusitis, diarrhea, stomatitis, hydrocephalus, status epilepticus, and ovarian cyst (2 patients each).

In the pediatric subpopulation, 74.4% of patients experienced AEs. Of these, 23.3% of patients had grade 3 AEs and 2.2% of patients had grade 4 AEs. The most frequent grade 3 AE was stomatitis (4 patients, 4.4%). All the other grade 3 or 4 AEs were reported in 1 patient each. Grade 4 AEs included acute respiratory failure, gastroenteritis, near drowning, and aspiration pneumonia.

Table 2: Overview of Included Studies

Study	Patient age (years) in analysis population	N	Trial phase (analysis)	Author (year)	Included in previous CDA-AMC review?
EXIST-1 (Phase III, double-blind, placebo-controlled, multicentre)	0 to 65	117	Core double-blind phase	Franz et al. (2013)[17]	Yes
	0 to 65	111	Open-label extension phase (2-year interim analysis)	Franz et al. (2014)[18]	No
	0 to 65	111	Open-label extension phase (5-year final analysis)	Franz et al. (2016)[19]	No
	< 3	8	Subgroup analysis (aged under 3 years)	Kotulska et al. (2013)[19]	No
	< 3	18	Subgroup analysis (aged under 3 years)	Jozwiak et al. (2016)[20]	No
Study 2485 (Phase I and II, open-label, noncomparative, single-centre)	≥ 3	28	Core phase	Krueger et al. (2010)[21]	Yes
	≥ 3	25	Extension phase (3-year analysis)	Krueger et al. (2013)[22]	Yes
	≥ 3	22	Extension phase (5-year final analysis)	Franz et al. (2015)[23]	No
EFFECTS (Phase IIIb, open-label, noncomparative, multicentre, expanded-access)	≥ 3	120	Safety	Fogarasi et al. (2016)[24]	No

CDA-AMC = Canada's Drug Agency.

Critical Appraisal

The EXIST-1 study was a double-blind trial; patients were given masked study treatment, and the primary outcome was adjudicated by central radiological review. Patients were masked to study treatment (identical everolimus and placebo) unless the study drug was discontinued due to unacceptable toxicity during the double-blind core phase. There is a potential that patients could have become unblinded due to the imbalances in known harms of everolimus across treatment groups. The baseline characteristics were mostly balanced between treatment arms. The primary end point of the EXIST-1 trial was SEGA response, which is considered an important outcome in this setting.

The inclusion and exclusion criteria of the EXIST-1 trial were clinically relevant, and the administration of everolimus in the EXIST-1 trial was consistent with common practice. The clinical expert noted that as, in the trial, dose adjustments are often made based on tolerability. The final analyses provide long-term data regarding the efficacy and harms of everolimus. Although important, these are based on the open-label extension phase, which lacked a randomized comparison group.

Both Study 2485 and the EFFECTS study were nonrandomized, single-arm studies. Therefore, no interpretation regarding the comparative efficacy and safety of everolimus can be made.

Cost Information

In adult and pediatric patients, the annual cost of everolimus (5 mg or 10 mg daily, regular tablets) is $62,873 per patient in jurisdictions with more costly wholesale pricing, and $18,492 per patient in jurisdictions with less costly wholesale pricing. For patients requiring a dosage of 7.5 mg daily, the annual cost is expected to be $125,747 and $36,985 in jurisdictions with higher and lower pricing, respectively. For patients requiring everolimus tablets for suspension, the annual per-patient cost ranges from $70,627 to $141,254. The annual cost of sirolimus in the adult patient population ranges from $6,891 to $10,337, depending on dosage, while the annual cost of sirolimus in the pediatric patient population varies between $1,723 and $10,337, also depending on dosage.

Thus, the use of everolimus for adult patients with SEGA associated with TSC is more costly than sirolimus. In jurisdictions with more costly wholesale pricing for everolimus, the incremental cost ranges from $52,537 to $118,856 per patient annually, and, in jurisdictions with less costly wholesale pricing, the incremental cost ranges from $8,155 to $30,093 per patient annually. As the annual cost of sirolimus varies between $1,723 and $10,337 per pediatric patient, in jurisdictions with more costly wholesale pricing for everolimus, the incremental cost ranges from $52,537 to $124,024 per patient annually, and, in jurisdictions with less costly wholesale pricing, the incremental cost ranges from $8,155 to $35,262 per patient annually. Finally, the incremental cost of everolimus tablets for suspension compared to sirolimus ranges from $60,290 to $139,531 in pediatric patients, and from $60,290 to $134,363 in adult patients. Costs are based on publicly available wholesale prices and may not reflect actual prices paid by public drug plans in Canada.

Conclusions

Evidence from the EXIST-1 trial suggests a benefit of everolimus for increased SEGA response and delayed SEGA progression in patients with TSC not requiring immediate surgery compared with placebo. The long-term analysis of the core phase and open-label extension phase of the trial suggests sustained SEGA response over time, with no additional or late-emerging toxicities. However, the analysis was limited by a small sample size and lack of a randomized comparator. There is an unmet clinical need for systemic treatments for SEGA associated with TSC to address the multisystem nature of the disease. For growing SEGAs that are asymptomatic, either surgery or mTOR inhibitors can be considered. However, surgical resection is highly burdensome to patients, carries significant risks, and does not prevent recurrence of SEGAs. Everolimus appears to meet a key treatment goal in patients with SEGAs, which is to slow down tumour growth or reduce tumour size and prevent the need for surgical intervention. There is no evidence to inform the benefits and harms of everolimus compared with sirolimus among patients with SEGAs associated with TSC.

The comparison of drug-acquisition costs demonstrates that everolimus is more costly than sirolimus for the treatment of SEGA associated with TSC. The incremental cost is dependent on the wholesale price of everolimus and the population treated (adult or pediatric patients). For adult patients with SEGA associated with TSC, in jurisdictions with more costly wholesale pricing, the incremental cost of everolimus ranges from $52,537 to $118,856 per patient annually compared with sirolimus; in jurisdictions with less costly wholesale pricing, the incremental cost of everolimus ranges from $8,155 to $30,093 per patient annually compared

with sirolimus. For pediatric patients, in jurisdictions with higher wholesale pricing, the incremental cost of everolimus ranges from $52,537 to $124,024 per patient annually; in jurisdictions with lower wholesale pricing, the incremental cost ranges from $8,155 to $35,262 per patient annually compared to sirolimus.

Based on the clinical review conclusions, no literature was identified comparing everolimus with sirolimus. Therefore, the comparative clinical efficacy of these treatments is unknown. Hence, based on publicly available pricing information, everolimus is associated with incremental drug-acquisition costs and unknown clinical benefit compared with sirolimus.

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 that are involved in the mTOR cell signalling.[5] In about one-third of cases, an affected person inherits a mutation in the *TSC1* or *TSC2* gene from a parent who has the disorder, while the remaining two-thirds of individuals with TSC are born with new variants in the *TSC1* or *TSC2* gene.[25] The incidence of TSC is between 1 in 6,000 to 1 in 10,000, according to different estimates.[1-3] TSC affects 3,500 individuals in Canada.[4] The disease is characterized by the development of nonmalignant tumours across multiple organ systems, including the brain, eyes, heart, lung, liver, kidney, and skin, and is highly variable in its expression in terms of age of onset, severity of disease, and symptoms. Different clinical features of the disease can manifest over the course of an individual's life; many individuals with TSC show signs of the disorder as early as the first year of life.[5,13] Given the complexities and variety of manifestations across the lifespan, TSC presents a severe physical, mental, and financial burden to both the individuals with TSC and their caregivers. The diagnosis of TSC can be made clinically or through genetic testing, but genetic testing is recommended, where available, to support a clinical diagnosis.[2,13] Although most TSC-related tumours are benign, many manifestations can be associated with severe morbidity and, potentially, death. Therefore, early diagnosis and appropriate lifetime management are essential to achieve optimal outcomes, as all individuals with TSC are at risk for life-threatening conditions related to the brain tumours and kidney or lung lesions.[13]

The most common manifestations of TSC are neurologic, followed by renal and pulmonary symptoms. Neurologic manifestations are present in up to 90% of patients and include subependymal nodules (SENs), malformations of the cerebral cortex (tubers), SEGA, epilepsy, and TAND, which is broad and may include hyperactivity, aggression, intellectual disability, and autism spectrum disorder.[5] SEGAs, which are benign glioneural brain tumours, are observed in up to 20% of patients with TSC, almost exclusively in the first 2 decades of life.[6-9] They typically occur either unilaterally or bilaterally in the region of the foramen of Monro and are identified by serial growth or association with hydrocephalus on neuroimaging studies.[10,11] SEGAs rarely invade the brain parenchyma; more typically, the tumours project into the ventricle and may cause acute or subacute hydrocephalus by obstructing the cerebrospinal fluid through the foramen of Monro.[5] Although often asymptomatic and slow-growing, SEGAs can reach sufficient size to cause symptoms from

ventricular obstruction and hydrocephalus, and they may require surgery. Although minimally invasive surgical techniques have led to better outcomes, these procedures are associated with considerable risks as well as postoperative complications.[12] Therefore, careful management, including periodic neuroimaging, every 1 to 3 years, is recommended to screen for SEGA occurrence, even in the absence of symptoms, to enable early intervention.[2,13] An important goal of treatment in patients with TSC-related tumours, including SEGA, is to stop or slow down tumour growth to eliminate the need for surgical intervention.

Standards of Therapy

The management of TSC-related SEGA depends on the clinical signs and symptoms of the individual. The International Tuberous Sclerosis Complex Consensus Group recommends that patients with SEGA presenting with acute deterioration due to obstructive hydrocephalus, or tumoural hemorrhage, should undergo urgent surgical treatment.[13] Treatment with mTOR inhibitors, such as sirolimus and everolimus, is primarily recommended for individuals with asymptomatic growing or large SEGAs, those with mild to moderate symptoms (including asymptomatic ventriculomegaly), and those who are not surgical candidates or prefer medical treatment over surgery.[13] mTOR inhibitors may also be favoured for potential benefit to treat additional manifestations of TSC that frequently coexist in patients with SEGA, such as medically refractory epilepsy or renal angiomyolipoma.[13]

The clinical experts we consulted indicated that, currently in Canada, the standard of care for patients with TSC-related SEGAs that do not require immediate surgery is treatment with an mTOR inhibitor. Everolimus has been used since 2005 (through special-access programs) to treat SEGA. Its efficacy and acceptable side-effect profile has positioned it as the main therapeutic option and current standard of practice for SEGAs that do not require urgent surgery. However, medical treatment with an mTOR inhibitor is not always possible due to lack of availability or coverage of mTOR inhibitors. The approach in the care of patients with TSC in Canada currently entails regular screening for SEN and SEGA; watchful waiting in the absence of SEGAs or presence of very small SEGAs; and increased monitoring with MRI, referral to surgery for discussion, and consideration of mTOR inhibitor treatment for confirmed small SEGAs. For patients who are clinically symptomatic or have signs of hydrocephalus from larger or confirmed SEGAs, rapid surgical intervention is needed. mTOR inhibitor treatment may also be considered as adjunctive treatment before and after surgical intervention to decrease lesion size before surgery or to treat remaining SEGAs.

Drug

Everolimus is a rapamycin derivative that inhibits the mTOR pathway by acting on the mTOR complex 1 (mTORC1). Everolimus is indicated for a variety of neoplasms, including breast cancer (human epidermal growth factor receptor 2–negative), metastatic renal cell carcinoma, and pancreatic neuroendocrine tumours. For TSC, everolimus is indicated for the treatment of patients with SEGA (aged > 1 year) associated with TSC that have demonstrated serial growth, who are not candidates for surgical resection and for whom immediate surgical intervention is not required, and for the treatment of adult patients (aged ≥ 18 years) with renal angiomyolipoma associated with TSC who do not require immediate surgery.[26]

For SEGAs associated with TSC, everolimus dose selection and dose adjustments are individualized (based on body surface area [BSA], in square metres) and must be done in conjunction with therapeutic drug monitoring. The recommended starting daily dose for all patients with SEGAs is 4.5 mg/m^2.[26] Titration may be required to attain target everolimus trough concentrations (5 ng/mL to 15 ng/mL, subject to tolerability), and further titration may be needed to obtain the optimal therapeutic effect within this range.

In 2015, we completed a reimbursement review of everolimus for the treatment of SEGA associated with TSC, and CDEC recommended that everolimus not be reimbursed for this indication. The committee noted insufficient evidence regarding the benefit of everolimus for improving quality of life and other clinical outcomes, including seizure frequency, hydrocephalus, and the need for neurosurgery, as well as lack of data on long-term safety and uncertain cost-effectiveness.[14] Everolimus for TSC-related angiomyolipomas was also initially reviewed by CADTH in 2013, and CDEC issued a similar recommendation not to reimburse, based on insufficient evidence regarding clinical outcomes and long-term safety.[15] In 2023, we received a request from caregivers of patients with TSC and renal angiomyolipomas to conduct a new review of everolimus for the treatment of TSC-related renal angiomyolipomas, in light of new data and long-term studies that were not available at the time of the original reimbursement review in 2013. We conducted a new review of the evidence, and, in April 2024, FMEC issued a recommendation that everolimus be reimbursed (with conditions) for the treatment of angiomyolipomas in patients with TSC.[16] Following that review, the Formulary Working Group requested that the evidence for everolimus in the treatment of SEGA in patients with TSC also be reviewed again to include new evidence since the original review for this indication.

Stakeholder Perspectives

Patient Group Input

This section was prepared by CDA-AMC staff based on the input provided by patient groups. The full patient group input is posted on the CDA-AMC website.

One patient group, Tuberous Sclerosis Canada Sclérose Tubéreuse, provided input for this review. Information regarding SEGA, kidney angiomyolipomas, and seizures was gathered from patients and caregivers in Canada through a member survey conducted in September 2023. Eleven responses were received. Among the 11 respondents to the survey, 4 had lived experience with SEGAs in their children. All commented on the stress of not knowing when or how much a SEGA would grow or what the outcomes would be. Although SEGA is typically slow-growing, it can reach emergency status between MRI scans and doctor visits. The respondents said that having a SEGA is like living with a time bomb — you do not know when it will cause an emergency, but you know it likely will. This is a hugely stressful way to live. Parents whose child has a SEGA live with this fear every day.

With regard to their experiences with how TSC-related SEGAs are currently managed, 2 respondents indicated that their children underwent emergency surgery for SEGAs. Another respondent talked about the burden of repeated MRI scans, especially with sedation. They mentioned the constant fear they feel about

their children needing brain surgery — either an initial operation or repeated operations — and asked why treatments available in the US, UK, and Europe are not covered in Canada.

One of the caregivers, whose son has been on everolimus for 5 years for renal angiomyolipomas through a special-access program, indicated that the results have been “a miracle.” The kidney tumours have shrunk, there have been no further bleeds, and the SEGAs that were being watched for growth shrank to a nodule. Another caregiver from British Columbia said their request for access to everolimus was denied.

Clinician Input

Input From Clinical Experts We Consulted

All CDA-AMC 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 2 clinical specialists with expertise in the diagnosis and management of SEGA in patients with TSC.

Unmet Needs

The clinical experts consulted for this review indicated that the goals of treatment for patients with TSC-related SEGA are prevention and elimination of symptoms of hydrocephalus (such as headache, nausea, vomiting, and vision loss) and of secondary permanent disability due to hydrocephalus, as well as prevention of further growth of SEGA, progression of disease, and need for neurosurgery in emergency situations (e.g., acute intracranial hypertension), which carries significant risk. Maintaining health with noninvasive treatment is an important goal in this patient population, who may already be affected by several other features of the disease. These treatment goals are not met by surgical intervention. Surgical treatment is invasive, risky (up to 6% mortality, according to the clinical experts), stressful to families, and traumatizing for children. Minimally invasive treatments (laser or endoscopic procedures) are possible only for smaller lesions, are still problematic because of location of the tumours, and may result in morbidity. In patients with larger lesions or multiple lesions, a complete resection is often not possible, and regrowth is common. Treatments that are better tolerated and can prevent regrowth and treat multiple lesions at same time are necessary.

mTOR inhibitors are currently the only noninvasive treatment that can target the underlying disease mechanism of TSC and SEGA, thus preventing regrowth of SEGA and eliminating the need for invasive surgical procedures. mTOR inhibitors also have a secondary benefit for other disease manifestations such as renal angiomyolipomas. Although mTOR inhibitors are the standard of care in clinical practice and show clear benefit in treatment of patients with SEGA, they are not always available or covered by public drug plans and many patients do not have access to this standard of care. There are limited options for disease-modifying therapies in TSC.

Place in Therapy

Everolimus, an mTOR inhibitor, is the main therapeutic option for patients with SEGA. Other mTOR inhibitors, such as sirolimus, are effective, but published data on their efficacy and safety are lacking.

Surgery is usually reserved for patients who require immediate surgical intervention for a life-threatening condition (e.g., hydrocephalus). Therefore, for patients not in need of immediate surgery, everolimus would be used as first-line treatment. It may also be used before and/or after surgery, if necessary, to reduce tumour size. The clinical experts noted that everolimus has been used since 2005 to treat SEGA. Its efficacy and acceptable side-effect profile has positioned it as the main therapeutic option for SEGAs that do not require urgent surgery. One clinical expert noted that, in 15 years since the start of the use of everolimus for TSC-related SEGA in their institution, no patient that they have treated has required surgery. The clinical experts emphasized that, in their experience, everolimus is effective, well tolerated, and can treat bilateral SEGA (bilateral surgery is associated with more complications). mTOR inhibitors are unique in that they target the underlying disease mechanism of TSC and SEGAs rather than only treating symptoms and can therefore prevent possible regrowth of SEGAs, sparing patients from invasive surgical procedures. Importantly, mTOR inhibitors also offer secondary benefit for other TSC manifestations such as skin and kidney lesions.

Patient Population

Surgery is reserved for patients needing it urgently, such as those presenting with acute intracranial hypertension caused by SEGAs. All other patients with a growing SEGA near the foramen of Monro should receive everolimus.

Patients most likely to benefit from everolimus are those with multiple SEGAs, large SEGAs not accessible to minimally invasive surgery, SEGAs with difficult attachment (which pose a high risk for morbidity from surgery), small lesions that do not yet require surgery but have potential to grow and cause future damage (to prevent disease progression), and patients with prior incomplete resection (to prevent regrowth).

Patients least likely to benefit from everolimus treatment are those with acute symptoms of hydrocephalus or clear lesions on MRI, who need more urgent intervention. Patients with continued tumour growth despite mTOR inhibitor treatment may need surgery to control SEGA growth. In some cases, the treatment effect of mTOR inhibition may be delayed. In young children with rapid tumour growth and a surgically accessible lesion (high risk of adverse effects from mTOR inhibitors), surgery may be preferred.

Assessing Response to Treatment

Important outcomes are improved survival, reduction in size of SEGA, and, therefore, reduction in risks associated with enlarging SEGAs, including acute intracranial hypertension, hydrocephalus, and associated symptoms, as well as prevention of disability secondary to hydrocephalus or surgery.

Evaluating treatment response involves assessing tumour size on MRI. Evaluating response may also involve assessing indirect effects of treatment, including seizure control, and progression of disease in other organs, including the kidneys, lungs, and skin.

The standard of practice for screening and follow-up of patients with TSC-related SEGA is repeat MRI scanning (every 1 to 3 years) after TSC diagnosis. (SEGAs occur mainly in children and rarely appear after age 25.) More intense follow-up (every 6 months) may be needed when small SEGAs are suspected. Clinical follow-up and educating caregivers for awareness of hydrocephalus symptoms are also part of clinical care

of these patients. The clinical experts noted that late diagnosis or late follow-up due to limited access to MRI or MRI with sedation in many provinces is a major barrier to timely care of patients. Similarly, lack of access to specialized care when symptoms suggestive of hydrocephalus occur poses a considerable risk to patients.

Discontinuing Treatment

Discontinuing treatment with everolimus may be considered in cases of disease progression to a clinical symptomatic stage, which requires immediate surgical intervention, and disease progression after sufficiently long treatment periods (i.e., a minimum 6 months, as some patients may have delayed effects). Intolerable harms of treatment (e.g., recurrent severe infections) may warrant discontinuation of everolimus. However, 1 of the clinical experts noted that disease progression on everolimus is very rare and has not happened in their practice.

Prescribing Conditions

The clinical experts noted that treatment involves regular monitoring of disease progression, treatment response, and possible side effects, ideally by a specialist (in pediatrics, neurology, or neurosurgery) experienced in the treatment of TSC and SEGA at specialty or outpatient clinics of a hospital. On-call help, with the possibility to discuss new-onset harms of treatment (e.g., acute infection) should be available; regular laboratory tests to monitor for harms of treatment and MRI follow-up are necessary. Access to specialist care may be challenging in some remote areas. Patients may have some degree of immunosuppression that causes them to be considered immunocompromised, requiring intensive and rapid medical attention during episodes of infections.

Treatment Monitoring

With respect to specific harms that should be monitored while patients are on everolimus treatment, the clinical experts indicated that hyperlipidemia and hyperglycemia are the main harms that are monitored with blood tests. Recurrent infections — especially nasopharyngeal, gastrointestinal, upper and lower respiratory tract, and urinary tract infections — fever, stomatitis, diarrhea, and vomiting are other possible harms of everolimus treatment.

Additional Comments

One of the clinical experts further emphasized that, in children with TSC-related SEGA, secondary positive effects of mTOR inhibition on seizures and psychiatric manifestations could lead to fewer hospitalizations and emergency department visits. These are important considerations in the treatment of this patient population, which are affected by several manifestations of the disease with a high burden of care.

Clinician Group Input

No input from clinician groups was received.

Drug Program Input

The drug programs provide input on each drug being reviewed through our nonsponsored reimbursement review process by identifying issues that may impact their ability to implement a recommendation. The drug plans highlighted that the EXIST-1 trial was placebo-controlled, as there are no pharmacological therapies

other than mTOR inhibitors for SEGA. The drug plans also asked questions about outcomes and appropriate assessments to determine drug efficacy in clinical practice and whether everolimus may be discontinued in patients who have no disease progression. The implementation questions and corresponding responses from the clinical experts we consulted are summarized and are available online.

Industry Input

No input was provided to us from the industry.

Clinical Evidence

The clinical evidence included in the review of everolimus is presented in 3 sections. The first section (Protocol Selected Studies) includes studies that were selected according to an a priori protocol. The second section (Other Relevant Evidence) includes additional studies that did not meet the eligibility criteria but were considered to address important gaps in the evidence included in the systematic review. The third section would include indirect evidence selected from the literature that met the selection criteria specified in the review; however, no indirect evidence was considered relevant for inclusion.

Methods

A systematic review was performed to identify evidence on the efficacy and safety of everolimus for the treatment of SEGAs in patients with TSC. Details of the search and selection procedures are available in Appendix 1. Studies selected for inclusion in the systematic review included those meeting the selection criteria presented in Table 3. Outcomes included in the CDA-AMC review protocol reflect outcomes considered to be important to patients, clinicians, and drug plans.

In total, 243 records were identified via the searches and 234 were excluded by title and abstract. Nine potentially relevant full-text reports were retrieved for scrutiny. In total, 9 reports of 3 unique studies are included in the review (Appendix 2, Figure 1).

Table 3: Inclusion Criteria for the Systematic Review

Detail	Criteria
Patient population	Patients (children and adults) with SEGA associated with TSC
Intervention	Oral everolimus (RAD001, Afinitor), 4.5 mg/m^2 body surface area once daily
Comparators	Placebo Oral sirolimus (rapamycin)
Outcomes	Efficacy: • Tumour response (i.e., reduction in SEGA volume) • Tumour progression • Time to tumour progression • Episodes of acute hydrocephalus • Need for neurosurgery

Detail	Criteria
	Safety: • AEs • SAEs • Discontinuation due to adverse events • Mortality from adverse events Notable harms (expected AEs): • Recurrent infection • Gastrointestinal upset and/or lesions, stomatitis • Elevated cholesterol
Study design	Randomized controlled trials

AE = adverse event; SAE = serious adverse event; SEGA = subependymal giant cell astrocytoma; TSC = tuberous sclerosis complex.

Evidence Base

The first section of the report describes 5 publications of 1 pivotal randomized controlled trial of everolimus in SEGA associated with TSC — the EXIST-1 trial, which included 1 original report of the core double-blind phase, 1 2-year interim analysis, 1 long-term final analysis of the open-label extension phase,[17,18,27] and 2 additional analyses of a pediatric subpopulation (aged 3 years and younger).[19,20] The second section (Other Relevant Evidence) describes 3 publications of Study 2485, which preceded the EXIST-1 trial and formed the evidence base for the initial regulatory approval of everolimus.[21-23] Although Study 2485 was a phase I and II noncomparative trial and thus did not meet the systematic review protocol for study design, it is included because the 3- and 5- year long-term analyses were considered important evidence for the review. This section also includes a phase III, noncomparative, expanded-access study (EFFECTS) reporting safety data in patients with SEGA treated with everolimus.[24]

Protocol Selected Studies

Study Design

The EXIST-1 trial was a pivotal, phase III, double-blind, randomized, placebo-controlled trial that randomized 117 patients in a 2:1 ratio to either everolimus 4.5 mg/m^2 BSA per day administered orally or placebo (Table 4). Randomization was achieved via interactive internet-response system and was stratified based on the use of enzyme-inducing antiepileptic drugs. Patients and all study personnel were masked to group assignment. EXIST-1 was multinational, with sites in Canada. The trial was sponsored by Novartis Pharmaceuticals, the manufacturer of everolimus. The trial consisted of a core double-blind phase from the start of the trial to the time when the last patient had been treated with everolimus or placebo for 6 months and a planned extension phase in which all patients would be given the option of starting open-label everolimus if the results of the core phase favoured everolimus. The extension phase continued until 4 years after the last patient was randomly assigned to treatment, ensuring follow-up of 4 to 5 years.

Inclusion and Exclusion Criteria

Eligible patients (aged 0 to 65 years) had a definite diagnosis of TSC, at least 1 target SEGA with the largest diameter 1 cm or greater as assessed via MRI and 1 or more of the following: serial worsening

(defined as an increase of at least 25% in volume of SEGAs); presence of a new lesion 1 cm or greater in diameter; or new or worsening hydrocephalus, as assessed by comparing a current MRI to a previous one (hydrocephalus was assessed via central radiological assessment). Patients had to be medically stable and unlikely to require surgery for SEGA, with no critical hydrocephalus or imminent cerebral herniation.

Interventions

Everolimus was administered orally at a starting dose of 4.5 mg/m^2 BSA per day and subsequently adjusted to attain blood trough concentrations of 5 to15 ng/mL. The starting dosage was chosen to be just less than the maximum tolerated dosage (5 mg/m^2 per day) in children with malignancies. Dose modifications were allowed to manage toxicity.

Concomitant Medications

Patients were prohibited from using strong and moderate inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (except antiepileptic drugs), strong inducers of CYP3A4 (except antiepileptic drugs), and concomitant use of antiproliferative drugs. (Those who had previously used antiproliferative agents were excluded from the study.)

Outcomes

The primary end point was the proportion of patients with confirmed tumour response, defined as a reduction in the total volume of all target SEGAs of 50% or more relative to baseline, in the absence of worsening of nontarget SEGAs, new lesions of 1 cm or greater in diameter, and new or worsening hydrocephalus. The initial tumour response was confirmed with an MRI scan 8 to 12 weeks later.

Key secondary end points were absolute change from baseline to 24 weeks in seizure frequency per 24 hours, time to progression of SEGAs, and skin lesion response rate. SEGA progression was defined as an increase from nadir of at least 25% in SEGA volume to a value greater than baseline SEGA volume or unequivocal worsening of nontarget SEGA lesions, or appearance of a new SEGA lesion of at least 1.0 cm in largest diameter, or new or worsening hydrocephalus, defined by central radiological assessment of ventricular configuration changes, ventricular cap signs (periventricular edema), and qualitative assessment of cerebrospinal fluid flow dynamics. Other secondary end points were angiomyolipoma response rate, as well as time to, duration of, and correlation of response of SEGAs with *TSC1* and *TSC2* gene mutation status.

Brain MRI scanning was done at months 3, 6, and 12 after initiation of the treatment and yearly thereafter until discontinuation of the patient from the study. All scans were assessed by central radiological review. All patients completed a 24-hour video electroencephalogram at baseline and at 24 weeks (or end of treatment for those who discontinued) that was sent for independent central review.

AEs were monitored continuously throughout the study with the Common Terminology Criteria for Adverse Events (CTCAE, version 3.0). At each visit, patients or their carers were assessed for pulmonary symptoms consistent with interstitial pneumonitis, a known AE of mTORC1 inhibition.

Statistical Analysis

Efficacy analyses included all randomized patients, and safety analyses included all patients who were given at least 1 dose of the study drug and had at least 1 postbaseline assessment. The everolimus and placebo arms were compared with a 1-sided exact Cochran-Mantel-Haenszel test for response rate of SEGAs, a 1-sided stratified log-rank test for the time to progression of the SEGAs, stratified by antiepileptic drug use versus no antiepileptic drug use and done at the 2.5% alpha level. Patients with unknown SEGA response were considered nonresponders.

Table 4: Details of the EXIST-1 Trial

Detail	EXIST-1 Trial
Designs and populations	
Study design	Phase III, double-blind, randomized placebo-controlled trial
Locations	24 centres in 10 countries (Australia, Belgium, Canada, Germany, UK, Italy, Netherlands, Poland, Russian Federation, and US)
Patient enrolment dates	August 20, 2009, to September 2, 2010 **Database cut-off:** Double-blind core phase: March 2, 2011 2-year interim analysis (open-label extension): January 11, 2013 Long-term final analysis: October 2, 2014
Randomized (N)	117 patients (everolimus arm, n = 78; placebo, n = 39)

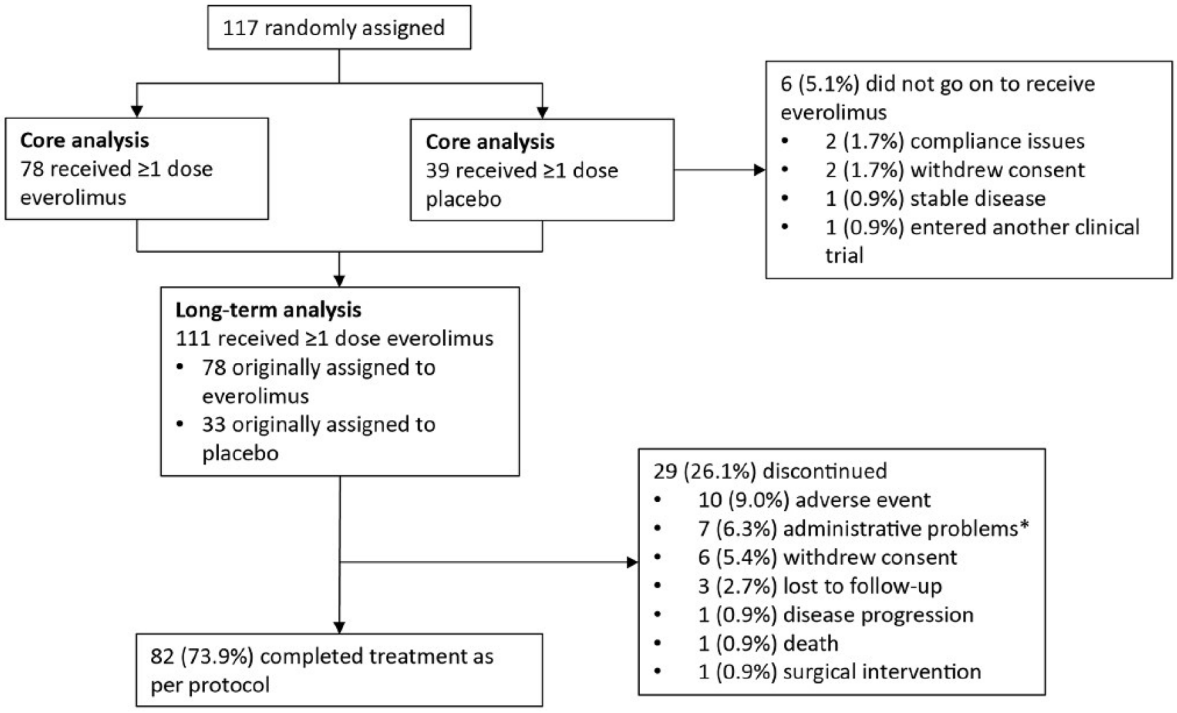
Eligibility criteria	• Age 0 to 65
	• A definite diagnosis of TSC, according to consensus criteria[28,29]
	• At least 1 target subependymal giant cell astrocytoma with the largest diameter 1 cm or greater, as assessed with multiphase MRI, and 1 or more of the following when the results of an MRI scan done within 4 weeks of randomization were compared with an earlier MRI scan:
	  ◦ Serial worsening (i.e., an increase of at least 25% in volume of SEGAs) based on the results of local imaging and radiographic assessment
	  ◦ Presence of a new lesion ≥ 1 cm in diameter
	  ◦ New or worsening hydrocephalus (according to central radiological assessment of changes in ventricular configuration, periventricular edema, and qualitative assessment of the dynamics of cerebrospinal fluid flow)
	• Medically stable and unlikely to require surgery for SEGAs with no critical hydrocephalus or imminent cerebral herniation

Drugs	
Intervention	Everolimus 4.5 mg/m^2 body surface area per day, administered orally, and subsequently adjusted to attain blood trough concentrations of 5 to 15 ng/mL
Comparator(s)	Placebo
Duration	
Phases	Screening: 2 weeks Double-blind phase: 6 months Extension phase: 4 to 5 years of follow-up

Detail	EXIST-1 Trial
Outcomes	
Primary end point	Proportion of patients with confirmed tumour response (reduction in the total volume of all target SEGAs of ≥ 50% relative to baseline, in the absence of worsening of nontarget SEGAs, new lesions of ≥ 1 cm, and new or worsening hydrocephalus)
Secondary end points	• Absolute change from baseline to 24 weeks in seizure frequency per 24 hours by use of a video electroencephalogram • Time to progression of SEGAs • Skin lesion response rate in patients with at least 1 skin lesion at baseline • Angiomyolipoma response rate (defined as a reduction in the total volume of all target angiomyolipomas identified at baseline of ≥ 50% relative to baseline, with no new angiomyolipoma ≥ 1 cm in longest diameter, no increases in volume of kidney of more than 20% from nadir, and no angiomyolipoma-related bleeding of grade 2 or worse) in patients with 1 or more target angiomyolipomas • Time to, duration of, and correlation of response of SEGAs with *TSC1* and *TSC2* gene mutation status
Notes	
Publications	Double-blind core phase: Franz et al. (2013)[17] 2-year interim analysis (open-label extension): Franz et al. (2014)[18] Long-term final analysis: Franz et al. (2016)[27] Pediatric patients (< 3 years old): Kotulska et al. (2013)[19] Jozwiak et al. (2016)[20]
Sources of support	Novartis Pharmaceuticals

SEGA = subependymal giant cell astrocytoma; TSC = tuberous sclerosis complex.

Figure 1: Patient Disposition — EXIST-1 Trial



* Administrative problems were defined as noncompliant with study visit or noncompliant with study drug.

Source: Franz et al., Copyright 2016.[27] This work is licensed under the Creative Commons Attribution 4.0 International Licence. Full text available here: https://creativecommons.org/licenses/by/4.0/.

Results

Baseline Characteristics and Patient Disposition

Double-blind core phase: Between August 20, 2009, and September 2, 2010, 117 patients who had TSC-related SEGAs were randomly assigned to receive everolimus (n = 78) or placebo (n = 39). The median age of patients was 9.5 years (range, 0.8 to 26.6 years), with most (69%) aged 3 to less than 18 years. Eight patients (7%) had a history of surgery related to their SEGAs. Baseline characteristics were generally well balanced between the treatment arms, but the everolimus arm had a higher proportion of males than the placebo arm (63% versus 46%) and a higher proportion of patients with hydrocephalus than the placebo arm (10% versus 0). There were also baseline imbalances in the number of target lesions; a smaller proportion of patients in the everolimus group compared with the placebo group had 1 target lesion (56% versus 64%, respectively), whereas a larger proportion of patients had 2 target lesions (44% versus 36%, respectively). The median SEGA volume was higher in the everolimus group (1.63 cm^3 [range, 0.18 to 25.15 cm^3]) compared with the placebo group (1.30 cm^3 [range, 0.32 to 9.75 cm^3]).

After a median follow-up of 9.7 months, 76 (97%) patients in the everolimus arm and 31 (79%) in the placebo arm were still undergoing double-blind treatment. The most common reason for discontinuation was disease progression (6 patients [15%] in the placebo arm). These patients were switched to open-label everolimus, and their data for the double-blind analysis were censored at that point for the analysis of the

double-blind period. The median duration of study treatment was 41.9 weeks (range, 24.0 to 78.9 weeks) in the everolimus arm and 36.1 weeks (range, 13.9 to 79.7 weeks) in the placebo arm. The median dosage intensity of everolimus was 5.9 mg/m^2 per day (range, 2.3 to 11.8 mg/m^2 per day).

Two-year interim analysis: Median follow-up was 28.3 months (range, 1.9 to 38.8 months; interquartile range [IQR], 19.3 to 33.0 months). The median duration of everolimus exposure was 29.3 months (range, 1.9 to 40.5 months; IQR, 19.4 to 33.8).

Long-term final analysis: At the end of the study, median duration of everolimus exposure was 47.1 months (range, 1.9 to 58.3 months) and median dosage intensity was 5.89 mg/m^2 per day (range, 1.0 to 13.8 mg/m^2 per day).

Table 5: Baseline Patient Characteristics — EXIST-1 Trial

Characteristic	Everolimus (N = 78)	Placebo (N = 39)
Age, years, median (range)	9.5 (1.0 to 23.9)	7·1 (0.8 to 26.6)
< 3, n (%)	13 (17)	7 (18)
3 to < 18, n (%)	55 (71)	26 (67)
≥ 18, n (%)	10 (13)	6 (15)
Sex, n (%)		
Male	49 (63)	18 (46)
Female	29 (37)	21 (54)
Ethnic origin, n (%)		
White	73 (94)	36 (92)
Black	3 (4)	1 (3)
Other	2 (3)	2 (5)
Body surface area, m^2, median (range)	1.07 (0.42 to 2.16)	0.96 (0.40 to 2.14)
Two or more main features of TSC, n (%)	78 (100)	39 (100)
Use of enzyme-inducing antiepileptic drug, n (%)	15 (19)	7 (18)
Presence of seizure on baseline electroencephalogram, n (%)	27 (35)	13 (33)
One or more skin lesion, n (%)	72 (92)	38 (97)
One or more angiomyolipoma, n (%)	30 (38)	14 (36)
Hydrocephalus, n (%)	8 (10)	0
Previous treatment for SEGAs, n (%)	6 (8)	2 (5)
Drug	0	0
Surgery	6 (8)	2 (5)
Worsening SEGAs confirmed by central review, n (%)	66 (85)	34 (87)
Serial growth	63 (81)	32 (82)

Characteristic	Everolimus (N = 78)	Placebo (N = 39)
New lesion 1 cm or more in longest diameter	7 (9)	5 (13)
New or worsening hydrocephalus	5 (6)	0
Number of target lesions of SEGAs, n (%)		
0	2 (3)	0
1	40 (51)	25 (64)
2	34 (44)	14 (36)
3	1 (1)	0
≥ 4	1 (1)	0
Volume of SEGAs, cm^3, median (range)	1·63 (0.18 to 25.15)	1·30 (0.32 to 9.75)
TSC mutation status, n (%)		
TSC1 and *TSC2*	1 (1)	0
TSC1	10 (13)	3 (8)
TSC2	55 (71)	29 (74)
None	11 (14)	7 (18)

SEGA = subependymal giant cell astrocytoma; TSC = tuberous sclerosis complex.

Source: Franz et al. (2013).[17]

Efficacy Results

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

Tumour Response

Double-blind core phase: Twenty-seven of 78 patients (35%) in the everolimus arm and none of 39 in the placebo arm had a response in terms of a reduction in the total volume of all target SEGAs of 50% or more relative to baseline (difference = 35%; 95% CI, 15% to 52%; 1-sided exact Cochran-Mantel-Haenszel test, P < 0.0001). At the data cut-off, 107 patients (76 in the everolimus arm and 31 in the placebo arm) were still undergoing treatment; 9 had discontinued; and 1 in the everolimus arm was lost to follow-up. None of the patients in the everolimus arm had progression of SEGAs at data cut-off. All responses of SEGA were ongoing at the data cut-off date, and the duration of response ranged from more than 63 days to more than 255 days.

Two-year interim analysis: Fifty-four of 111 patients (49%; 95% CI, 39% to 58%), all of whom had taken at least 1 dose of everolimus (i.e., were either randomized to the everolimus arm in the double-blind core phase or had crossed over to the everolimus arm from the placebo arm), showed SEGA response of at least 50% reduction in SEGA volume relative to baseline. The median time to SEGA response was 3.58 months (IQR, 2.83 to 5.65 months). SEGA volume reductions of at least 30% were reported in about 75% of patients at time points past 3 months, and reductions of 50% or greater were reported in about 40% of patients. Among

SEGA responders, 94% of responses persisted at the data cut-off date, with a duration of response ranging from 63 to 946 days (i.e., 2.1 to 31.1 months).

Long-term final analysis: At study completion, SEGA response had been achieved at any time by 64 of 111 patients (57.7% [95% CI, 47.9% to 67.0%]) treated with everolimus per central radiology review. Median time to SEGA response was 5.32 months (95% CI, 3.02 to 5.59 months) and ranged from approximately 2.5 to 33.1 months.

Tumour Progression

Double-blind core phase: Six of 39 patients (15.4%), all in the placebo arm, had progression of SEGAs at the time of analysis in the main phase of the trial. This end point was not tested statistically.

Two-year interim analysis: Nine of 111 patients (8.1%) treated with everolimus had SEGA progression. In 7 patients, progression occurred either after treatment was stopped (n = 3; 3 days, 1 month, and 3 months after cessation) or was associated with everolimus C_{min} values of 0 or C_{min} values that were markedly reduced (n = 4) while on treatment. Of the remaining 2 patients, progression was reversed in 1 with continued everolimus treatment; the other patient developed hydrocephalus in the absence of SEGA growth (this patient had a SEGA volume reduction larger than 70%), and the hydrocephalus resolved with continued everolimus treatment.

Long-term final analysis: Thirteen of 111 patients (11.7%) treated with everolimus had SEGA progression at any time during the study. One of these patients discontinued everolimus treatment because of SEGA progression. For 6 patients, progression was detected at the end-of-treatment visit, after everolimus had already been discontinued for other reasons (completed treatment [n = 2], AE [n = 2], noncompliance [n = 1], withdrew consent [n = 1]). In the other 6 patients, although progression was noted, everolimus was continued at the discretion of the investigator. SEGA progression occurred approximately 250 to 1,700 days after everolimus initiation. Five of the 13 patients with progression had achieved response before progression.

Time to Tumour Progression

Double-blind core phase: The median time to tumour progression was not reached in either treatment arm, but the estimated progression-free rates at 6 months were 100% for everolimus and 86% for placebo (P = 0.0002).

Two-year open-label extension: Not reported.

Long-term final analysis: Because of the low number of SEGA progressions, median time to SEGA progression could not be determined. The progression-free survival rate at 3 years after treatment initiation was 88.8% (95% CI, 80.6% to 93.6%).

Episodes of Acute Hydrocephalus

Double-blind core phase: Episodes of hydrocephalus were not reported. Although the absence of new or worsening hydrocephalus was required for classifying patients as SEGA responders, episodes of hydrocephalus (or other reasons for being classified as nonresponders) were not reported separately.

Twp-year open-label extension: One patient developed hydrocephalus in the absence of SEGA growth (this patient had a SEGA volume reduction larger than 70%), and the hydrocephalus resolved with continued everolimus treatment.

Need for Neurosurgery

No patient required surgery for SEGA progression during the trial.

Harms Results

Only those harms identified in the review protocol are reported in this section (Table 6).

AEs, SAEs, and Discontinuations

Double-blind phase: Ninety-six percent of patients in the everolimus arm and 90% of patients in the placebo arm had at least 1 AE. The most common AEs in the everolimus group were mouth ulceration (32% versus 5% in the placebo group), stomatitis (31% versus 21% in the placebo group), convulsion (23% versus 26% in the placebo group), and pyrexia (22% versus 15% in the placebo group). The most common grade 3 AEs in the everolimus group were stomatitis (8% versus 3% in the placebo group), pyrexia (6% versus 0% in the placebo group), and convulsion (5% versus 5% in the placebo group); grade 4 events were rare. Infections, mostly of the upper respiratory tract, were reported by 56 (72%) patients in the everolimus arm and 26 (67%) in the placebo arm. Other than 1 (1%) case of grade 1 herpes zoster in the everolimus group, no opportunistic infections were reported; 1 (1%) infection (gastroenteritis in the everolimus group) was classified as grade 4.

Thirty-eight patients (49%) in the everolimus arm and 4 (10%) in the placebo arm had AEs requiring dose reduction or temporary interruption of treatment; most common were stomatitis (13 patients [17%] in the everolimus arm and 1 patient [3%] in the placebo arm), mouth ulceration (6 [8%] versus 0), pyrexia (5 [6%] versus 1 [3%]), and pneumonia (4 [5%] versus 0). No AEs led to discontinuation from the study.

Twp-year interim analysis: Mouth ulceration (33 patients [30%]) and stomatitis (48 [43%]), were the 2 most frequently reported AEs. These events were commonly reported by investigators to be related to everolimus treatment (mouth ulceration in 32 patients [29%] and stomatitis in 47 patients[42%]) and were the most common reasons for dose reduction, temporary interruption, or both. These were also among the most common AEs requiring additional therapy. Thirty-three patients (30%) had convulsions noted as an AE.

Eighteen patients (16%) had SAEs with suspected relation to the study drug. The most frequently occurring SAE by system organ class was infections and infestations; 15 patients (14%) had a total of 25 events, including pneumonia (10 patients[9%]) and viral gastroenteritis (3 [3%]). The only other SAEs occurring in more than 2 patients were pyrexia and dehydration (2 [2%] each).

Six (5%) patients were discontinued from the study drug as a result of a total of 8 AEs (1 case each of *Acinetobacter* bacteremia, aggression, anemia, increased blood alkaline phosphatase concentrations, neutropenia, pneumonia, sinusitis, and viral infection).

Long-Term Final Analysis

All but 1 patient (99.1%) experienced an AE during the long-term phase of the study. Most patients (89.2%) experienced at least 1 AE that was suspected to be related to everolimus. The most common AEs (by preferred term) suspected to be treatment-related in more than 10% of patients were stomatitis (43.2%), mouth ulceration (32.4%), pneumonia (13.5%), blood cholesterol level increase (11.7%), hypercholesterolemia (11.7%), nasopharyngitis (10.8%), and pyrexia (10.8%). Among all patients, 36.0% experienced a grade 3 treatment-related AE. The most common grade 3 AEs, experienced by at least 5% of patients, were stomatitis (10.8%), pneumonia (8.1%), and neutropenia (5.4%). Five patients (4.5%) experienced a grade 4 AE, which included neutropenia (2 patients, 1.8%), pneumonia, febrile infection, gastroenteritis, and pneumothorax (1 patient each, 0.9%); febrile infection and gastroenteritis occurred in the same patient.

Most patients (n = 101 [91.0%]) required at least 1 dose interruption or reduction during the study. The most common reason for dose interruption or reduction was an AE (n = 80 [72.1%]). Eleven patients (9.9%) experienced an AE that led to discontinuation. These AEs included *Acinetobacter* bacteremia, aggression, anemia, azoospermia, blood alkaline phosphatase level increase, focal segmental glomerulosclerosis, need for neurosurgery, neutropenia, pneumonia, pneumothorax, sinusitis, stomatitis, and viral infection (1 patient each, 0.9%). Among these, viral infection, blood alkaline phosphatase level increase, and *Acinetobacter* bacteremia were all reported in the same patient. One patient experienced an AE that led to discontinuation, but the main reason for treatment discontinuation was withdrawal of consent.

Mortality

Double-blind phase: No deaths were reported.

Two-year interim analysis: No deaths were reported.

Long-term final analysis: One death (accidental asphyxiation) was reported and was not suspected by the investigator to be related to treatment.

Table 6: Adverse Events — EXIST-1 Trial (Main Phase)

	Everolimus (N = 78), n (%)		Placebo (N = 39), n (%)	
Adverse event	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Any adverse event	75 (96)	26 (33)[a]	35 (90)	9 (23)[b]
Mouth ulceration	25 (32)	1 (1)[c]	2 (5)	0
Stomatitis	24 (31)	6 (8)[c]	8 (21)	1 (3)[c]
Convulsion	18 (23)	4 (5)[c]	10 (26)	2 (5)[c]
Pyrexia	17 (22)	5 (6)[c]	6 (15)	0
Nasopharyngitis	14 (18)	0	9 (23)	0
Vomiting	13 (17)	1 (1)[c]	5 (13)	0
Upper respiratory tract infection	12 (15)	1 (1)[c]	7 (18)	0
Fatigue	11 (14)	0	1 (3)	0

Adverse event	Everolimus (N = 78), n (%)		Placebo (N = 39), n (%)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Cough	10 (13)	0	4 (10)	0
Diarrhea	10 (13)	0	2 (5)	0
Rash	9 (12)	0	2 (5)	0
Bronchitis	8 (10)	3 (4)[c]	4 (10)	1 (3)[c]
Otitis media	8 (10)	1 (1)[c]	2 (5)	1 (3)[c]
Pharyngitis	8 (10)	0	1 (3)	0

[a]All grade 3 except one grade 4 gastroenteritis.

[b]All grade 3 except one grade 4 hyperuricemia.

[c]All grade 3.

Note: Adverse events of any cause in more than 10% of patients in the everolimus arm.

Source: Franz et al. (2013).[17]

Additional Analyses in Patients Aged Younger Than 3 Years in the EXIST-1 Trial

Effect of Everolimus on Epilepsy and Growth in Patients Aged Younger Than 3 Years (Kotulska et al. 2013)

Eight children (2 girls and 6 boys) under the age of 3 years from a participating centre of the EXIST-1 trial who received everolimus were included in this study. In all the children, everolimus treatment was introduced before 3 years of age (range, 12 to 35 months; mean 24.1 months), at a dose of 4.5 mg/m^2, and then adjusted according to pharmacokinetic analysis and/or tolerability. The mean follow-up of these children at the time of the study was 35 months (range, 33 to 38). All children presented with a history of epilepsy. In 3 children, epilepsy was well controlled with 1 or 2 antiepileptic drugs and they were seizure-free at screening. Five children had active drug-resistant epilepsy, with at least 1 seizure per week, despite the use of 2 or 3 antiepileptic drugs. In 3 children, adrenocorticotropic hormone (ACTH) therapy for infantile spasms was completed before enrolment in the EXIST-1 study. In all 3 of these children, the infantile spasms were well controlled, but they continued to suffer from partial seizures.

In 6 out of 8 children, at least a 50% reduction in SEGA volume was observed. In 1 child with drug-resistant epilepsy, everolimus treatment resulted in cessation of seizures, and, in 2 other children, at least a 50% reduction in the number of seizures was noted.

Adverse Events

A total of 142 AEs were noted in all patients; of these, 74 were assessed to be drug-related; 127 of 142 AEs were grade 1 and 2. Fifteen grade 3 AEs and no grade 4 AEs were observed. Dose reductions due to an AE were necessary in 7 of 8 patients.

Every patient experienced at least 1 AE. The most frequent AE was aphthous stomatitis, observed in 7 of 8 patients throughout the follow-up. Grade 1 stomatitis was reported 29 times, mostly (19 times) in the first year of treatment. Grade 2 stomatitis or mouth ulcers were reported 25 times in 5 of 8 patients. Grade 3 stomatitis was observed in 5 of 8 patients. In 3 patients, grade 2 and grade 3 stomatitis was observed when

the dose level was increased to 6 mg/m^2 or 10.67 mg/m^2, respectively. After dose reductions, no further episodes of stomatitis were noted in these patients. In 2 patients, grade 2 and 3 stomatitis were observed at the dose level of 4.5 mg/m^2 and 3.38 mg/m^2, respectively. After dose reductions, stomatitis did not occur. All stomatitis episodes resolved completely.

At least 1 upper respiratory tract infection was noted in all patients. All infections were grade 1 or 2. Upper respiratory infections developed more frequently in the first (31 episodes) than in the second (16 episodes) and third (9 episodes) year of treatment.

Four patients experienced mild gastrointestinal disturbances, including vomiting and diarrhea, as well as transient constipation.

Safety of Everolimus in Patients Aged Younger Than 3 Years (Jozwiak et al. 2016)

This study assessed the long-term safety of everolimus in 18 patients aged younger than 3 years (median age 1.82 years) from the EXIST-1 trial. Sixteen patients were still receiving everolimus at the analysis cut-off date of January 11, 2013. One-half of the patients had 1 target SEGA lesion, and the other half had 2 target lesions. The median sum of volumes of target SEGA lesions at baseline was 0.90 cm^3 (range, 0.28 to 3.59 cm^3). SEGAs were bilateral in 15 patients (83.3%) and unilateral in 3 patients (16.7%). The median duration of exposure to everolimus was 31.1 months (range, 11.5 to 39 months), and the median dosage intensity was 5.86 mg/m^2 per day (range, 2.5 to 9.5 mg/m^2 per day).

AEs were reported in all 18 patients (100%). Most AEs were considered by the investigator to be grade 1 or grade 2 in severity. The most common AEs were stomatitis, cough, pharyngitis, and pyrexia. Fourteen patients (77.8%) experienced grade 3 or 4 AEs, which were suspected to be related to everolimus in 11 patients (61.1%). Grade 3 AEs, irrespective of relationship to study medication, occurred in 12 patients (66.7%). The most frequent (> 10%) grade 3 AEs were stomatitis, pyrexia, and bronchitis in 4 patients (22.2%) each; convulsion in 3 patients (16.7%); and neutropenia, pneumonia, and decreased blood fibrinogen in 2 patients (11.1%) each. Convulsions were reported in patients with a history of epilepsy preceding the start of everolimus treatment and included febrile seizure in 1 patient, single epileptic seizure in 1 patient, and increased number of seizures in 1 patient with severe drug-resistant epilepsy. None of the grade 3 convulsions were considered by the investigators to be related to everolimus; convulsions resolved after concomitant medication for 2 patients, but an increased number of seizures reported in 1 patient remained at the data cut-off. Two patients (11.1%) experienced grade 4 AEs. Grade 4 AEs, irrespective of study medication relationship, consisted of pneumonia, upper respiratory tract infection, febrile infection, and gastroenteritis and were reported in 1 patient (5.6%) each.

SAEs were reported in 50.0% of the patients. SAEs that were suspected by the investigator to be related to everolimus occurred in 4 patients (22.2%). SAEs, irrespective of relationship to study medication, occurring in more than 10% of patients consisted of pneumonia in 3 patients (16.7%) and pyrexia, bronchitis, upper respiratory tract infection, and convulsion in 2 patients each (11.1%). Infections and infestations occurred in all patients, followed by stomatitis and related events, which occurred in 12 patients (66.7%), and cytopenia, which occurred in 5 patients (27.8%).

The dose was reduced or interrupted for 17 patients (94.4%), and all patients (100.0%) required additional therapy because of AEs. Fifteen patients (83.3%) had a dose reduction; 12 patients (66.7%) had more than 1 dose reduction. A reduction in everolimus dose was needed following an AE in 7 patients (38.9%), a dosing error in 1 patient (5.6%), and a change in BSA in 3 patients (16.7%). Sixteen patients (88.9%) had at least 1 dose interruption, mainly due to AEs. AEs requiring dose reduction or interruption occurring in more than 10% of patients were stomatitis (7 patients [38.9%]), cough and pyrexia (5 patients [27.8%] each), pneumonia (4 patients [22.2%]), bronchitis (3 patients [16.7%]), and decreased blood fibrinogen, diarrhea, ear infection, neutropenia, otitis media, upper respiratory tract infection, and viral infection (2 patients [11.1%] each). The median duration of dose interruption because of an AE was 10 days (range, 1 to 47 days).

There were no deaths.

Critical Appraisal

Internal Validity

The EXIST-1 study was a double-blind trial; patients were randomized 2:1, and allocation concealment was ensured through an interactive internet-response system. The baseline characteristics were mostly balanced between treatment arms, although imbalances were noted in sex, the presence of hydrocephalus, SEGA volume, and the number of target lesions. Total SEGA volume at baseline was higher in the everolimus arm, indicating larger tumour burden compared to the placebo arm. If larger tumours are more mitotically active and thus more responsive to mTOR inhibition, this could potentially bias results in favour of everolimus. Details of patient disposition were reported, and reasons for discontinuation from the study were provided. Following the double-blind core phase, 111 patients entered the open-label extension phase (including patients randomized to everolimus and patients who crossed over to everolimus from the placebo group). As the open-label extension phase lacked a randomized comparison group, causal conclusions based on results for both benefits and harms from this phase of the trial are limited. Results specific to patients aged 3 or younger were also limited by small sample sizes and a lack of randomized comparison group.

Patients were masked to study treatment (identical everolimus and placebo), unless the treatment was discontinued due to unacceptable toxicity, during the double-blind core phase. Patients could have become unblinded due to the imbalances in known harms of everolimus across treatment groups. If patients had become unblinded, there could be a risk of bias in the measurement of subjective outcomes (e.g., subjective harms); however, the presence and direction of the potential bias is uncertain. The primary outcome was adjudicated by central radiological review, which reduces the risk of bias for this outcome. Patients were unblinded on progression, and those in the placebo arm were offered open-label everolimus. However, the primary end point of SEGA response is unlikely to be affected by the unblinding of a few patients at progression. As the long-term extension portion of the trial was open-label, there is a risk of bias in the measurement of subjective harms during this phase.

The primary end point of the EXIST-1 trial was SEGA response, which is considered the most important outcome in this setting. The statistical analyses of the primary end point were appropriate. Multiplicity was supposed to be controlled using a hierarchical testing procedure in which testing would continue with a predefined list of outcomes until statistical significance was not achieved. However, testing continued, and

the outcomes of these tests were reported for outcomes that did not reach statistical significance. Therefore, the planned hierarchical testing procedure does not appear to have been followed.

Patients with unknown SEGA response status were treated as nonresponders in the calculation of the SEGA response rate in the full analysis sample at the end of the trial. Other missing data were simply noted as missing on appropriate tables and listings.

External Validity

The trial inclusion and exclusion criteria of the EXIST-1 trial were clinically relevant, and, according to the clinical experts consulted by CDA-AMC, the trial population resembled patients who would be treated with everolimus in clinical practice.

The administration of everolimus in the EXIST-1 trial was consistent with common practice. The clinical expert noted that, as in the trial, dose adjustments are often made based on tolerability. The core 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. The final analyses provide long-term data regarding the efficacy and harms of everolimus. Although these analyses are important, these are based on the open-label extension phase, which lacked a randomized comparison group.

SEGA response required a 50% reduction in the target SEGAs, no worsening of nontarget SEGAs, no new lesions of 1 cm or greater, and no new or worsening hydrocephalus. Although the absence of new or worsening hydrocephalus was required for classifying patients as SEGA responders, episodes of hydrocephalus (or other reasons for being classified as nonresponders) were not reported separately.

Other Relevant Evidence

Study 2485

Study 2485 was a phase II, nonrandomized (single-arm) trial that recruited 28 patients aged 3 years or older treated with everolimus. It was a single-centre study conducted at a hospital in the US, sponsored by Novartis Pharmaceuticals, the manufacturer of everolimus. The trial had an initial 6-month treatment phase and an extension phase that followed patients up to 5 years. The primary outcome was change from baseline in volume of the primary SEGA lesion after 6 months of treatment with study drug. Secondary end points included changes in quality of life using the Quality of Life in Childhood Epilepsy (QOLCE) scale, neuropsychological evaluations, cognitive evaluations, and safety (Table 7).

Table 7: Details of Study 2485

Detail	Study 2485
Designs and populations	
Study design	Open-label, phase I to II, nonrandomized (single-arm)
Locations	Single centre (Cincinnati Children's Hospital Medical Center)
Patient enrolment dates	January 2007 to December 2008
Number of patients	28 patients treated with everolimus

Detail	Study 2485
Eligibility criteria	• Aged 3 years or older • A definitive diagnosis of tuberous sclerosis complex (according to the modified Gomez criteria[28] or a positive genetic test) and serial growth of a SEGA (defined as an increase in size, compared with baseline, on at least 2 successive MRI scans) • Medically stable, without signs of cerebral herniation or critical hydrocephalus
Drugs	
Intervention	Everolimus at a starting dosage of 3.0 mg/m^2 body surface area per day, administered orally, and subsequently adjusted to attain blood trough concentrations of 5 to 15 ng/mL
Comparator(s)	No comparators
Duration	
Phases and follow-up	Core phase: 6 months, followed by open-label long-term extension phase Extension phase (3-year analysis) cut-off date: 31 December 2010 Extension phase (5-year analysis) cut-off date: 28 January 2014
Outcomes	
Primary end point	Change in the volume of SEGAs during the core 6-month treatment phase
Secondary end points	• Effect on seizures • Quality of life • Effect on neurocognition
Notes	
Publications included	Core phase: Krueger et al. (2010)[21] Extension phase (3-year analysis): Krueger et al. (2013)[22] Extension phase (5-year analysis): Franz et al. (2015)[23]
Sources of support	Novartis Pharmaceuticals

SEGA = subependymal giant cell astrocytoma.

Baseline Characteristics and Patient Disposition

Twenty-eight patients (17 male, 11 female) were enrolled in the trial. The median age was 11 years (range, 3 to 34 years); 22 patients were under 18 years of age. Sixteen were aged under 12 years, and 6 patients were aged between 12 and 18 years. Twelve patients (42.9%) had bilateral SEGAs, 15 (53.6%) had 1 SEGA lesion, and 13 (46.4%) had 2 SEGA lesions. Six patients (21.4%) presented with hydrocephalus. Four patients (14.3%) had tumour recurrence after incomplete surgical resection of SEGA at outside centres before enrolment. The majority of patients (25 of 28 [89.3%]) had facial angiofibromas, and 24 patients (82.1%) were receiving antiepileptic medications. Thirteen patients (46%) had a secondary, smaller SEGA (12 in the contralateral ventricle). Four patients (14%) had previously undergone partial resection or gamma knife treatment of SEGA but met the enrolment criteria because the residual SEGA regrew.

As of December 9, 2009, the median duration of treatment was 21.5 months (range, 4.7 to 34.4 months). One patient discontinued treatment after 4.5 months due to nonadherence to the medication regimen and worsening hyperkinesis. The remaining 27 patients completed the core 6-month treatment phase and continued everolimus therapy; 2 of the 27 subsequently discontinued treatment (after 17.5 and 21.5 months)

because of the frequency of monitoring visits. Another patient met the prespecified criteria for treatment success (i.e., a reduction of ≥ 75% in the volume of the SEGA), and therapy was stopped but was then restarted 4.5 months later, when regrowth of the SEGA was evident.

Of 28 patients enrolled in the trial, 27 (96.4%) entered the extension phase and 25 (89.3%) were still continuing treatment at the 3-year interim analysis (data cut-off of December 31, 2010). Three patients withdrew consent at 142, 532, and 653 days for reasons that included nonadherence with antiepileptic drugs, inability to maintain study visits, and withdrawal of parental consent.

As of the study completion date (5-year final analysis, data cut-off date: January 28, 2014), 22 of 28 patients (78.6%) initially enrolled finished the study per protocol. At the conclusion of the study, the median duration of exposure to everolimus was 67.8 months or 5.65 years (range, 4.7 to 83.2 months).

Efficacy Results

Tumour Response

Core 6-month treatment phase: Per central review, 21 patients (75%) had at least a 30% reduction in tumour volume, relative to baseline; 9 (32%) had reductions of 50% or more.

Extension phase (3-year analysis): Primary SEGA volume was reduced by at least 30% from baseline in 79.2% (19 of 24), 64.7% (11 of 17), and 77.8% (7 of 9) of patients at 24, 30, and 36 months, respectively, and by at least 50% from baseline in 50.0% (12 of 24), 41.2% (7 of 17), and 55.6% (5 of 9) of patients, respectively. Nine patients had between 30% and 50% reduction in primary SEGA volume within 6 months. Six of these patients had a reduction in primary SEGA volume of at least 50% at 6 months. In 2 of these 3 patients, the primary lesion volume reverted to volume at baseline, while in the other patient, an increase in volume of 51% compared with baseline was observed. However, based on the investigators' judgment of overall clinical benefit, these 3 patients continued treatment.

Extension phase (5-year analysis): In the final long-term follow-up, 82.1% (23 of 28) of patients were noted to have a 50% or greater reduction in primary SEGA volume relative to baseline at some point during the treatment period, including 12 patients (12 of 23 [52.2%]) at month 60; 92.9% of patients (26 of 28) achieved at least 30% reduction in primary SEGA volume relative to baseline at some time during the treatment period, and 60.9% (14 of 23) had a at least 30% reduction at month 60.

Time to Tumour Progression

At the final long-term analysis, among the 23 patients with at least a 50% reduction at any time, 95.7% were progression-free at their last radiological assessment before the data cut-off date, initiation of further systemic anti-SEGA therapy, or study discontinuation. The median duration from first response (≥ 50% reduction) to progression or the last radiological assessment in this group was 53.9 months (range, 0 to 77.1 months). Of the 26 patients achieving at least 30% reduction, 92.3% (24 of 26) were progression-free at their last radiological assessment before the data cut-off date, initiation of further systemic anti-SEGA therapy, or study discontinuation. The median duration from first response (≥ 30% reduction) to progression or last radiological assessment in this group was 56.7 months (range, 5.7 to 77.1 months).

Episodes of Acute Hydrocephalus

No patient had worsening hydrocephalus or worsening symptoms attributable to increased intracranial pressure. Furthermore, no new lesions developed, and no patient needed to undergo surgical resection or other therapy for the tumour. One patient had initial shrinkage of the tumour (an 18% reduction in volume at 6 months relative to baseline) that was followed by progression (resulting in a 16% increase at 18 months, relative to baseline).

Need for Neurosurgery

No patient required surgery or additional therapy for SEGA or hydrocephalus.

Harms Results

Core 6-month treatment phase: All patients had at least 1 AE. Stomatitis and upper respiratory tract infections were the most common (22 patients [79%] each). Grade 3 AEs were reported in 10 patients, and 1 grade 4 event (convulsion) occurred in 1 patient. Four patients had SAEs. One patient with a history of reactive airway disease was hospitalized after recurrent upper respiratory infection (grade 3 viral bronchitis) developed, with cough and sinusitis that exacerbated breathing difficulties and was associated with leukopenia. Another patient was hospitalized for grade 3 pneumonia; later in the study, this same patient also had grade 3 vomiting. Two additional patients were hospitalized for convulsions (grade 2 and grade 4).

Extension phase (3-year analysis): All patients reported at least 1 drug-related AE, mostly mild (grade 1) to moderate (grade 2) in severity, which were managed through dose reduction, temporary interruption of therapy, or administration of concomitant drug therapy. No AEs resulted in discontinuation of everolimus therapy. The type, incidence, and severity of AEs reported by the new cut-off date were similar to those reported in the primary treatment phase. The most frequently reported AEs were upper respiratory infections (24 patients [85.7%]), stomatitis (24 patients [85.7%]), sinusitis (13 patients [46.4%]), and otitis media (10 patients [35.7%]). Of 13 patients who experienced grade 3 AEs, 6 were considered related to everolimus therapy by the investigators. The most frequently reported grade 3 AEs were stomatitis (2 patients [7.1%]) and neutropenia (2 patients [7.1%]). The only grade 4 AE was a convulsion that was not suspected to be related to everolimus therapy. No deaths were reported during the study. Six patients experienced 9 SAEs, 3 of which were suspected to be related to everolimus: 1 patient with pneumonia, 1 patient with viral bronchitis, and 1 patient with an abscess of the right leg (all grade 3 reactions). The SAEs were managed by hospitalization, concomitant drug therapy, and interruption of everolimus therapy or dose reduction.

Extension phase (5-year analysis): No new safety signals were noted at this final analysis. During the study, all patients experienced at least 1 AE and at least 1 AE that was suspected to be related to treatment. The most common treatment-related AEs reported were upper respiratory tract infection (26 of 28 [92.9%]) and stomatitis (25 of 28 [89.3%]), which were mostly grade 1 or 2 in severity. There was no treatment discontinuation due to AEs. There was 1 death reported in the 5-year analysis.

Table 8: Adverse Events — Study 2485 (5-Year Final Analysis)

Adverse event	Everolimus, N (%)					
	≤ 12 months, n = 28	13 to 24 months, n = 27	25 to 36 months, n = 25	37 to 48 months, n = 24	49 to 60 months, n = 24	> 60 months, n = 24
Stomatitis	19 (67.9)	16 (59.3)	11 (44.0)	6 (25.0)	10 (41.7)	5 (20.8)
Upper respiratory tract infection	16 (57.1)	14 (51.9)	12 (48.0)	11 (45.8)	8 (33.3)	6 (25.0)
Otitis media	10 (35.7)	7 (25.9)	4 (16.0)	3 (12.5)	1 (4.2)	1 (4.2)
Sinusitis	10 (35.7)	2 (7.4)	6 (24.0)	9 (37.5)	3 (12.5)	2 (8.3)
Pyrexia	7 (25.0)	2 (7.4)	0	1 (4.2)	0	0
Diarrhea	6 (21.4)	5 (18.5)	2 (8.0)	2 (8.3)	3 (12.5)	1 (4.2)
Dermatitis acneiform	6 (21.4)	1 (3.7)	0	0	0	0
Cellulitis	5 (17.9)	3 (11.1)	4 (16.0)	3 (12.5)	4 (16.7)	1 (4.2)
Convulsion	5 (17.9)	3 (11.1)	1 (4.0)	1 (4.2)	0	0
Vomiting	5 (17.9)	3 (11.1)	0	3 (12.5)	4 (16.7)	3 (12.5)
Body tinea	5 (17.9)	0	1 (4.0)	0	0	1 (4.2)
Gastroenteritis	4 (14.3)	1 (3.7)	6 (24.0)	5 (20.8)	2 (8.3)	1 (4.2)
Otitis externa	2 (7.1)	5 (18.5)	3 (12.0)	1 (4.2)	1 (4.2)	0
Abnormal behaviour	1 (3.6)	1 (3.7)	4 (16.0)	0	0	1 (4.2)
Skin infection	1 (3.6)	1 (3.7)	4 (16.0)	0	0	0
Pneumonia	1 (3.6)	1 (3.7)	2 (8.0)	4 (16.7)	1 (4.2)	1 (4.2)
Mouth ulceration	0	4 (14.8)	3 (12.0)	9 (37.5)	4 (16.7)	4 (16.7)
Nasopharyngitis	0	2 (7.4)	5 (20.0)	4 (16.7)	3 (12.5)	1 (4.2)
Conjunctivitis	0	1 (3.7)	1 (4.0)	2 (8.3)	4 (16.7)	1 (4.2)
Laceration	0	0	5 (20.0)	1 (4.2)	1 (4.2)	1 (4.2)

Source: Franz et al. (2015).[23]

EFFECTS

The EFFECTS study was a phase IIIb, open-label, noncomparative, multicentre, expanded-access study of everolimus for the treatment of patients with SEGA associated with TSC carried out in 44 sites in 9 countries between March 2011 and June 2013. This study aimed to make everolimus accessible to patients with SEGA associated with TSC in countries where it was not yet commercially available. The inclusion criteria were intended to enable a maximum number of patients to participate and were less restrictive than those of the EXIST-1 trial. Eligible patients were aged 3 years or older, had a definite diagnosis of TSC (as per the modified Gomez criteria),[28] and had at least 1 SEGA lesion identified by MRI or CT scan (according to local requirements by size and/or location). Patients had to be medically stable, with no need of SEGA-related surgery, and with no use of an investigational study drug within 30 days before enrolment; they should not have participated in the EXIST-1 study. The study was funded by Novartis Pharma AG.

Everolimus was administered orally once daily with a starting dose of determined by BSA: 2.5 mg for BSA of 1.2 m^2 or less, 5 mg for BSA of 1.3 to 2.1 m^2, and 7.5 mg for BSA of 2.2 m^2 or more. The dose was titrated upward to attain a trough level in the range 5 to 15 ng/mL.

The primary objective of the study was to evaluate the safety of everolimus in patients with SEGA associated with TSC. Efficacy (tumour response and progression) was evaluated as a secondary objective.

Baseline Characteristics and Patient Disposition

Overall, 120 patients were enrolled; 90 patients (75%) were aged less than 18 years (pediatric subpopulation) and 30 patients (25%) were aged 18 years or older. A total of 100 patients (83.3%) overall, and 79 patients (87.8%) in the pediatric subpopulation, completed the study. The median age of patients was 11 years (range, 1 to 47; 1 patient was aged 1 year [protocol deviation]). The median time since TSC diagnosis was 9.1 years (range, 0.2 to 30.7), and the median time since SEGA diagnosis was 3.8 years (range, 0 to 24). In addition to SEGA, most patients also had other major neurologic features of TSC, including subependymal nodule (85%) and cortical tuber (88.3%). Other major features frequently seen in this population included hypomelanotic macules (79.2%), facial angiofibromas or forehead plaques (77.5%), and renal angiomyolipoma (49.2%).

Median daily dose of everolimus was 5.82 mg (range, 2.0 to 11.8 mg), including days of temporary interruption of the study drug. Median duration of exposure for all 120 patients was 56.5 weeks (range, 0.3 to 130 weeks). Everolimus was administered to 57.5% of patients for at least 48 weeks and 31.7% for at least 88 weeks.

Results

Overall, 89 patients (74.2%) had at least 1 AE. The most common AEs were aphthous stomatitis (18%), pyrexia (18%), bronchitis (9.2%), and stomatitis (8.3%). Grade 3 and 4 AEs were reported in 20.8% and 2.5% of patients, respectively. The most frequent grade 3 AE was stomatitis (3.3%). Grade 4 AEs included acute respiratory failure, gastroenteritis, increased gamma-glutamyltransferase, near drowning, and aspiration pneumonia. Amenorrhea was reported in 12.5% of females of childbearing potential. A total of 62 patients (51.7%) had AEs with a suspected relation to everolimus (11.7% of grade 3 and 0.8% of grade 4). The suspected drug-related AEs reported in at least 5% of patients were aphthous stomatitis (15%), stomatitis (7.5%), pyrexia (6.7%), and mouth ulceration (5%).

SAEs were reported in 26.7% of patients. The most common SAEs were pyrexia (4.2%) and bronchitis (2.5%). Other SAEs reported (in at least 2 patients [1%] each) included diarrhea, gastroenteritis, viral gastroenteritis, hydrocephalus, ovarian cyst, pneumonia, pneumonitis, sinusitis, status epilepticus, stomatitis, urinary tract infection, and vomiting. Grade 3 SAEs were reported in 18.3% of patients and grade 4 SAEs in 1.6% of patients.

A total of 29 patients (24.2%) had AEs leading to hospitalization or prolonged hospitalization. Of these, 23 were pediatric patients. The most commonly reported AEs were pyrexia (4 patients), bronchitis (3 patients), and gastroenteritis, viral gastroenteritis, pneumonia, sinusitis, diarrhea, stomatitis, hydrocephalus, status epilepticus, ovarian cyst (2 patients each).

AEs leading to everolimus discontinuation were reported in 8 (6.7%) patients; 4 of them were pediatric patients. These AEs included increase in gamma-glutamyltransferase (2 patients) and decreased white blood cell count, atrioventricular block, stomatitis, headache, hydrocephalus, somnolence, ovarian cyst, and respiratory tract inflammation (1 patient each).

In the pediatric subpopulation, 74.4% of patients experienced AEs. Of these, 23.3% of patients had grade 3 AEs and 2.2% of patients had grade 4 AEs. The most frequent AE (reported in more than 2% of patients) of grade 3 was stomatitis (4 patients, 4.4%). All of the other AEs of grade 3 or 4 were reported in 1 patient each. Grade 4 AEs included acute respiratory failure, gastroenteritis, near drowning, and aspiration pneumonia. Half of the patients had suspected drug-related AEs; those reported in at least 5% of patients were aphthous stomatitis (14.4%), stomatitis (7.8%), pyrexia (7.8%), mouth ulceration (5.6%), and pneumonitis (5.6%). Twelve patients (13.3%) were reported to have suspected drug-related AEs of grade 3; the only suspected drug-related AE of grade 3 reported in more than 1 patient was stomatitis (4 patients, 4.4%); no patient reported a suspected drug-related AE of grade 4.

Critical Appraisal

Study 2485 and the EFFECTS study were single-arm studies. The lack of a randomized comparison group limits causal conclusions regarding the efficacy and safety of everolimus.

Indirect Evidence

A total of 32 references were identified from the indirect treatment comparisons (ITCs) search. After title and abstract screening, none met the selection criteria. No ITCs were included in this review.

Economic Evidence

The economic review consisted of a cost comparison between everolimus and sirolimus for the treatment of SEGA associated with TSC.

CDA-AMC Analyses

The comparators presented in Table 9 have been deemed to be appropriate based on feedback from clinical experts and participating drug plans. Clinical expert feedback obtained by CDA-AMC noted that sirolimus, while not indicated for patients with SEGA associated with TSC, is the only relevant comparator for this indication. Recommended doses were based on each product's respective product monograph and validated by clinical experts. If discrepancies in dose between the product monograph and clinical practice in Canada were noted, the dose specified by clinical experts was used.

Based on wholesale prices reported in the IQVIA DeltaPA database (accessed on June 12, 2024), 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, and at $50.66 per tablet in Manitoba, New Brunswick, Newfoundland and Labrador, Nova Scotia, and Prince Edward Island.[1] Pricing for comparator products was based on publicly available list prices.

In adult and pediatric patients, the annual cost of everolimus (5 mg or 10 mg daily, regular tablets) is $62,873 per patient in jurisdictions with more costly wholesale pricing, and $18,492 per patient in jurisdictions with less costly wholesale pricing. For patients requiring a dose of 7.5 mg daily, the annual cost is expected to be $125,747 and $36,985 in jurisdictions with higher and lower pricing, respectively. For patients requiring everolimus tablets for suspension, the annual per-patient cost ranges from $70,627 to $141,254. The annual cost of sirolimus in the adult patient population ranges from $6,891 to $10,337, depending on dose, while the annual cost of sirolimus in the pediatric patient population varies between $1,723 and $10,337, also depending on dose.

Thus, the use of everolimus for adult patients with SEGA associated with TSC is more costly than sirolimus. In jurisdictions with more costly wholesale pricing for everolimus, the incremental cost ranges from $52,537 to $118,856 per patient annually, and, in jurisdictions with less costly wholesale pricing, the incremental cost ranges from $8,155 to $30,093 per patient annually. As the annual cost of sirolimus varies between $1,723 and $10,337 per pediatric patient, in jurisdictions with more costly wholesale pricing for everolimus, the incremental cost ranges from $52,537 to $124,024 per patient annually, and, in jurisdictions with less costly wholesale pricing, the incremental cost ranges from $8,155 to $35,262 per patient annually. Finally, the incremental cost of everolimus tablets for suspension compared to sirolimus ranges from $60,290 to $139,531 in pediatric patients, and from $60,290 to $134,363 in adult patients. 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: CDA-AMC Cost-Comparison Table for Adults and Pediatric Patients With SEGA Associated With TSC

Treatment	Strength or concentration	Form	Price ($)	Recommended dosage	Daily cost ($)	Annual cost ($)
Everolimus (generics)	2.5 mg 5 mg 10 mg	Tablet	50.6637[a] OR 172.2559[b] per tablet	Starting dosage: 4.5 mg/m^2 BSA daily, followed by titration to attain trough concentrations of 5 to 15 ng/mL	50.66 to 101.33[c] OR 172.26 to 344.51[c]	18,492 to 36,985[c] OR 62,873 to 125,747[c]
Everolimus (Afinitor Disperz)	2 mg 3 mg 5 mg	Tablet for oral suspension	193.4990[d]		193.50 to 387.00[c]	70,627 to 141,254[c]
Other mTOR inhibitor						
Sirolimus (Rapamune)	1 mg 1 mg/mL	Tablet Oral solution	9.4400[d]	Adult: 2 to 3 mg once daily[e] Pediatric: Initially 0.5 mg/m^2 daily, up to 2 mg to 3 mg daily[e,f]	Adult: 18.88 to 28.32 Pediatric: 4.72 to 28.32	Adult: 6,891 to 10,337 Pediatric: 1,723 to 10,337

BSA = body surface area; mTOR = mechanistic target of rapamycin; SEGA = subependymal giant cell astrocytoma; TSC = tuberous sclerosis complex.

[a]Although a price is listed for everolimus in the Ontario Drug Database, the review relied on wholesale pricing, given that everolimus is not on formulary. Wholesale price reported by IQVIA DeltaPA (June 2024) for generic everolimus in Manitoba, New Brunswick, Nova Scotia, Prince Edward Island, and Newfoundland and Labrador is $50.6637 per tablet.[30]

[b]Wholesale price reported by IQVIA DeltaPA (June 2024) for generic everolimus in Alberta, British Columbia, Ontario, Saskatchewan, and the 3 territories is $172.2559 per tablet.[30]

[c]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; 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.[31]

[d]Wholesale price according to IQVIA DeltaPA (June 2024) per tablet or per millilitre.[30]

[e]Sirolimus is not indicated for SEGA associated with TSC. Dosage was derived from a recent CDA-AMC nonsponsored review of everolimus for the treatment of renal angiomyolipoma associated with TSC and validated by clinical expert feedback.[32]

[f]Median baseline BSA reported in the EXIST-1 trial was 1.07 m^2 for pediatric patients.[33]

Issues for Consideration

- Currently, sirolimus is available only under the brand name Rapamune.[34] A generic brand of sirolimus received authorization from Health Canada in 2011 but is not marketed in Canada.[35] Should this or another generic brand of sirolimus become available in the future, the incremental cost of everolimus compared to sirolimus may increase.
- Clinical expert feedback indicated that there would be no anticipated differences in hospitalizations, outpatient visits, treatment monitoring, disease management, or subsequent therapy between patients treated with everolimus and patients treated with sirolimus.
- No cost-effectiveness studies were identified based on a literature search conducted on June 12, 2024.

Discussion

Summary of Available Evidence

The main evidence base for this review was the EXIST-1 trial, a randomized, double-blind, placebo-controlled, phase III trial of oral everolimus (n = 78) versus placebo (n = 39) in patients with SEGA associated with TSC. Patients were treated for 6 months in the double-blind phase and up to 5 years in the open-label extension phase. The primary end point was the proportion of patients with a SEGA response, defined as a reduction in 50% of target SEGA volume, in the absence of worsening nontarget SEGAs, new lesions of at least 1 cm in diameter, and new or worsening hydrocephalus.

Two other studies, both noncomparative, were included as other relevant evidence. Study 2485 was a single-centre study conducted at 1 hospital in the US that recruited 28 patients aged 3 years and older treated with everolimus. The trial had an initial 6-month treatment phase and an extension phase that followed patients for up to 5 years. The primary outcome was change from baseline in volume of the primary SEGA lesion after 6 months of treatment with the study drug. The second study, EFFECTS, was an open-label, multicentre, expanded-access study of everolimus for the treatment of 120 patients with TSC-related SEGA aged 3 years and older who should not have participated in the EXIST-1 study.

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 CDA-AMC systematic review. Therefore, the

efficacy and harms of everolimus compared to sirolimus among patients with SEGAs associated with TSC is not known.

Interpretation of Results

Efficacy

SEGA response was the primary outcome of the EXIST-1 trial; 35% of patients in the everolimus arm and no patients in the placebo arm achieved a SEGA response. The long-term analysis of the core phase and open-label extension phase of the EXIST-1 trial supports the long-term efficacy of everolimus, showing sustained SEGA response over time. At the 2-year interim analysis, 49% of patients showed SEGA response, and, at study completion, SEGA response was reported in 57.7% of patients. Median time to SEGA response was 5.32 months (95% CI, 3.02 to 5.59 months) and ranged from approximately 2.5 to 33.1 months. Among most patients with an initial response, SEGA responses persisted; although most responses occurred within the first few months of treatment, some occurred more than 2.5 years into the study. This is aligned with the input from the clinical experts we consulted, who indicated that, in their experience, responses can take a few months to occur (i.e., up to 6 months or more). During the 2-year extension phase, 1 patient had radiological evidence of hydrocephalus in the absence of SEGA growth (this patient had a SEGA volume reduction larger than 70%) and the hydrocephalus resolved with continued everolimus treatment. In the EXIST-1 trial, no patients required neurosurgery to treat SEGAs (including patients randomized to the placebo group). In the long-term extension phase of the EXIST-1 trial, Study 2485, and the EFFECTS study, causal conclusions regarding efficacy of everolimus were limited due to the lack of a randomized comparison group. There were no cases of hydrocephalus, and the proportion of patients undergoing neurosurgery was not reported.

In our initial review of everolimus for SEGA, CDEC noted that, although the EXIST-1 trial demonstrated that treatment with everolimus reduces the size of SEGA lesions, the clinical significance of this finding was uncertain, as reducing lesion size had not been shown to improve outcomes of importance to patients, including quality of life, seizure frequency, hydrocephalus, or need for neurosurgery. At the time of the initial review, long-term efficacy and safety outcomes were unknown. Indeed, the core phase duration of the EXIST-1 trial was inadequate to assess the long-term efficacy of everolimus in patients with SEGA. Although some limitations remain and are not addressed in the long-term analysis of the extension phase of the EXIST-1 trial (e.g., absence of health-related quality of life measures), these analyses provide evidence regarding the long-term efficacy and harms associated with everolimus. This evidence is limited by a lack of a randomized comparison group, challenging causal conclusions. The goal of treatment with an mTOR inhibitor in patients with TSC-related SEGA is to decrease or stabilize the size and number of tumours and prevent SEGA-related clinical events, including hydrocephalus (a component of SEGA response, which was the primary composite outcome) and need for neurosurgery. The long-term results of the extension phase of the EXIST-1 trial supported the long-term efficacy of everolimus with respect to these treatment goals.

Treatment with everolimus is continuous. Until there is a tolerability issue, patients are continued on the systemic treatment with mTOR inhibitors. The clinical experts we consulted noted that patients often choose to continue everolimus treatment even into adulthood. There was insufficient data from the trial to indicate whether treatment with everolimus should be discontinued if SEGA volume is reduced below a particular

threshold. There is also uncertainty regarding the timing of initiating treatment with everolimus. The trial recruited patients with SEGAs 1 cm or larger. However, as the clinical experts for this review noted, the goal of systemic treatment with a mTOR inhibitor is to slow down SEGA growth and prevent or delay the need for surgical intervention.

Harms

In the EXIST-1 trial, 96% of patients treated with everolimus and 90% of patients treated with placebo experienced at least 1 AE. The longer-term safety profile of everolimus was consistent with what was previously reported, although it is difficult to distinguish between true harms of everolimus and effects attributable to the natural history of TSC after the placebo arm was discontinued. The most common grade 3 AEs were stomatitis, pyrexia, and convulsion; grade 4 events were rare. All but 1 patient experienced an AE during the long-term extension phase of the trial. Similar results were reported in Study 2485, in which all patients experienced at least 1 AE and at least 1 AE that was suspected to be related to treatment. The most common treatment-related AEs reported were upper respiratory tract infection (92.9%) and stomatitis (89.3%), which were mostly grade 1 or 2 in severity. There was no treatment discontinuation due to AEs. The clinical experts consulted indicated that AEs were consistent with the mechanism of action of everolimus. Mouth ulcerations, for example, are attributed to the downregulation of cellular turnover and are a known effect of mTOR inhibition. In the EXIST-1 trial, the frequency of emerging AEs of all types decreased over time, with stomatitis and mouth ulceration remaining the most common. The clinical experts indicated that these events are anticipated and managed in clinical practice.

The AE profile in the subgroup of pediatric patients aged 3 years and younger was generally consistent with those in the adult population of the EXIST-1 trial. All patients experienced AEs; most AEs were considered by the investigator to be grade 1 or grade 2 in severity. The most common AEs were stomatitis, cough, pharyngitis, and pyrexia. Fourteen patients (77.8%) experienced grade 3 or 4 AEs, which were suspected to be related to everolimus in 11 patients (61.1%). The most frequent (at least 10%) grade 3 AEs were stomatitis, pyrexia, and bronchitis in 4 patients (22.2%) each; convulsion in 3 patients (16.7%); and neutropenia, pneumonia, and decreased blood fibrinogen in 2 patients (11.1%) each. Pneumonia, upper respiratory tract infection, febrile infection, and gastroenteritis were reported in 1 patient (5.6%) each. SAEs were reported in 50.0% of the patients and consisted of pneumonia and pyrexia, bronchitis, upper respiratory tract infection, and convulsion. Most of this pediatric subgroup required a dose reduction or interruption (94.4%), and all patients (100.0%) required additional therapy because of AEs.

The safety data from the EFFECTS expanded-access study were comparable to the those from the EXIST-1 trial. Most AEs were grade 1 or 2 and were manageable. Stomatitis and infections were the most common AEs, and the AEs observed in the full population and the pediatric subpopulation appeared to be similar. Few patients discontinued due to AEs. Grade 3 or 4 AEs were reported in 23.3% of patients, which is less frequent than in the EXIST-1 trial. In the EXIST-1 trial, 33% of the patients in the everolimus arm and 23% of the patients in the placebo arm experienced a grade 3 or 4 AE, and, in the 2-year extension analysis, 51% of the patients were reported to have grade 3 or 4 AEs.

Cost

In adult and pediatric patients, the annual cost of everolimus (5 mg or 10 mg daily, regular tablets) is $62,873 per patient in jurisdictions with more costly wholesale pricing, and $18,492 per patient in jurisdictions with less costly wholesale pricing. For patients requiring a dosage of 7.5 mg daily, the annual cost is expected to be $125,747 and $36,985 in jurisdictions with higher and lower pricing, respectively. For patients requiring everolimus tablets for suspension, the annual per-patient cost ranges from $70,627 to $141,254. The annual cost of sirolimus in the adult patient population ranges from $6,891 to $10,337, depending on dose, while the annual cost of sirolimus in the pediatric patient population varies between $1,723 and $10,337, also depending on dose.

Thus, the use of everolimus for adult patients with SEGA associated with TSC is more costly than sirolimus. In jurisdictions with more costly wholesale pricing for everolimus, the incremental cost ranges from $52,537 to $118,856 per patient annually, and, in jurisdictions with less costly wholesale pricing, the incremental cost ranges from $8,155 to $30,093 per patient annually. As the annual cost of sirolimus varies between $1,723 and $10,337 per pediatric patient, in jurisdictions with more costly wholesale pricing for everolimus, the incremental cost ranges from $52,537 to $124,024 per patient annually, and, in jurisdictions with less costly wholesale pricing, the incremental cost ranges from $8,155 to $35,262 per patient annually. Finally, the incremental cost of everolimus tablets for suspension compared to sirolimus ranges from $60,290 to $139,531 in pediatric patients, and from $60,290 to $134,363 in adult patients. Costs are based on publicly available wholesale prices and may not reflect actual prices paid by public drug plans in Canada.

Conclusions

Evidence from the EXIST-1 trial suggests a benefit of everolimus for increased SEGA response and delayed SEGA progression in patients with TSC not requiring immediate surgery compared with placebo. The long-term analysis of the core phase and open-label extension phase of the trial suggests sustained SEGA response over time, with no additional or late-emerging toxicities; however, it was limited by a small sample size and lack of randomized comparator. There is an unmet clinical need for systemic treatments for SEGA associated with TSC to address the multisystem nature of the disease. For growing SEGAs that are asymptomatic, either surgery or mTOR inhibitors can be considered. However, surgical resection is highly burdensome to patients, carries significant risks, and does not prevent recurrence of SEGAs. Everolimus appears to meet a key treatment goal in patients with SEGAs, which is to slow down tumour growth or reduce tumour size and prevent the need for surgical intervention. There is no evidence to inform the benefits and harms of everolimus compared with sirolimus among patients with SEGAs associated with TSC.

Results of the cost comparison of drug acquisition costs demonstrate that everolimus is more costly than sirolimus for the treatment of SEGA associated with TSC. The incremental cost is dependent on the wholesale price of everolimus and the population treated (adult or pediatric patients). For adult patients with SEGA associated with TSC, in jurisdictions with more costly wholesale pricing, the incremental cost of everolimus ranges from $52,537 to $118,856 per patient annually compared with sirolimus; in jurisdictions

with less costly wholesale pricing, the incremental cost of everolimus ranges from $8,155 to $30,093 per patient annually compared with sirolimus. For pediatric patients, in jurisdictions with higher wholesale pricing, the incremental cost of everolimus ranges from $52,537 to $124,024 per patient annually; in jurisdictions with lower wholesale pricing, the incremental cost ranges from $8,155 to $35,262 per patient annually compared to sirolimus.

Based on the clinical review conclusions, no literature was identified comparing everolimus with sirolimus. Therefore, the comparative clinical efficacy of these treatments is unknown. Hence, based on publicly available pricing information, everolimus is associated with incremental drug acquisition costs and unknown clinical benefit compared with sirolimus.

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Appendix 1: Literature Search Strategy

Please note that this appendix has not been copy-edited.

Clinical Literature Search

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

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 and SEGA. 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.

The initial search was completed on January 8, 2024. Regular alerts updated the search until the meeting of FMEC on September 19, 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 (US FDA and European Medicines Agency). Google was used to search for additional internet-based materials. 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 ITCs dealing with everolimus and SEGA was run in MEDLINE on January 8, 2024. No search limits were applied.

Two 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.

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: January 8, 2024

Alerts: Bi-weekly search updates until project completion

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

Limits:

- Conference abstracts: excluded

Table 10: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a 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
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Keyword heading word
.dq	Candidate term word (Embase)
.pt	Publication type
.rn	Registry number
.nm	Name of substance word (MEDLINE)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

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. 1 or 2
4. exp Astrocytoma/
5. ((subependym* or sub-ependym*) adj3 (giant-cell* or astrocytoma* or glioma* or heterotopi* or layer* or neoplasm* or nodule*)).ti,ab,kf.
6. (astrocyt* adj2 (brain or tumor* or tumour*)).ti,ab,kf.
7. (SEGA* or SGCA* or SGCT*).ti,ab,kf.
8. or/4-7
9. 3 and 8

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. 1 or 2
4. exp subependymal giant cell astrocytoma/
5. ((subependym* or sub-ependym*) adj3 (giant-cell* or astrocytoma* or glioma* or heterotopi* or layer* or neoplasm* or nodule*)).ti,ab,kf,dq.
6. (astrocyt* adj2 (brain or tumor* or tumour*)).ti,ab,kf,dq.
7. (SEGA* or SGCA* or SGCT*).ti,ab,kf,dq.
8. or/4-7
9. 3 and 8
10. (conference abstract or conference review).pt.
11. 9 not 10

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 subependymal giant cell astrocytoma]

WHO ICTRP

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

[Search -- Studies with results | everolimus AND subependymal giant cell astrocytoma]

Health Canada's Clinical Trials Database

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

[Search -- Studies with results | everolimus AND subependymal giant cell astrocytoma]

EU Clinical Trials Register

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

[Search -- Studies with results | everolimus AND subependymal giant cell astrocytoma]

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 -- Studies with results | everolimus AND subependymal giant cell astrocytoma]

Grey Literature

Search dates: December 15 to 20, 2023

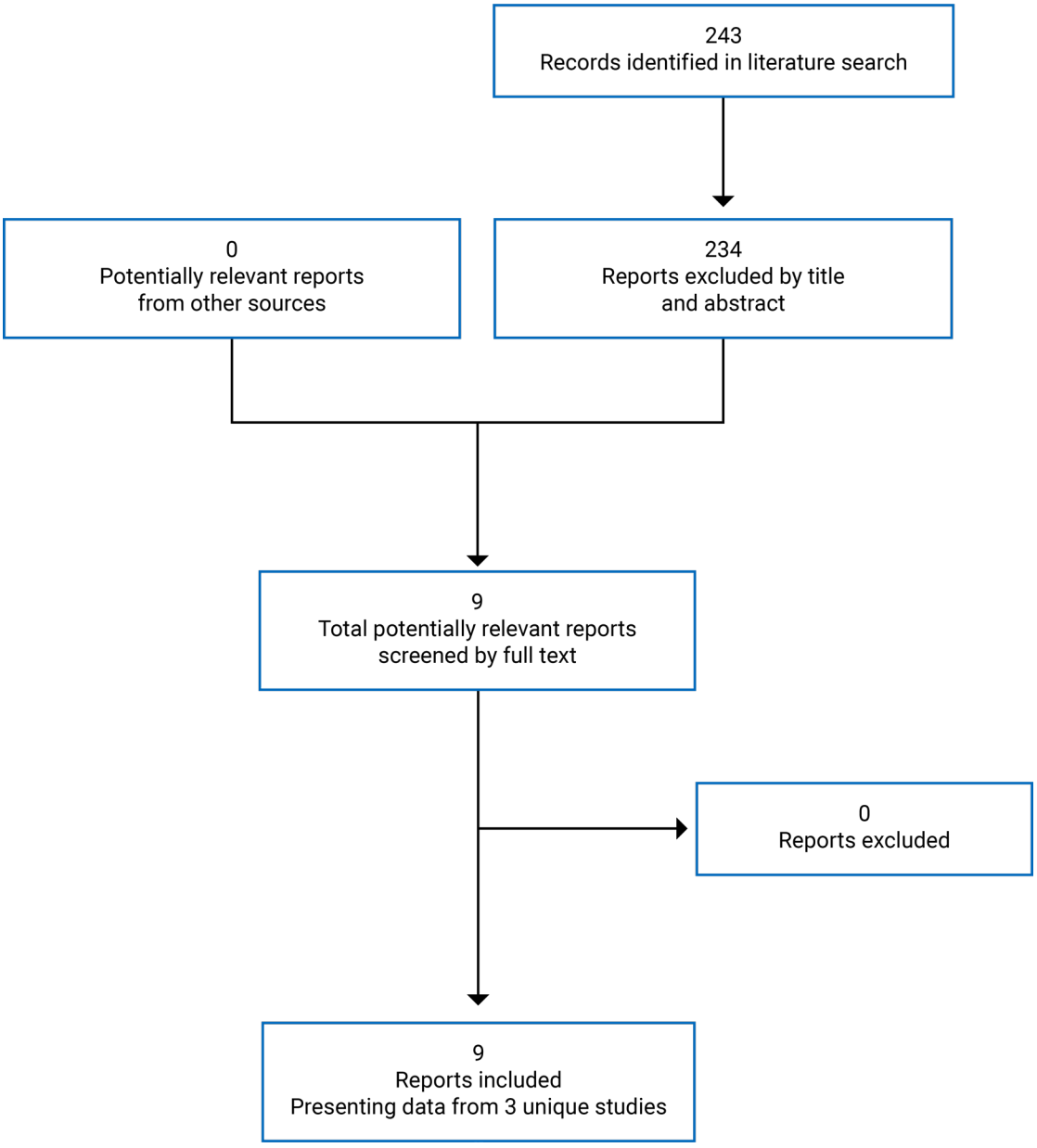
Keywords: everolimus, subependymal giant cell astrocytoma, tuberous sclerosis

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)
- Health Statistics
- Internet Search
- Open Access Journals

Appendix 2: Study Selection

Figure 2: Flow Diagram for Inclusion and Exclusion of Studies



Canada's Drug Agency
L'Agence des médicaments du Canada
Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

Canada's Drug Agency (CDA-AMC) is a pan-Canadian health organization. Created and funded by Canada's federal, provincial, and territorial governments, we're responsible for driving better coordination, alignment, and public value within Canada's drug and health technology landscape. We provide Canada's health system leaders with independent evidence and advice so they can make informed drug, health technology, and health system decisions, and we collaborate with national and international partners to enhance our collective impact.

Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.