Common Drug Review
Clinical Review Report

September 2017

Drug	everolimus (Afinitor) (oral tablets)
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
Listing request	Per indication
Manufacturer	Novartis Pharmaceuticals Canada Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in pediatrics who provided input on the conduct of the review and the interpretation of findings.

This report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). Through the Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

The information in this report is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment with respect to the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of this document to ensure that its contents are accurate, complete, and up-to-date as of the date of publication, CADTH does not make any guarantee to that effect. CADTH is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in the source documentation. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the information in this document or in any of the source documentation.

This document is intended for use in the context of the Canadian health care system. Other health care systems are different; the issues and information related to the subject matter of this document may be different in other jurisdictions and, if used outside of Canada, it is at the user's risk. This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

CADTH takes sole responsibility for the final form and content of this document, subject to the limitations noted above. The statements and conclusions in this document are those of CADTH and not of its advisory committees and reviewers. The statements, conclusions, and views expressed herein do not necessarily represent the views of Health Canada or any Canadian provincial or territorial government. Production of this document is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon.

TABLE OF CONTENTS

Tables

Figure

ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
BSA	body surface area
CDR	CADTH Common Drug Review
CSF	cerebrospinal fluid
CSR	clinical study report
CI	confidence interval
CMH	Cochran–Mantel–Haenszel
DBRCT	double-blind randomized controlled trial
EIAED	enzyme-inducing anti-epileptic drugs
FAS	full analysis set
GTP	guanosine triphosphate
HRQoL	health-related quality of life
LOCF	last observation carried forward
MCID	minimal clinically important difference
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
mTORC1	mammalian target of rapamycin subtype C1
NOC/c	Notice of Compliance with conditions
PgP	P-glycoprotein
PP	per protocol
PPS	per-protocol set
QOLCE	Quality of Life in Childhood Epilepsy Questionnaire
RCT	randomized controlled trial
SAE	serious adverse event
SEGA	subependymal giant cell astrocytoma
SEN	subependymal nodules
SD	standard deviation
SSQ	seizure severity questionnaire
TSC	tuberous sclerosis complex
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

At the time everolimus was submitted to the CADTH Common Drug Review (CDR) for review, the Health Canada indication (Notice of Compliance with conditions [NOC/c]) was for the treatment of patients three years of age or older 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. The NOC/c was based on data from study 2485 only.

CDR was, however, notified by the manufacturer (via comments on the draft clinical and pharmacoeconomic reviews) that a new product monograph for everolimus had been issued (date of revision: November 3, 2014) with a change to the indication whereby the age limit (≥ 3 years) was removed. According to the manufacturer, the revision was based on inclusion of the EXIST-1 data as part of the post-approval commitment following the initial NOC/c. Because these data were already included in the CDR review, the revision in the indication does not affect the reported results or the conclusions of the review.

Of note:

- The revised indication also includes Afinitor Disperz (everolimus tablets for oral suspension), which was not part of the current submission to CDR and therefore was not within the scope of this review.
- Although the age limit was removed from the indication, the revised product monograph states that, for pediatric populations, "Afinitor and Afinitor Disperz have not been studied in pediatric patients with SEGA < 1 year of age and are not recommended for use in this age group. There are limited efficacy and safety data in patients 1 to 3 years of age with Afinitor."[1]

Introduction

TSC is an autosomal dominant condition, usually caused by a mutation in either the *TSC1* gene (which encodes hamartin) or the *TSC2* gene (which encodes tuberin),[2] and can affect any racial or ethnic group.[3] This mutation, which can be hereditary or spontaneous,[4] causes deficiency in TSC1 or TSC2. When TSC1 or TSC2 are deficient, there is limited activation of mammalian target of rapamycin complex 1 (mTORC1), which is then upregulated and leads to the formation of hamartomas throughout the body. TSC affects one in 6,000 live births and there are approximately 1 million people living with the disease. The expression of TSC is highly variable,[2] although it is often identified by Vogt's triad (facial angiofibromas, mental retardation, intractable epilepsy). However, less than 40% of patients present with all three.[3]

SEGAs are slow-growing benign tumours associated with TSC. SEGAs consist of mixed lineage, and are thus more appropriately termed subependymal giant cell tumour (SGCTs), rather than subependymal giant cell astrocytomas. Symptomatic SGCTs occur in 6% to 9% of patients with TSC, and usually become symptomatic between 10 and 30 years of age.[5] The tumours typically arise in the periventricular area and thus one of the major complications is hydrocephalus, when one or more ventricles become obstructed. The tumours can also lead to seizures, as well as vision loss, fatigue, depression, and decreased appetite.

There are limited options for disease-modifying medical therapies in TSC, and SEGAs specifically. Surgery has traditionally been the intervention that has the greatest and most dramatic impact on the disease itself. As an example, surgery has been used in the past to reduce the severity of seizures. Surgery can include not just resection of the tumour, but placement of shunts to facilitate drainage of cerebrospinal fluid (CSF). There are also drugs that are used to address complications of SEGAs, such as anti-epileptic agents for seizures.[5]

Everolimus is a mammalian target of rapamycin (mTOR) subtype C1 inhibitor. mTOR plays an important role in regulating cell growth, proliferation and survival. The *TSC1* and *TSC2* genes are oncogenic suppressors and the proteins they encode regulate mTORC1 signalling. The loss or activation of *TSC1* or *TSC2* leads to constitutive upregulation of the mTORC1 complex acting through Ras homolog enriched in brain protein -guanosine triphosphate (rheb-GTP) which leads to dysregulation of normal cell growth and development of the hamartomas seen in TSC.

Everolimus is indicated for the treatment of patients with SEGAs associated with TSC that have demonstrated serial growth, who are not candidates for surgical resection and for whom immediate surgical intervention is not required. For SEGAs associated with TSC, everolimus dose selection and dose adjustments are individualized (based on body surface area [BSA], in square metres [m^2]) 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.

Indication under review
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.
Listing criteria requested by sponsor
Per indication

The objective of this review is to perform a systematic review of the beneficial and harmful effects of everolimus for the treatment of patients three years of age or older with SEGAs associated with TSC that have demonstrated serial growth, who are not candidates for surgical resection and for whom immediate surgery is not required.

Results and Interpretation

Included Studies

Two studies, EXIST-1 and study 2485, met the inclusion criteria for this review. EXIST-1 was a pivotal phase 3 double-blind randomized controlled trial (DBRCT) that randomized 117 patients in a 2:1 ratio to either everolimus or placebo. Patients were treated for six months in the double-blind phase, and there is an ongoing four-year open-label extension. EXIST-1 was multinational with Canadian sites, and was sponsored by the manufacturer of everolimus. The primary outcome was the proportion of patients with confirmed tumour response (reduction of 50% in total target SEGA volume), in the absence of worsening of non-target SEGAs, new lesions of at least 1 cm in diameter, and new or worsening hydrocephalus. The key secondary outcomes included change in seizure frequency per 24 hours, time to SEGA progression, and the skin lesion response rate. Study 2485 was a pivotal phase 2 single-treatment group study (N = 28) with an initial six-month treatment phase and with an extension phase that

followed patients out to five years. This was a single-centre study, conducted at a hospital in the US, and sponsored by the manufacturer of everolimus. The primary outcome was change from baseline in volume of the primary SEGA lesion after six months of treatment with study drug. Secondary end points included changes in quality of life using the Quality of Life in Childhood Epilepsy scale (QOLCE), neuropsychological evaluations, cognitive evaluations, and safety.

Key issues related to bias included the lack of a control group in study 2485, which limits the conclusions that can be drawn from this study. EXIST-1 was not powered to assess clinical outcomes, such as need for neurosurgery or episodes of hydrocephalus. Additionally, there were some differences in baseline characteristics in this study — particularly for tumour burden and for baseline seizure frequency — that may have either biased results in favour of or against everolimus.

Efficacy

There were no deaths in the six-month double-blind phase of EXIST-1. [redacted]. There do not appear to have been any cases of acute hydrocephalus in either the everolimus or placebo groups in EXIST-1, and no episodes of acute hydrocephalus with everolimus in study 2485. No patients required neurosurgery in EXIST-1 and the requirement for neurosurgery was not reported in study 2485. There was no statistically significant difference between everolimus and placebo with respect to change in daily seizure frequency (median difference of 0.00; 95% confidence interval [CI], 0.00 to 0.00; *P* = 0.2004). Study 2485 reported a statistically significant reduction from baseline in daily seizure frequency for everolimus (median reduction in daily seizures of 0.99; *P* = 0.022). Quality of life was not investigated in EXIST-1, but in study 2485, there was a statistically significant improvement from baseline to month 6 on the QOLCE (least squares mean change from baseline of 3.47 [95% CI, 0.19 to 6.74]). However, the interpretation of this finding is complicated by the lack of a control group in this study, and the lack of an established minimal clinically important difference (MCID).

Best SEGA response was the primary outcome of EXIST-1. By week 24, 35% of everolimus patients and no placebo patients had achieved a response, for a difference in response rates of 35% (95% CI, 15 to 52; *P* < 0.0001). Best SEGA response was not evaluated in study 2485. In EXIST-1, the estimate of the difference in least squares means for change from baseline in total SEGA volume between everolimus and placebo was –0.88 cm^3 (95% CI, –1.24 to –0.52; *P* < 0.0001. Therefore, everolimus reduced total SEGA volume compared with placebo. Change in total SEGA volume was the primary outcome of study 2485, but there was no comparator in this study. The median reduction in SEGA volume from baseline was 0.83 cm^3 (95% CI, 0.5 to 1.2).

Time to SEGA progression was reported in EXIST-1, and no everolimus patients and 15% of placebo patients progressed during the 24-week study. The statistical significance of the outcome could not be declared as the hierarchical testing procedure was stopped prior to this outcome. The proportion of patients developing new lesions was not reported. Neuropsychological findings were also not reported due to issues with administration of the instrument and irregularities in scoring.

Harms

There were 96% of everolimus patients and 90% of placebo patients with an adverse event in EXIST-1. The most common adverse event with everolimus was mouth ulceration (32% of everolimus patients versus 5% placebo), and stomatitis (31% versus 21%, respectively). All (100%) patients experienced an adverse event in study 2485.

Serious adverse events occurred in 19% of everolimus patients and 8% of placebo patients in EXIST-1. The most common serious adverse events were convulsion (4% of everolimus versus 5% placebo) and pyrexia (4% versus 0%, respectively). [redacted]

There were no withdrawals due to adverse events in either study. Notable harms included infection, which occurred in 72% of everolimus patients and 67% placebo, and increased total cholesterol (87% versus 49%, respectively). [redacted].

Conclusions

One DBRCT and one single-group study in patients with SEGAs associated with TSC were included in this review. EXIST-1 (N = 117) randomized patients 2:1 to either everolimus or placebo, over a double-blind treatment period of six months. Study 2485 enrolled 28 patients at a single centre in the US. There were no deaths in EXIST-1 and [redacted], and no patients required neurosurgery or had episodes of acute hydrocephalus in either study. The incidence and severity of seizures, a key complication of SEGAs, were not reduced with everolimus treatment compared with placebo. However, interpretation of all hard clinical outcomes is complicated by the small sample size and relatively short duration of the study. Quality of life was not assessed in EXIST-1. Everolimus was statistically significantly superior to placebo for the proportion of patients achieving a SEGA response, which was the primary outcome of EXIST-1. EXIST-1 was not powered to detect differences in harms between everolimus and placebo, [redacted].

TABLE 1: SUMMARY OF RESULTS

Outcome	EXIST-1		Study 2485
	Everolimus N = 78	Placebo N = 39	Everolimus N = 28
Mortality			
Deaths n, N (%)	0	0	[redacted]
Episodes of acute hydrocephalus			
Patients by week 24, n (%)	0[a]	0[a]	0
Patients requiring neurosurgery			
n (%)	0	0	NR
Seizure frequency/24h			
Mean (SD) baseline	3.41 (8.36)	5.58 (14.98)	6.30 (7.880)
Change from baseline to week 24/LOCF	–1.24 (6.12)	–0.24 (5.70)	–2.65 (6.089) N = 16
Median	0.00	0.00	–0.99
95% CI for the median	[0.00, 0.00]	[0.00, 0.00]	
Range			[–17.0, 10.8]
P value	P = 0.2004[b]		P = 0.022[c]
Symptoms: SSQ			
Mean (SD) global change score, week 24	[redacted]	[redacted]	NE
Median	[redacted]	[redacted]	
SEGA Response			
Response by week 24, n (%)	27 (35)	0	NE
Difference in response rates [95% CI]	34.6 (15.1 to 52.4), P < 0.0001[d]		NE
Withdrawals			
Total, N (%)	2 (3)	8 (21)	28 (100)
Serious AEs			
n, N (%)	15 (19)	3 (8)	9 (32)
WDAEs			
n, N (%)	0	0	0
Notable harms(s)			
Infection	56 (72)	26 (67)	28 (100)
Increased total cholesterol	[redacted]	[redacted]	[redacted]
Cytopenias	[redacted]	[redacted]	[redacted]
• Decreased neutrophil count	[redacted]	[redacted]	[redacted]
• Neutropenia	[redacted]	[redacted]	[redacted]
Proteinuria	NR	NR	4 (14)

AE = adverse event; ANCOVA = analysis of covariance; CDR = CADTH Common Drug Review; CI = confidence interval; EIAED = enzyme-inducing anti-epileptic drugs; LOCF = last observation carried forward; NE = not evaluated; SD = standard deviation; SEGA = subependymal giant cell astrocytoma; SSQ = seizure severity questionnaire; WDAE = withdrawals due to adverse events.

[a] Based on CDR review of individual patient data.

[b] *P* value obtained from rank ANCOVA (one-sided test) with baseline seizure frequency as covariate, stratified by use of EIAED at randomization (EIAED use versus EIAED non-use).

[c] *P* value obtained from a sign test.

[d] *P* value is obtained from the one-sided exact Cochran–Mantel–Haenszel test, stratified by the protocol stratification factor (EIAED use versus EIAED non-use).

Source: EXIST-1 Clinical Study Report[6]; Source: Study 2485.[7]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Tuberous sclerosis complex (TSC) is an autosomal dominant condition, usually caused by a mutation in either the *TSC1* gene (located on chromosome 9, encoding hamartin) or the *TSC2* gene (located on chromosome 16, encoding tuberin),[2] and can affect any racial or ethnic group.[3] This mutation, which can be hereditary or spontaneous,[4] causes deficiency in TSC1 or TSC2. When TSC1 or TSC2 is deficient, there is limited activation of mammalian target of rapamycin complex 1 (mTORC1), which is then upregulated and leads to the formation of hamartomas throughout the body.

TSC affects one in 6,000 live births and there are approximately one million people living with the disease. The expression of TSC is highly variable,[2] although it is often identified by Vogt's triad (facial angiofibromas, mental retardation, intractable epilepsy). However, fewer than 40% present with all three.[3]

A subependymal giant cell astrocytoma (SEGA) is a slow-growing benign tumour associated with TSC. According to UpToDate, SEGAs consist of mixed lineage, and are thus more appropriately termed subependymal giant cell tumours (SGCTs), rather than SEGAs. Symptomatic SGCTs occur in 6% to 9% of patients with TSC, and usually become symptomatic between 10 and 30 years of age. The tumours typically arise in the periventricular area and thus one of the major complications is hydrocephalus, when one or more ventricles become obstructed. The tumours can also lead to seizures, as well as vision loss, fatigue, depression, and decreased appetite. (See Appendix 7: REVIEW OF TUBEROUS SCLEROSIS COMPLEX WITH SUBEPENDYMAL GIANT CELL ASTROCYTOMA for further details.)

1.2 Standards of Therapy

There are limited options for disease-modifying medical therapies in TSC, and SEGAs specifically. Surgery has traditionally been the intervention that has the greatest and most dramatic impact on the disease itself. Surgery has been used in the past to reduce the severity of seizures, for example. Surgery can include not just resection but placement of shunts to facilitate drainage of cerebrospinal fluid (CSF). There are also drugs that are used to address complications of SEGAs, such as anti-epileptic agents for seizures.

1.3 Drug

Everolimus is a mammalian target of rapamycin (mTOR) subtype C1 inhibitor. mTOR plays an important role in regulating cell growth, proliferation and survival. Tuberous sclerosis complex genes (*TSC1* and *TSC2*) are oncogenic suppressors and the proteins they encode regulate mTORC1 signalling. The loss or activation of *TSC1* or *TSC2* leads to constitutive upregulation of the mTORC1 complex acting through Ras homolog enriched in brain protein -guanosine triphosphate (rheb-GTP) which leads to dysregulation of normal cell growth and development of the hamartomas seen in TSC.

Everolimus is indicated for the treatment of patients with SEGAs associated with TSC that have demonstrated serial growth, who are not candidates for surgical resection and for whom immediate surgical intervention is not required. (Note: Please refer to the EXECUTIVE SUMMARY for additional background regarding the indication reviewed by the CADTH Common Drug Review (CDR). For SEGAs associated with TSC, everolimus dose selection and dose adjustments are individualized (based on body surface area [BSA], in square metres [m^2]) 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. Titration may

be required to attain target everolimus trough-concentrations (5 ng/mL to 15 ng/mL, subject to tolerability) and further titrated to obtain the optimal therapeutic effect within this range. Concomitant anti-epileptic therapy may affect the metabolism of everolimus and may contribute to individual patient variance in effect and tolerability (see Appendix 6: REVIEW OF PHARMACOLOGY: DRUG INTERACTIONS).

Everolimus has several other indications. The indication closest to that currently under review is for the treatment of adult patients (≥ 18 years of age) with renal angiomyolipoma associated with TSC and who do not require immediate surgery. Everolimus is also indicated for a variety of neoplasms, including breast cancer (human epidermal growth factor receptor 2 negative), metastatic renal cell carcinoma, and pancreatic neuroendocrine tumours.

Indication under review
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.
Listing criteria requested by sponsor
Per indication

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of everolimus for the treatment of patients with SEGAs associated with TSC that have demonstrated serial growth, who are not candidates for surgical resection and for whom immediate surgery is not required.

2.2 Methods

Studies were selected for inclusion in the systematic review based on the selection criteria presented in Table 2.

TABLE 2: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEWS

Patient Population	Patients with SEGAs associated with TSC that have demonstrated serial growth, who are not candidates for surgical resection and for whom immediate surgical intervention is not required
Intervention	Everolimus administered orally at recommended doses based on BSA[a]
Comparators	Placebo
Outcomes	**Key efficacy outcomes:** Mortality Episodes of acute hydrocephalus Quality of life Symptoms due to increased intracranial pressure Number of patients requiring neurosurgery **Other efficacy outcomes:** Objective response Change in SEGA volume Development of new lesions Progression-free survival Neuropsychological findings **Harms outcomes:** AEs SAEs WDAEs Notable harms: infection, elevated cholesterol, bone marrow suppression, proteinuria
Study Design	Published and unpublished RCTs

AE = adverse event; BSA = body surface area; RCT = randomized controlled trial; SAE = serious adverse events; SEGA = subependymal giant cell astrocytoma; TSC = tuberous sclerosis complex; WDAE = withdrawal due to adverse events.
[a] Dosing and dose adjustments should be individualized based on target trough levels of 5 ng/mL to 15 ng/mL, as tolerated.

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Afinitor (everolimus) and Subependymal Giant Cell Astrocytomas (SEGA), associated with Tuberous Sclerosis Complex.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on October 1, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on February 18, 2015. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Databases (free), Internet Search and Open Access Journals. Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

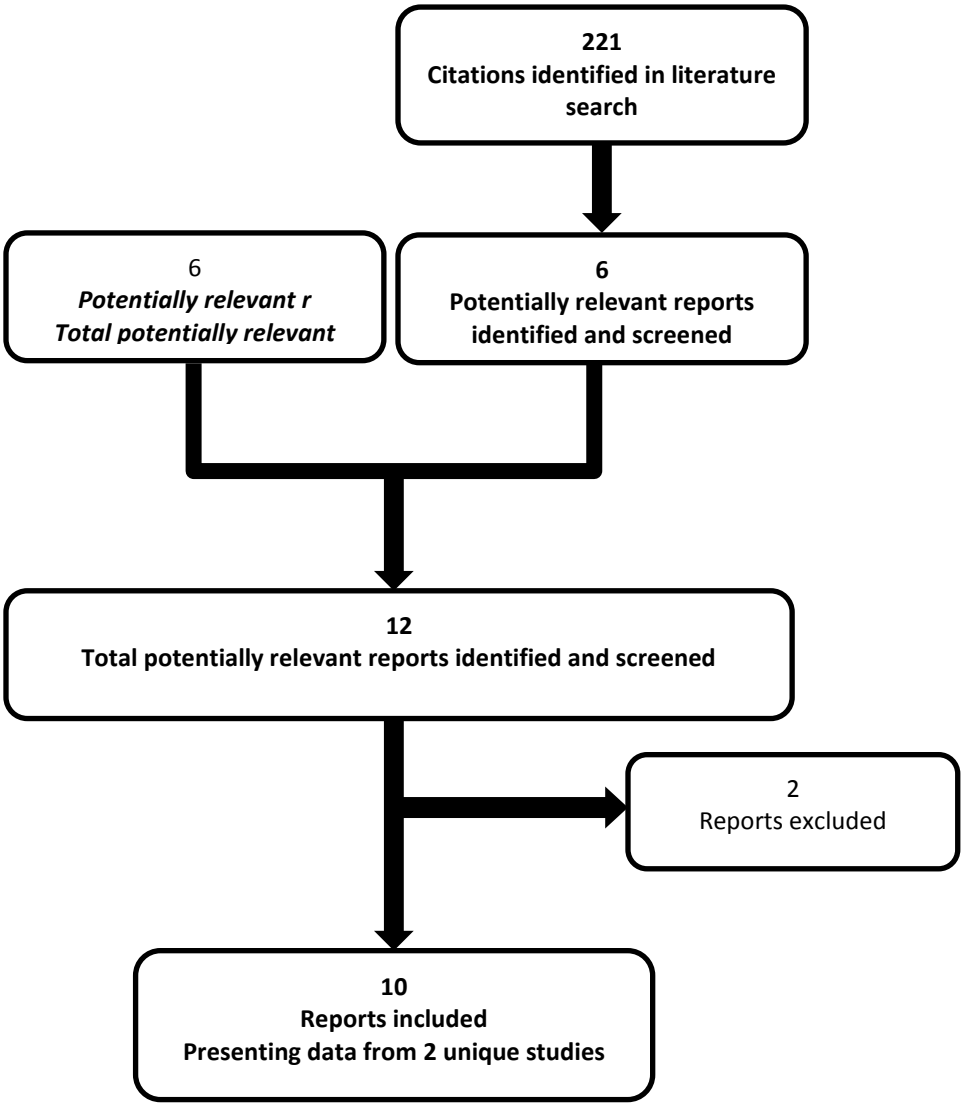
Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the pre-determined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 3; excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings from the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 2 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES



QUOROM = QUALITY OF REPORTING OF META-ANALYSES.

TABLE 3: DETAILS OF INCLUDED STUDIES

		EXIST-1	Study 2485
DESIGNS & POPULATIONS	**Study Design**	DBRCT	Non-RCT, single-group study
	Locations	24 centres: Canada, Australia, US, EU	Single centre: Cincinnati Children's Hospital
	Study period	August 10, 2009, to ongoing	January 7, 2007, to January 28, 2014
	Randomized (N)	N = 117	N = 28
	Inclusion Criteria	Age 0 to 65 years TSC according to consensus criteria At least one target SEGA with longest diameter ≥ 1 cm assessed with multiphase MRI, and ≥ 1 of the following when the results of an MRI done within 4 weeks of randomization were compared with an earlier MRI: Serial worsening (defined as increase of ≥ 25% in volume of SEGAs based on 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 CSF flow	Age ≥ 3 years TSC according to modified Gomez criteria or genetic test Presence of giant cell astrocytoma as defined by imaging characteristics and serial increase in size of lesion on ≥ 2 MRI scans Adequate renal function (creatinine < 1.5 mg/dL)
	Exclusion Criteria	Patients for whom SEGA-related surgery is likely to be required, in the opinion of the investigator	Clinical evidence of impending herniation or focal neurologic deficit related to the patient's astrocytoma
DRUGS	**Intervention**	Everolimus 4.5 mg/m^2 BSA daily Adjusted to obtain blood trough of 5 ng/mL to 15 ng/mL	Everolimus 3 mg/m^2, once daily or on alternate days Subsequent titration to blood concentrations of 5 ng/mL to 15 ng/mL
	Comparator(s)	Placebo	None
DURATION	**Phase**		
	Screening	2 weeks	NR
	Double-blind	6 months	6 months (open label)
	Follow-up	4-year extension	5-year extension
OUTCOMES	**Primary End Point**	Proportion of patients with confirmed tumour response (reduction of 50% in total target SEGA volume), in the absence of worsening of non-target SEGA, new lesions of ≥ 1cm diameter and new or worsening hydrocephalus	Change from baseline in the volume of the primary SEGA lesion at 6 months after the start of treatment
	Other End Points	Key secondary: Change in seizure frequency/24h Time to SEGA progression Skin lesion response rate (in patients with ≥ 1 skin lesion at baseline)	QOLCE Neuropsychological evaluations Cognitive evaluation Safety
NOTES	**Publications**[a]	Kingswood 2014[8]; Franz 2013[9]	Krueger 2010[10]; Krueger 2013[11]

BSA = body surface area; CSF = cerebrospinal fluid; DBRCT = double-blind randomized controlled trial; MRI = magnetic resonance imaging; RCT = randomized controlled trial; QOLCE = Quality of Life in Childhood Epilepsy; SEGA = subependymal giant cell astrocytoma; TSC = tuberous sclerosis complex.

[a] Four additional reports were included (Manufacturer's submission[2], FDA Clinical and Statistical Reviews[12,13], HC Reviewers Report[14]).

Source: EXIST-1 Clinical Study Report (CSR); Study 2485 CSR.[7]

3.2 Included Studies

3.2.1 Description of studies

a) EXIST-1

Two studies, EXIST-1 and study 2485, met the inclusion criteria for this review. EXIST-1 was a pivotal phase 3 DBRCT that randomized 117 patients in a 2:1 ratio to either everolimus or placebo. Randomization was stratified based on the use of enzyme-inducing anti-epileptic drugs (EIAEDs). Patients were treated for six months in the double-blind phase, and there was a four-year open-label extension. EXIST-1 was multinational with Canadian sites, and was sponsored by the manufacturer of everolimus. The primary outcome was the proportion of patients with confirmed tumour response, in the absence of worsening of non-target SEGAs, new lesions of at least 1 cm in diameter, and worsening hydrocephalus. The key secondary outcomes included change in seizure frequency per 24 hours, time to SEGA progression, and the skin lesion response rate.

All radiology evaluations were performed initially by the local radiologist. However, the designation of response and progression in the database was based only on the evaluations made by the Independent Central Radiology Review. The same radiologist/physician was to perform the evaluation for the entire duration of the study; in addition, the same method of assessment and technique was used for the characterization of SEGA lesions. Following receipt of each magnetic resonance imaging (MRI) scan, the Central Radiology Review was completed, and the results were to be communicated back to the participating centre within three weeks. If an initial observation of response was made, a confirmation scan was to be obtained approximately 12 weeks after the initial observation (and no sooner than eight weeks after). Volume was calculated by the independent central radiologist using a validated software platform (VS Production Platform). Target SEGA lesions were to be identified; at least one measurable target SEGA lesion with a longest diameter of ≥ 1.0 cm was to be observed at baseline for eligibility. Up to five target and non-target SEGA lesions were to be reported.

Core treatment phase: the period lasting from randomization of the first patient until the last randomized patient was treated with everolimus or placebo for six months. The core treatment phase was divided into the following:

- **Double-blind treatment period** in which all patients were randomized to everolimus or placebo. Treatment continued until SEGA progression or unacceptable toxicity.
- **Open-label period** in which patients who had been receiving placebo and experienced a SEGA progression (as per central review or unequivocal progression according to investigator assessment) during the blinded treatment phase were offered open-label everolimus
- **Extension phase:** if superiority of everolimus was shown during the core treatment phase, an extension phase was launched. All patients still receiving study treatment at this time, as well as those being followed for post-treatment evaluation, were given the option of starting open-label everolimus. The extension phase will run until four years after the last patient was randomized, ensuring patient follow-up of four to five years (assuming patient accrual over a period of approximately 12 months).

b) Study 2485

Study 2485 was a phase 2 non-RCT (N = 28) with an initial six-month treatment phase and an extension that followed patients out to five years. This was a single-centre study, conducted at a hospital in the US, and sponsored by the manufacturer of everolimus. The primary outcome was change from baseline in volume of the primary SEGA lesion after six months of treatment with study drug. Secondary end points included changes in quality of life using the Quality of Life in Childhood Epilepsy scale (QOLCE), neuropsychological evaluations, cognitive evaluations, and safety.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

Patients aged 0 to 65 years were enrolled into EXIST-1. Inclusion was based on characteristics of the SEGA lesion assessed by MRI, and included size (at least one target lesion with longest diameter of at least 1 cm) and at least one of: increased volume (at least 25% increase), new lesions (at least 1 cm diameter), or new or worsening hydrocephalus (according to changes in ventricular configuration, periventricular edema, dynamics of CSF flow). Patients also had to be medically stable and unlikely to require surgery for SEGAs, with no critical hydrocephalus or imminent cerebral herniation. Patients in study 2485 had to be at least three years of age, and inclusion was based on presence of a giant cell astrocytoma defined by imaging characteristics and a serial increase in lesion size on at least two MRI scans.

b) Baseline Characteristics

Patients in EXIST-1 were young, aged 10 years, and 57% were male. The vast majority (94%) were Caucasian, and 86% had worsening SEGAs when compared with pre-baseline. Almost all patients had either one or two target SEGA lesions and only a small proportion (7%) had prior anti-SEGA medication or surgery. No details regarding what constituted "prior anti-SEGA medication" were provided. When compared with EXIST-1, patients in study 2485 were slightly older (mean age 12.5 years), with a higher proportion of males (61%).

Demographics were generally similar between groups in EXIST-1, although there was a larger proportion of males in the everolimus group compared with placebo (63% versus 46%). There were some differences with respect to baseline disease characteristics. With respect to target SEGA lesions, fewer everolimus patients had one target lesion (51% versus 64%), and more everolimus patients had two target lesions (44% versus 36%) compared with placebo. The mean SEGA volume was also higher with everolimus than with placebo (2.8 ± 3.8 versus 1.8 ± 1.7). Additionally, 10% of everolimus patients had hydrocephalus at baseline, versus none in placebo.

TABLE 4: SUMMARY OF BASELINE CHARACTERISTICS

Title	EXIST-1		Study 2485
	EVEROLIMUS N = 78	**PLACEBO N = 39**	**EVEROLIMUS N = 28**
Mean age (SD)	10.1 (5.9)	10.3 (7.3)	12.5 (7.5)
Male, n (%)	49 (63)	18 (46)	17 (61)
Ethnicity, n (%)			
Caucasian	73 (94)	36 (92)	24 (86)
Black	3 (4)	1 (3)	2 (7)
Pacific islander	1 (1)	0	0
Other	1 (1)	2 (5)	2 (7)
SEGA, n (%)	78 (100)	39 (100)	NR
Subependymal nodule	[redacted]	[redacted]	NR
Cortical tuber	[redacted]	[redacted]	NR
Hypomelanotic macules (≥3)	[redacted]	[redacted]	NR
Facial angiofibromas or forehead plaque	[redacted]	[redacted]	25 (89)
Cardiac rhabdomyoma, single or multiple	[redacted]	[redacted]	NR
Renal angiomyolipoma	[redacted]	[redacted]	NR

Title	EXIST-1		Study 2485
Shagreen patch (connective tissue nevus)	[redacted]	[redacted]	NR
Non-traumatic ungual or periungual fibroma	[redacted]	[redacted]	NR
Multiple retinal nodular hamartomas	[redacted]	[redacted]	NR
Lymphangioleiomyomatosis	[redacted]	[redacted]	NR
Bilateral SEGA	[redacted]	[redacted]	12 (43)
SEGA characteristics, n (%)			
Worsening SEGA compared with pre-baseline	66 (85)	34 (87)	NR
Serial growth	63 (81)	32 (82)	NR
New SEGA lesion ≥ 1 cm in longest diameter	7 (9)	5 (13)	NR
New or worsening hydrocephalus	5 (6)	0	NR
Number of target SEGA lesions, n (%)			
0	2 (3)	0	
1	40 (51)	25 (64)	15 (54)
2	34 (44)	14 (36)	13 (46)
3	1 (1)	0	0
≥ 4	1 (1)	0	0
Number of non-target SEGA lesions, n (%)			
0	[redacted]	[redacted]	NR
1	[redacted]	[redacted]	NR
2	[redacted]	[redacted]	NR
3	[redacted]	[redacted]	NR
SEGA volume (sum of volumes of target) SEGA lesions [cm^3])			
Mean (SD)	2.83 (3.82)	1.77 (1.68)	NR
Hydrocephalus, n (%)			
Yes	8 (10.3)	0	6 (21)
Any prior anti-SEGA medication or surgery, n (%)			
Surgery	6 (7.7)	2 (5.1)	4 (14)

NR = not reported; SEGA = subependymal giant cell astrocytoma; SD = standard deviation.
Source: EXIST-1 Clinical Study Report (CSR)[6]; Study 2485 CSR.[7]

3.2.3 Interventions

In EXIST-1, everolimus was dosed based on body surface area (4.5 mg/m^2), and adjusted using blood trough levels (5 ng/mL to 15 ng/mL). Patients were treated for six months in the double-blind phase, and there was a four-year extension.

The use of other concomitant medication or therapy deemed necessary for the care of the patient (e.g., EIAEDs) was allowed. Randomization was stratified based on the use of EIAEDs. The investigator was to instruct the patient to notify the study site about any new medications taken after commencing treatment with the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient started

everolimus and for up to 84 days (12 weeks) after study drug discontinuation were listed on the Concomitant Medications/Significant Non-drug Therapies clinical report form.

3.2.4 Outcomes

The primary efficacy end point of EXIST-1 was the SEGA response rate, defined as the proportion of patients with a best overall SEGA response of "SEGA response" as per independent central radiological review. "SEGA response," which was confirmed with a second scan performed approximately 12 weeks later (and no sooner than eight weeks later), was defined as follows:

- A reduction in SEGA volume of ≥ 50% relative to baseline, where SEGA volume was the sum of the volumes of all target SEGA lesions identified at baseline
- No unequivocal worsening of non-target SEGA lesions, no new SEGA lesions (≥ 1 cm in longest diameter), and no new or worsening hydrocephalus (defined by central radiological assessment of ventricular configuration changes, ventricular cap signs [periventricular edema], and qualitative assessment of CSF flow dynamics).

Time to SEGA progression was defined as the time from the date of randomization to the date of the first documented SEGA progression as per the Independent Central Review. SEGA progression was defined as one or more of the following:

- Increase from nadir of ≥ 25% in SEGA volume to a value greater than baseline SEGA volume (where SEGA volume was the sum of the volumes of all target SEGA lesions identified at baseline, and where nadir was the lowest SEGA volume obtained for the patient previously in the trial [including baseline]), or
- Unequivocal worsening of non-target SEGA lesions, or
- Appearance of a new SEGA lesion ≥ 1.0 cm in longest diameter, or
- New or worsening hydrocephalus, defined by central radiological assessment of ventricular configuration changes, ventricular cap signs (periventricular edema) and qualitative assessment of CSF flow dynamics.

Quality of life was assessed using the QOLCE questionnaire. As the name suggests, QOLCE was developed for epilepsy, and is not specific for SEGAs. It is a 76-item questionnaire with 16 subscales (quality of life, physical restrictions, general health, energy/fatigue, behaviour, attention/concentration, stigma, memory, social activities, social interactions, language, other cognitive processes, anxiety, control/helplessness, and self-esteem) and five functional life domains (physical function, social function, cognition, behaviour, and emotional well-being).[15] The potential responses of excellent, very good, good, fair, and poor are provided by the parents, and these are subsequently numbered 1 to 5 (as per instructions) and converted to a 0 to 100-point scale (e.g., 1 = 0, 2 = 25, 3 = 50, etc.)[16] No minimal clinically important difference (MCID) has been identified.

Neuropsychological assessments were performed to assess the natural course of cognitive function and other neuropsychological aspects, as well as the potential effect of everolimus. One of the following assessments was required for patients aged ≥ 2 years (depending on age, the investigator's assessment of cognitive/behavioural status, and whether a validated version is available for a particular language or country):

- *Wechsler Preschool and Primary Scale of Intelligence* was used to assess general thinking and reasoning skills of children aged two to six years. This test has four main scores: verbal score, performance score, processing speed, and Full-Scale Intelligence Quotient score.
- *Wechsler Abbreviated Scale of Intelligence* was used to measure general intellectual function in older children and adults, aged six years or older. This instrument contains a total of four subtests

that are designed to measure vocabulary, block design, similarities, and matrix reasoning. The subtests combine to provide a verbal IQ, a performance IQ, and full-scale IQ.

If either of the above assessments could not be conducted due to cognitive or behavioural impairments, or if the patient was younger than two years, the patient's parent or caregiver was to complete the Vineland Adaptive Behavior Scale. This was an indirect measure of communication, socialization, motor, and daily living skills of individuals from birth to 90 years of age.

The absolute change from baseline in the number of seizures per 24 hours obtained by video-electroencephalogram (EEG) was compared between the everolimus and placebo arms using rank analysis of covariance (ANCOVA) with baseline seizure frequency as a covariate. The model was stratified by use of EIAEDs; the test was performed at the 2.5% significance level. The median change from baseline to week 24 in seizure frequency was presented along with the 95% confidence interval (CI) computed using the bootstrap percentiles method. A last observation carried forward (LOCF) approach was used.

Assessment of seizure severity was via the seizure severity questionnaire (SSQ), which comprised a review of various aspects of seizures and was to be completed by patients taking anti-epileptic drugs at baseline. The SSQ could be completed by the patient or by the patient's parent or legal guardian, if the patient was unable to do so themselves. People who observed the seizures could help answer some of the questions about events related to the seizure. There are 11 questions in four sections asking about events 1) before, 2) during, 3) after typical seizures, and then 4) an overall assessment of the seizures they have had in the recent past. Higher scores indicate worsening of seizures.

See APPENDIX 5: VALIDITY OF OUTCOME MEASURES for more details.

3.2.5 Statistical Analysis

EXIST-1

The primary analysis was a comparison of the SEGA response rates at 24 weeks in the everolimus and placebo arms using an exact Cochran–Mantel–Haenszel (CMH) test at the one-sided 2.5% level. The test was stratified by the use of EIAEDs versus non-use of EIAEDs, and the randomization was stratified on this variable. The full analysis set (FAS) was the primary population for assessment of efficacy.

Multiplicity was controlled via a predefined fixed-sequence testing procedure, where testing is intended to stop once a statistically non-significant result is found. The interpretation of the *P* values depended on the hierarchy used in the predefined fixed-sequence testing procedure. As a result of limited knowledge of this rare disease, the order of importance of the secondary efficacy end points was chosen with some degree of arbitrary assessment of clinical relevance: frequency of total seizures, time to SEGA progression, and skin lesion response rate. Therefore, the primary end point and three key secondary end points were tested via a closed-testing procedure using the following testing sequence (hierarchy):

- Test primary end point SEGA response rate (using a one-sided exact CMH test)
- Test change from baseline to week 24 on total seizure frequency (using a one-sided rank ANCOVA test)
- Test time to SEGA progression (using a one-sided stratified log-rank test)
- Test skin lesion response rate (using a one-sided exact CMH test).

Sample size was determined using simulation. The simulation approach involves randomly generating data according to the study assumptions for a large number of simulated trials, and then analyzing each

trial using the exact CMH test. The proportion of times that the test is significant (i.e., has a one-sided *P* value ≤ 0.025) indicates the power of the study. Different sample sizes can be assessed, and by trial and error, a sample size that guarantees a study power of at least 90% can be chosen. As a starting value, nQuery (V4.0) indicates that for analysis using Fisher's exact test (i.e., a different exact test, and one that does not take into account the stratification), a total of 99 patients would provide 93% power (2:1 randomization).

Missing Data: Patients with unknown SEGA response status were treated as non-responders in the calculation of the SEGA response rate in the FAS at the end of the trial. Other missing data were simply noted as missing on appropriate tables and listings.

Study 2485

The primary efficacy end point was the change from baseline in the volume of the primary SEGA lesion at six months after the start of treatment (or at the last available assessment if a patient ended treatment prior to this time point) as determined by Central Radiology Review. Descriptive statistics for the reduction from baseline in SEGA volume at each post-baseline visit were tabulated. The primary analysis was performed using a non-parametric, one-sided Wilcoxon signed rank test.

Sample Size: The sample size of 28, assuming a standard deviation of 1.33, would have ≥ 90% power to detect a mean reduction in SEGA volume of ≥ 1 cm^3 from baseline based on a one-sided t-test with alpha = 0.025. The non-parametric Wilcoxon signed rank test would also have approximately 90% power to detect a median reduction of 1 cm^3. It is not clear whether a power calculation was performed a priori or after patients had been enrolled.

Missing Data: The last available assessment on or before the date of first administration of study drug (i.e., on or before study day 1) was taken as the "baseline" assessment. Patients with no data on a particular parameter on or before study day 1 had a missing baseline for this parameter. For patients who started taking other anti-SEGA therapy after discontinuing study treatment, their efficacy data were censored so that brain MRIs made after the first administration of the further anti-SEGA therapy were not included in the analysis. Post-baseline measurements made by a different modality than at baseline were also excluded. In addition, post-baseline assessments made by methods other than MRI were not considered in the analyses. For example, if the baseline scan was performed by MRI but the month 3 and month 6 scans were performed by computed tomography scan, the primary end point was considered missing for this patient. No further details regarding the handling of missing data were reported.

Multiplicity: The manufacturer only alluded to multiplicity with respect to the primary outcome, stating that instead of assessing MRI at both three months and six months, and having to incorporate a multiplicity adjustment, they would only assess change in SEGA volume at six months.

a) Analysis populations

EXIST-1

The FAS was defined according to the intention-to-treat (ITT) principle. It consisted of all randomized patients. Patients were analyzed according to the treatment and stratum that they were assigned to at randomization. The FAS was the primary population in the assessment of efficacy, and demographic and other baseline characteristics for the double-blind period.

The Safety Set consisted of all patients who received at least one dose of the double-blind study drug, with a valid post-baseline assessment. Patients were analyzed according to the treatment they actually received in the double-blind period. The Safety Set was used in the assessments of safety and study treatment in the double-blind period.

The Per-protocol Set (PPS) consisted of all patients from the FAS without any major protocol deviations, who are evaluable for efficacy and who have completed a minimum exposure requirement. Patients were evaluable for efficacy if they had a best overall SEGA response status of response, stable disease, or progression. The minimum exposure requirement was defined as having received study treatment on ≥ 50% of days in the first 12 weeks since the start date of study treatment. The PPS was used for supportive analysis of the primary end point.

Study 2485
Efficacy analyses were performed on the FAS for this study. It appears that all patients were included in the FAS.

Safety analyses used the Safety population. No further information was provided on how the Safety population was defined, but all enrolled patients were included in this population.

3.3 Patient Disposition

TABLE 5: PATIENT DISPOSITION

	EXIST-1		Study 2485
	EVEROLIMUS N = 78	**PLACEBO N = 39**	**EVEROLIMUS N = 28**
Screened, N	NR		
Enrolled, N (%)	78 (100)	39 (100)	[redacted]
Discontinued, N (%)	2 (3)	8 (21)	[redacted]
- administrative problems	0	1 (3)[a]	[redacted]
- lost to follow-up	1 (1)	0	[redacted]
- patient withdrew consent	1 (1)	1 (3)	[redacted]
- disease progression	0	6 (15)	[redacted]
- death	NA	NA	[redacted]
- treatment duration completed per protocol			[redacted]
FAS, N (%)	78 (100)	39 (100)	[redacted]
PPS, N (%)	75 (96)	38 (97)	[redacted]
Safety, N (%)	78 (100)	39 (100)	[redacted]

FAS = full analysis set; NA = not applicable; PP = per protocol set.
[a] Patient was non-compliant with study visits.
Source: EXIST-1 Clinical Study Report.[6]

3.4 Exposure to Study Treatments

In EXIST-1, the mean exposure was 44.5 weeks for everolimus and 41.2 weeks for placebo.

[redacted]

3.5 Critical Appraisal

3.5.1 Internal Validity

EXIST-1 was a double-blind study, and appropriate measures appear to have been taken to maintain blinding. However, one challenge to maintaining blinding with everolimus that is beyond the control of investigators is the side effect profile of the drug. Everolimus has a relatively long history in other indications, and certain adverse effects such as stomatitis should be well known to patients. Stomatitis, and in particular mouth ulceration, were more common with everolimus than with placebo in EXIST-1, and patients who experienced these adverse events might have interpreted this as an indication that they were assigned to everolimus. Even if they were not assigned to everolimus, the belief that they were assigned to everolimus may have biased results. Ascertainment bias is more likely to affect more subjective, patient-reported outcomes such as quality of life, which was not assessed in EXIST-1, or assessment of symptoms. Otherwise, many of the key efficacy outcomes are either hard clinical outcomes such as death and need for neurosurgery, or objective outcomes such as change in tumour size. Change in tumour size was also assessed using a central radiologic review.

There appeared to be some between-group differences at baseline in EXIST-1 for important disease characteristics, most notably eight cases of hydrocephalus in the everolimus group compared to no cases in the placebo group. Consistent with this finding, there was also a relatively large difference in total SEGA volume at baseline, indicating larger tumour burden in the everolimus group compared to the placebo group. There appears to be a consistent trend for patients in the everolimus group to be more severely affected than the corresponding placebo group. This could potentially bias results in favour of everolimus, if larger tumours are more mitotically active and thus more responsive. Patients in the everolimus group had a lower baseline rate of seizures compared with placebo. A lower baseline rate of seizures may have biased results against everolimus, making it more difficult to achieve a larger reduction in seizure frequency compared with placebo.

Multiple comparisons were accounted for in EXIST-1 by use of a hierarchical testing procedure, in which testing continued on a predefined list of outcomes until statistical significance was not achieved, then testing was to stop. However, in EXIST-1, testing continued, and the outcomes of these tests were reported for outcomes that fell after failing to achieve statistical significance. Therefore the manufacturer failed to adhere to its own hierarchical testing procedure. In study 2485, there does not appear to have been any adjustments made for multiple comparisons.

Study 2485 did not have a control group, and this limits the conclusions that can be drawn regarding the efficacy or safety of everolimus from this study. Quality of life was assessed in this study, but the lack of a control group makes it difficult to place the results into perspective. In addition, the fact that all patients knew they were on a study drug is expected to bias the results. In a condition where there are no drugs that would even be considered as potential disease-modifying therapies, knowledge that they were on everolimus may have given patients hope that may have positively affected quality of life. Statistical testing for quality of life used the least squares mean to provide confidence intervals, but there was no mention of any test that was used, or what covariates were used.

3.5.2 External Validity

The EXIST-1 study was likely not of sufficient duration or size to assess key clinical outcomes such as mortality, need for neurosurgery, or episodes of hydrocephalus. The evidence in support of the efficacy of everolimus over placebo relies heavily on a composite outcome that is heavily reliant on the surrogate marker of objective response. Episodes of hydrocephalus were a component of the

composite. However, there were no episodes of hydrocephalus in either group, and this therefore contributed little to the primary outcome results.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 2). See APPENDIX 4: DETAILED OUTCOME DATA for detailed efficacy data.

3.6.1 Mortality

There were no deaths in EXIST-1. [redacted]

3.6.2 Episodes of Acute Hydrocephalus

The proportion of patients with acute hydrocephalus was not reported in EXIST-1. However, based on a CDR review of individual patient data, there do not appear to have been any cases of acute hydrocephalus in either the everolimus or placebo groups. There were no episodes of acute hydrocephalus in study 2485 (Table 6).

3.6.3 Patients Requiring Neurosurgery

No patients required neurosurgery in EXIST-1. Patients requiring neurosurgery were not reported in study 2485 (Table 6).

3.6.4 Symptoms

Seizure frequency over the course of 24 hours was reported in EXIST-1 (Table 6). There was no statistically significant difference in the mean ± SD change from baseline in seizure frequency, as both everolimus (–1.24 ± 6.12) and placebo (–0.24 ± 5.70) groups experienced a reduction in seizure frequency at 24 weeks versus baseline, and a reported *P* value of 0.2004. No differences were reported for the mean, but confidence intervals were reported for the median, which was 0.00 (95% CI, 0.00 to 0.00) in each group. SSQ data were also reported, with a mean ± SD global change score of 3.1 ± 1.1 with everolimus and 3.0 ± 1.1 with placebo at week 24. Higher scores indicate worsening of seizures.

In study 2485, there was a median reduction from baseline to 24 weeks in seizure frequency per 24 hours of 0.99 [range: –17.0 to 10.8]. This difference was reported as statistically significant, with *P* = 0.022. The proportion of patients experiencing seizures on a daily basis was 27% at baseline [redacted].

3.6.5 Quality of Life

Quality of life was not assessed in EXIST-1. In study 2485, quality of life was assessed using the QOLCE, and there was a statistically significant improvement from baseline to month 6 in the everolimus group in the overall quality of life score, with a least squares mean change from baseline of 3.47 (95% CI, 0.19 to 6.74) (Table 6). No *P* value was reported. No MCID has been established for this instrument.

3.6.6 Other Efficacy Outcomes

Best SEGA response was the primary outcome of EXIST-1. By week 24, 35% of everolimus patients and no placebo patients had achieved a response, for a difference in response rates of 35% (95% CI, 15 to 52; *P* < 0.0001) (Table 9). As this was a superiority analysis, everolimus achieved superiority over placebo for the primary outcome of this study. Best SEGA response was not evaluated in study 2485.

In EXIST-1, after 24 weeks, the estimate of the difference in least squares means for change from baseline in total SEGA volume between everolimus and placebo was –0.88 cm^3 (95% CI, –1.24 to –0.52; $P < 0.0001$), and this difference was statistically significant (Table 9). Therefore everolimus reduced total SEGA volume compared with placebo. Change in total SEGA volume was the primary outcome of study 2485, and everolimus did elicit a statistically significant reduction in SEGA volume after six months. However, there was no comparator in this study. The median reduction in SEGA volume was 0.83 cm^3 (95% CI, 0.5 to 1.2).

Time to SEGA progression was reported in EXIST-1, and no everolimus patients and 15% of placebo patients progressed during the 24-week study (Table 9). This outcome came after seizure frequency in the hierarchical testing procedure. As such, the statistical significance of this outcome could not be assessed as per the predetermined hierarchy.

The proportion of patients developing new lesions was not reported. Neuropsychological findings were also not reported due to issues with administration of the instrument and irregularities in scoring.

Results from the neuropsychological assessment analysis were uninterpretable because the three scales used were not validated in several countries (Poland, Russia, Germany, Belgium, and The Netherlands). Furthermore, scoring inconsistencies and errors were noted upon data review.

TABLE 6: KEY EFFICACY OUTCOMES

	EXIST-1		Study 2485
	Everolimus N = 78	**Placebo N = 39**	**Everolimus N = 28**
Mortality			
Deaths by week 24, N (%)	0	0	[redacted]
Episodes of acute hydrocephalus			
Patients by week 24, n (%)	0[a]	0[a]	0
Patients requiring neurosurgery			
Patients by week 24, n (%)	0	0	NR
Seizure frequency/24h			
Mean (SD) baseline	3.41 (8.36) N = 27	5.58 (14.98) N = 13	6.30 (7.880)
Mean change from baseline to Week 24/LOCF	–1.24 (6.12)	–0.24 (5.70)	–2.65 (6.089) N = 16
Median	0.00	0.00	–0.99
95% CI for the median	(0.00 to 0.00)	(0.00 to 0.00)	
Range			(–17.0 to 10.8)
P value	*P* = 0.2004[b]		*P* = 0.022[c]
Quality of life: QOLCE			
Mean (SD) baseline	NE	NE	57.82 (13.956)
Mean (SD) change from baseline to week 24	NE	NE	3.29 (8.421) N = 25
Least squares mean (standard error)	NE	NE	3.47 (1.582)
95% CI of least squares mean	NE	NE	0.19 to 6.74
Symptoms: SSQ			
Mean (SD) global change score, week	3.1 (1.1)	3.0 (1.1)	NE

	EXIST-1		Study 2485
24	N = 22	N = 10	
SEGA Response			
Response by week 24, n (%)	27 (35)	0	NE
Difference in response rates (95% CI)	34.6 (15.1 to 52.4), $P < 0.0001$[d]		NE

ANCOVA = analysis of covariance; CDR = CADTH Common Drug Review; CI = confidence interval; EIAED = enzyme-inducing anti-epileptic drugs; LOCF = last observation carried forward; NE = not evaluated; QOLCE = Quality of Life in Childhood Epilepsy; SD = standard deviation; SEGA = subependymal giant cell astrocytoma; SSQ = Seizure Severity Questionnaire.
[a] Based on CDR review of individual patient data.
[b] *P* value obtained from rank ANCOVA (one-sided test) with baseline seizure frequency as covariate, stratified by use of EIAED at randomization (EIAED use versus EIAED non-use).
[c] *P* value obtained from a sign test.
[d] *P* value is obtained from the one-sided exact Cochran–Mantel–Haenszel test, stratified by the protocol stratification factor (EIAED use versus EIAED non-use).
Source: EXIST-1 Clinical Study Report (CSR)[6]; Study 2485 CSR.[7]

3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). See APPENDIX 4: DETAILED OUTCOME DATA for detailed harms data.

3.7.1 Adverse Events

There were 96% of everolimus patients and 90% of placebo patients with an adverse event in EXIST-1. The most common adverse event with everolimus was mouth ulceration (32% of everolimus patients versus 5% placebo), and stomatitis (31% versus 21%, respectively).

All (100%) patients experienced an adverse event in study 2485. [redacted]

3.7.2 Serious Adverse Events

Serious adverse events occurred in 19% of everolimus patients and 8% of placebo patients. The most common serious adverse events were convulsion (4% of everolimus versus 5% placebo) and pyrexia (4% versus 0%, respectively).

[redacted].

3.7.3 Withdrawals Due to Adverse Events

There were no withdrawals due to adverse event in either study.

3.7.4 Notable Harms

Notable harms included infection, which occurred in 72% of everolimus patients and 67% placebo, and [redacted].

TABLE 7: HARMS: EXIST-1 (RANDOMIZED CONTROLLED TRIAL)

	EXIST-1	
	Everolimus N = 78	**Placebo N = 39**
Adverse Events		
Subjects with > 0 AEs, n (%)	75 (96)	35 (90)
Most common AEs		
Mouth ulceration	25 (32)	2 (5)
Stomatitis	24 (31)	8 (21)
Convulsion	18 (23)	10 (26)
Pyrexia	17 (22)	6 (15)
Nasopharyngitis	14 (18)	9 (23)
Vomiting	13 (17)	5 (13)
Upper respiratory tract infection	12 (15)	7 (18)
Fatigue	11 (14)	1 (3)
Serious Adverse Events		
Subjects with > 0 SAEs, n (%)	15 (19)	3 (8)
Most common SAEs		
Convulsion	3 (4)	2 (5)
Pyrexia	3 (4)	0
Bronchitis	2 (3)	1 (3)
Gastroenteritis	2 (3)	0
Gastroenteritis viral	2 (3)	0
Pneumonia	2 (3)	0
Status epilepticus	2 (3)	0
Upper respiratory tract infection	2 (3)	0
WDAEs		
WDAEs, n (%)	0	0
Notable harms		
Infection	56 (72)	26 (67)
Increased total cholesterol	[redacted]	[redacted]
Cytopenias	[redacted]	[redacted]
- decreased neutrophil count	[redacted]	[redacted]
- neutropenia	[redacted]	[redacted]
Proteinuria	NR	NR

AE = adverse event; NR = not reported; SAE = serious adverse event; WDAE = withdrawals due to adverse events.
Source: EXIST-1 Clinical Study Report.[6]

TABLE 8: HARMS: STUDY 2485 (NON-RANDOMIZED CONTROLLED TRIAL)

	Study 2485
	Everolimus N = 28
Adverse Events	
Subjects with > 0 AEs, n (%)	[redacted]
Most common AEs	
Upper respiratory tract infection	[redacted]
Stomatitis	[redacted]
Sinusitis	[redacted]
Mouth ulceration	[redacted]
Cellulitis	[redacted]
Diarrhea	[redacted]
Gastroenteritis	[redacted]
Otitis media	[redacted]
Pyrexia	[redacted]
Vomiting	[redacted]
Serious Adverse Events	
Subjects with > 0 SAEs, n (%)	[redacted]
Most common SAEs	
Abscess limb	[redacted]
Cellulitis	[redacted]
Convulsion	[redacted]
WDAEs	
WDAEs, n (%)	[redacted]
Notable harms	
Severe Infection, n (%)	[redacted]
Increased total cholesterol	[redacted]
Cytopenias, n (%)	[redacted]
- decreased neutrophil count	[redacted]
- neutropenia, n	[redacted]
Proteinuria, n (%)	[redacted]

AE = adverse event; SAE = serious adverse event; WDAE = withdrawals due to adverse events.
Source: Study 2485.[7]

4. DISCUSSION

4.1 Summary of Available Evidence

One phase 3 placebo-controlled DBRCT (EXIST-1) and one phase 2 non-RCT (study 2485) provided by the manufacturer met the inclusion criteria for this systematic review. EXIST-1 randomized 117 patients 2:1 to either everolimus dosed by BSA and titrated using therapeutic drug monitoring or placebo. Patients were treated for six months in the double-blind phase and there was a four-year open-label extension. The primary outcome was the proportion of patients with a SEGA response, defined as a reduction in 50% of target SEGA volume, in the absence of worsening non-target SEGAs, new lesions of at least 1 cm in diameter, and new or worsening hydrocephalus. There were no deaths in EXIST-1 and [redacted]. Cases of hydrocephalus were not specifically reported, although a review of individual patient data suggests there were no cases in either group during the trial. Seizure frequency was not statistically significantly different between everolimus and placebo, and there were no differences in responses in the SSQ. Quality of life was not reported. Best SEGA response was the primary outcome of EXIST-1 and 35% of everolimus patients versus no placebo patients achieved a SEGA response, which was statistically significantly different between groups. There was also a statistically significant reduction in total SEGA volume for everolimus versus placebo. In study 2485, efficacy was difficult to assess as there was no comparator. There were no cases of hydrocephalus and the proportion of patients undergoing neurosurgery was not reported. The QOLCE was reported in this study and there was an improvement from baseline that appeared to be statistically significant although no *P* value was reported. Serious adverse events occurred in 19% of everolimus patients and 8% of placebo patients in EXIST-1, and adverse events occurred in 96% of everolimus and 90% placebo patients. No patients withdrew due to an adverse event.

4.2 Interpretation of Results

4.2.1 Efficacy

The double-blind phase of EXIST-1 lasted only six months, and this is likely not of long enough duration to assess key clinical outcomes such as deaths, need for neurosurgery, or episodes of acute hydrocephalus. Instead, the primary outcome of EXIST-1 was a composite that appeared to rely heavily on an objective response, a shrinkage of target SEGA by 50%. Episodes of hydrocephalus were part of the composite outcome, but there did not appear to be any reports of hydrocephalus based on a review of individual patient data. Other than hydrocephalus, the other components of the composite outcome were also reliant on growth, such as new or worsening lesions. Therefore the evidence that everolimus has superior efficacy to placebo is based on a surrogate end point. Long-term follow-up data from the open-label extension to EXIST-1 suggest that SEGA response is durable, and in fact the proportion of responders once everolimus was extended to placebo patients increased to 49% (from 35% in the double-blind phase). There did not appear to be any cases of neurosurgery in the extension, although this outcome and cases of hydrocephalus were not specifically reported on in the extension. Therefore, everolimus clearly shrinks tumours; it is just not clear how this will affect clinical outcomes for the patient.

The Health Canada indication and the inclusion criteria for the pivotal studies exclude patients with SEGAs who are not candidates for surgical resection and for whom immediate surgical intervention is not required. However, patients still may have complications, such as obstructive hydrocephalus or intractable seizures, that require neurosurgery to address the complication, but not the underlying cause. Although everolimus appears to shrink tumours, this may not be associated with a decrease in the surgical morbidity or exposure for patients. Although no patients required neurosurgery in EXIST-1,

as mentioned, the lack of such a finding may be related to the design (sample size and duration) of the study.

According to the patient input provided to CDR, seizures are a major concern for patients with SEGAs. Based on data from EXIST-1, everolimus did not appear to reduce the risk of seizures for patients with SEGAs. Although there appeared to be one less seizure per 24-hour period for patients treated with everolimus versus placebo, this difference was not statistically significant. It is possible that the small sample size of EXIST-1 may have contributed to this lack of statistical significance, but at present it cannot be concluded that everolimus reduces risk of seizures, an important outcome for patients. Based on the SSQ, there was also no evidence of an impact of everolimus on seizure severity, although the sample for this questionnaire was small. A statistically significant reduction in median seizure frequency was reported in study 2485, but this study lacked a comparative group, making interpretation difficult. An additional non-RCT that did not meet the inclusion criteria for this CDR, Krueger et al. (2013), [17] reported that 60% of the 20 enrolled patients achieved a greater than 50% reduction in seizure frequency after 12 weeks of treatment with everolimus. However, SEGA was not mentioned as an inclusion criterion for this study, and it was a non-pivotal phase 1 to 2 non-RCT; therefore, it did not meet the inclusion criteria for this systematic review.[17]

Quality of life was not investigated in EXIST-1, the only RCT of everolimus in SEGAs associated with TSC. The impact of SEGAs and TSC in general on patient's quality of life is significant, as evidenced by the descriptions provided in the patient input summary to CDR. Therefore, the lack of quality of life data from EXIST-1 is a significant gap in evidence. Quality of life data were assessed in study 2485, but there was no comparator in this study and, aside from the inability to place the results into context, there is significant bias introduced with the lack of blinding. Therefore, at present the impact of everolimus on quality of life in SEGA patients is uncertain. No results from neuropsychological testing were available, either; thus, there was no assessment of parameters such as intellectual function, socialization, or daily living, which were all aspects of living with SEGA described by patients in their input to CDR.

4.2.2 Harms

There are a number of serious and/or severe adverse effects associated with the use of everolimus. Everolimus is an immunosuppressant, and therefore infections — particularly, serious opportunistic infections — are a concern according to the product monograph. [18] EXIST-1 was not powered to detect differences in the risk of harms for everolimus versus placebo, and the overall proportion of patients with an infection was 72% with everolimus versus 67% with placebo. This does not suggest a large difference in risk. A number of infections were identified as serious adverse events in patients who received everolimus, but not in those who received placebo (e.g., viral gastroenteritis, pneumonia, upper respiratory tract infection: 3% of patients with each). Therefore, although data from EXIST-1 do not clearly indicate that the risk of serious infection is elevated with everolimus, the mechanism and history of this drug in other indications would suggest that it is of concern. Also as noted in the product monograph, there is no clear indication of how long patients may be treated with everolimus for SEGAs in TSC, and there has been tumour regrowth in patients who discontinued everolimus. [18] After 60 months of therapy in the non-RCT study 2485, all patients had experienced at least one severe infection.

Elevated cholesterol has also been reported as a harm associated with everolimus. [18]The product monograph recommends a fasting lipid profile be performed prior to initiation of therapy. [18] In EXIST-1, increased total cholesterol was reported as an adverse event in 87% of everolimus patients and 49% of placebo patients. Once again, it is not known how long a given patient may continue on everolimus, and as the drug is often used in children, it is not clear what the impact of long-term elevations in cholesterol

will be on the health of a child. Given that everolimus is a chronic therapy that will be used in children, the potential impact on overall growth and development is also relevant. The impact of everolimus on growth and development has also not been established. Long-term, uncontrolled follow-up data from EXIST-1 (median follow-up of 28.3 months) has not found any cases of delayed onset of puberty. There were five patients who developed amenorrhea, although all but one of these cases has resolved. The one unresolved case began on Day 1039 (July 1, 2012) and is still ongoing as of the data cutoff for the most recent update (January 11, 2013).

5. CONCLUSIONS

One DBRCT and one single-group study in patients with SEGAs associated with TSC were included in this review. EXIST-1 (N = 117) randomized SEGA patients 2:1 to either everolimus or placebo, over a double-blind treatment period of six months. Study 2485 enrolled 28 patients at a single centre in the US. There were no deaths in EXIST-1 and [redacted], and no patients required neurosurgery or had episodes of acute hydrocephalus in either study. The incidence and severity of seizures, a key complication of SEGA, were not reduced with everolimus treatment compared with placebo. However, interpretation of all hard clinical outcomes is complicated by the small sample size and relatively short duration of the study. Quality of life was not assessed in EXIST-1. Everolimus was statistically significantly superior to placebo for the proportion of patients achieving a SEGA response, which was the primary outcome of EXIST-1. EXIST-1 was not powered to detect differences in harms between everolimus and placebo, [redacted].

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH staff based on the input provided by patient groups. It has not been systematically reviewed. It has been reviewed by the submitting patient groups.

1. Brief Description of Patient Group Supplying Input

Tuberous Sclerosis Canada Sclérose Tubéreuse (TSCST) is non-profit, volunteer-run, charitable organization that aims to raise public awareness of tuberous sclerosis complex (TSC), encourages support among families with affected members, and promotes research and education. In 2013-2014, the TSCST received funding from Novartis Pharmaceuticals Canada Inc.

The TSCST declared no conflicts of interest in the preparation of this submission.

2. Condition and Current Therapy-Related Information

Information was collected for this patient input submission from an online survey, telephone interviews, personal conversations, messages posted on Facebook and Twitter, and unsolicited letters sent to TSCST. Of the 51 respondents, one-third were patients and two-thirds were caregivers.

TSC is a disorder characterized by abnormal tissue growths (benign tumours) that develop in multiple organ systems including the brain, heart, skin, eyes, kidneys, and lungs. These growths can arise slowly or quickly and are often painful. Individuals can have one or all possible manifestations of the disorder. One patient reported: "TSC affects my brain, skin, teeth, eyes, kidneys, spine, and other internal organs — I have tumours everywhere." Subependymal giant-cell astrocytomas (SEGAs) are a type of benign brain tumour associated with TSC, which mainly arise in the ventricles of the brain. Patients can experience severe headaches, epilepsy (some have multiple seizures per day), hydrocephalus, intellectual disabilities, behavioural issues, and mood disorders, as a result of SEGAs.

As the disease progresses and symptoms worsen, the burden of the disease for patients and families increases and may affect careers. A patient noted, "I could not get a job because my seizures could not be controlled."

TSC with SEGAs negatively affects the lives of the patients, families, and caregivers as they constantly experience uncertainty and stress. This stress can be due to the uncertainty of potential unexpected emergencies, requirements for surgery, requirements for travel to obtain treatment, and patient care. As one caregiver said, "We are always on high alert…" Some patients feel they can never have children because they "would not want to pass this condition onto their children."

No disease-modifying drugs are available to treat patients with SEGAs. Surgical resection of the tumours may be possible if they are in operable locations in the brain. Multiple brain surgeries are often needed as the tumours can reappear in the same tissue and they can result in permanent cognitive disabilities, damage to motor skills, changes in personality, and other behavioural issues. Most patients also take anti-epileptic medications to control their seizures, which are not always effective and can have serious side effects.

3. Related Information About Afinitor

Patients and their families expect that Afinitor will aid in stabilizing or reducing tumour growth and subsequently decrease the requirement for surgery. A respondent noted, "It is a critical alternative to invasive and possibly life-threatening surgeries." There is hope that this will improve quality of life and spare organ function. Afinitor is also an attractive option as there is no other drug treatment for TSC SEGA, it is non-invasive, and it could benefit patients in remote areas, as surgery often requires extensive travel and time away from home. Patients also hope that it can treat all aspects of this multi-organ disease.

Patients who have experience with Afinitor were overwhelmingly positive toward its effectiveness. In some patients, it has been observed to shrink tumours (both SEGAs and tumours in other organs) to the point where surgery is no longer necessary and thereby reducing or eliminating seizure incidence. In addition, three-quarters of patients experienced "much" improved appearance of skin cysts and 60% experienced "much" improved cognitive functioning. Half experienced "much" improved kidney functioning, seizure episodes, and behaviour. About one-third experienced "much" improved lung functioning.

Long-term health of some patients who have used Afinitor has been enhanced and maintained, which has reduced the stress and anxiety for both patients and families. Patients reported few side effects, with the only side effect noted in this submission being the presence of mouth sores, which were manageable.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	October 1, 2014, 2014
Alerts:	Weekly search updates until February 18, 2015
Study Types:	Randomized controlled trials; controlled clinical trials; multicenter studies; cohort studies; cross-over studies; case control studies; comparative studies; epidemiologic studies; also costs and cost analysis studies, quality of life studies, and economic literature.
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	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
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
Line	**Strategy**
1	Sirolimus/aa [Analogs & Derivatives]
2	(Afinitor or everolimus or Zortress or Disperz or Advacan or Certican or Votubia or Vience V or VeniceV or RAD001 or "RAD 001" or SDZRAD or SDZ RAD or UNII-9HW64Q8G6G or UNII9HW64Q8G6G or 15935169-6 or 159351-69-6 or "159351696" or 159351 696 or 1245613-55-1 or 124561355-1 or 1245613-551 or "1245613551").ti,ab,ot,sh,hw,rn,nm.
3	(UNII-9HW64Q8G6G or UNII9HW64Q8G6G or 15935169-6 or 159351-69-6 or "159351696" or 159351 696 or 1245613-55-1 or 124561355-1 or 1245613-551 or "1245613551").rn,nm.
4	1 or 2 or 3
5	exp Astrocytoma/ or exp Glioma, Subependymal/ or exp Brain Neoplasms/
6	(Astrocytom* or Astrocytic* or SEGA* or SGCA* or SGCT* or subependymal* or glioma* or Astrogliom*).ti,ab,ot,sh,hw,rn,nm.
7	5 or 6
8	4 and 7
9	8 use pmez
10	exp *everolimus/
11	(Afinitor or everolimus or Zortress or Disperz or Advacan or Certican or Votubia or Vience V or VeniceV or RAD001 or "RAD 001" or SDZRAD or SDZ RAD or UNII-9HW64Q8G6G or UNII9HW64Q8G6G or 15935169-6 or 159351-69-6 or "159351696" or 159351 696 or 1245613-55-1 or 124561355-1 or 1245613-551 or "1245613551").ti,ab.
12	10 or 11
13	exp astrocytoma cell/ or exp astrocytoma/
14	(Astrocytom* or Astrocytic* or SEGA* or SGCA* or SGCT* or subependymal* or glioma* or Astrogliom*).ti,ab.
15	13 or 14
16	12 and 15
17	16 use oemezd
18	9 or 17
19	exp animals/
20	exp animal experimentation/ or exp animal experiment/
21	exp models animal/
22	nonhuman/
23	exp vertebrate/ or exp vertebrates/
24	animal.po.
25	or/19-24
26	exp humans/
27	exp human experimentation/ or exp human experiment/
28	human.po.
29	or/26-28
30	25 not 29
31	18 not 30
32	31 not conference abstract.pt.
33	remove duplicates from 32

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	To September 25, 2014
Keywords:	Afinitor, everolimus, Zortress, Advacan, Certican, Votubia, RAD001, RAD 001, astrocytoma, astrocytomas, SEGA
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

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

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Cardamone M, Flanagan D, Mowat D, Kennedy SE, Chopra M, Lawson JA. Mammalian target of rapamycin inhibitors for intractable epilepsy and subependymal giant cell astrocytomas in tuberous sclerosis complex. J Pediatr. 2014 May;164(5):1195-200.	Non-RCT
Curran MP. Everolimus: in patients with subependymal giant cell astrocytoma associated with tuberous sclerosis complex. Paediatr Drugs. 2012 Feb 1;14(1):51-60.	Review

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 9: OTHER EFFICACY OUTCOMES

	EXIST-1		Study 2485
	Everolimus N = 78	**Placebo N = 39**	**Everolimus N = 28**
Time to SEGA progression			
Patients progressing, n (%)	0	6 (15)	NR
	P = 0.0002		
Best SEGA response			
Response by week 24, n (%)	27 (35)	0	NE
Difference in response rates (95% CI)	34.6 (15.1 to 52.4), *P* < 0.0001[a]		NE
Stable, n (%)	[redacted]	[redacted]	NE
Progression, n (%)	[redacted]	[redacted]	NE
Not evaluable, n (%)	[redacted]	[redacted]	NE
Change in total SEGA volume			
Mean (SD) baseline, cm^2	2.687 (3.598)	1.859 (1.775)	2.45 (2.813)
Mean (SD) change from baseline to week 24	–1.379 (2.571)	0.014 (0.231)	–1.19 (1.433) N = 27
Estimate of the difference in least squares means (95% CI)	–0.88 (–1.24 to –0.52) *P* < 0.0001[b]		
Median reduction from baseline (95% CI)			–0.83 (–0.5 to –1.2][c]
Patients with ≥ 30% reduction in total SEGA volume, n (%)	58 (78)	4 (15)	21 (78)
≥50% reduction, n (%)	31 (42)	1 (3)	9 (33)
Mean (SD) change from baseline, month 12			–1.07 (1.276) N = 26
Month 24			–1.25 (1.994) N = 24
Month 36			–1.41 (1.814) N = 23
Month 48			–1.43 (2.267) N = 24
Month 60			[redacted]

CI = confidence interval; EIAED = enzyme-inducing anti-epileptic drugs; NE = not estimable; NR = not reported; SD = standard deviation; SEGA = subependymal giant cell astrocytoma.

[a] *P* value is obtained from the one-sided exact Cochran–Mantel–Haenszel test, stratified by the protocol stratification factor (EIAED use versus EIAED non-use).

[b] *P* value from the Wald test (one-sided).

[c] The 95% CI for the median reduction from baseline was obtained by bootstrap simulation.

Source: EXIST-1 Clinical Study Report (CSR)[6]; Study 2485 CSR.[7]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

1. Objective

To provide information on the characteristics, validity, and reliability of the Quality of Life for Childhood Epilepsy (QOLCE) questionnaire used in the EXIST-1 trial.[6]

2. Findings

Quality of Life in Childhood Epilepsy Questionnaire

The QOLCE questionnaire is a multifaceted scale specific to evaluating the health-related quality of life (HRQoL) in children aged four to 18 years with epilepsy.[15] It was first developed in Australia and then adapted to the North American population by performing a primary validation analysis on epileptic children who had not had neurosurgery. This was followed by a second analysis of epileptic children who had undergone surgery for seizure-related issues.[15] In addition, it has since been translated and culturally adapted into Hindi[16] and Polish.[19] The QOLCE originally began as a 91-item questionnaire and, upon analysis and validation for the North American population, has since been reduced to 76 items with 16 subscales[15] (14 of which are multi-item and two are single-item).[15,16] These 16 subscales include: quality of life, physical restrictions, general health, energy/fatigue, behaviour, attention/concentration, stigma, memory, social activities, social interactions, language, other cognitive processes, anxiety, control/helplessness, and self-esteem.[15] Five functional life domains represented in the questionnaire included physical function, social function, cognition, behaviour, and emotional well-being.[15] Responses such as excellent, very good, good, fair, and poor are provided by the parents, and then these are subsequently numbered 1 to 5 (as per instructions) and converted to a 0- to 100-point scale (e.g., 1 = 0, 2 = 25, 3 = 50, etc.)[16]

Evidence supporting the validity, reliability, and a lack of ceiling or floor effects of the new 76-item (16-subscale) QOLCE questionnaire was obtained in a broad range of children with confirmed epilepsy on anti-epileptic drugs, both with and without having received surgery as treated (all were patients of the Comprehensive Epilepsy Center at the Miami Children's Hospital, Florida, US).[15] In general, the independence of the subscales in these children was demonstrated by the lack of strong correlations between them (with the exception of cognition and emotional well-being, both of which are a part of the same functional domain). Internal consistency reliability of the multi-item scales was good, as the level was above the criterion set to determine adequacy when group comparisons are made (the value fell between 0.76 and 0.97).[15] In addition, these subscales had good construct validity, being moderately to highly significantly correlated with those of the theoretically similar Child Health Questionnaire (often used as a surrogate HRQoL measure).[15] Eleven of the 16 QOLCE scores were also moderately to highly correlated with the severity of seizures (after controlling for variables such as age of onset of epilepsy, IQ, in-patient status, and estimated family income — all of which were found to have an impact on HRQoL.[15] Important limitations that the authors noted included the lack of test–retest reliability (as this was not assessed in this cross-sectional study design), the absence of testing in a well-controlled prospective longitudinal study (observed information came from a study with a cross-sectional design), and the fact that this is a parent-answered questionnaire (the inter-rater reliability was not assessed; hence, the accuracy of domains that are not directly observable, such as anxiety, is not known).[15] Cowen and Baker[20] further evaluated the evidence regarding the validity and reliability of the QOLCE by performing a literature review. They observed additional limitations. They noted that some of the subscales had a low number of items and, due to this, it would be difficult to ascertain acceptable reliability within these subscales.[20] They also observed that, even though this measure was supposed to be appropriate for a broad age range, there was no evidence of any kind of age effects analysis.[20] In

addition, they did note the small sample size (N = 71) and were particularly critical that this questionnaire was tested only on the parents of children with average intelligence. The fact that children with lower mental capacity and learning disabilities were excluded suggests that evidence of the QOLCE's reliability and validity may not be generalizable to a significant proportion of children with epilepsy.[20] The authors did note its potential strengths such as the incorporation of generic measures (which is difficult to do in a population with a chronic condition) and the fact that research in HRQoL measures specific to pediatrics remains in its early stages.[20]

3. Summary

There is evidence to support the validity and reliability of the new QOLCE questionnaire, built upon that of the Australian original, in children of average intelligence with epilepsy who are being treated with anti-epileptic drugs and who either have or have not undergone surgery for seizure-related issues. However, there remain some prominent limitations to this outcome measure that require further investigation. These include the fact that the generalizability to children with learning disabilities is uncertain, assessments of its test–retest reliability and responsiveness have not yet been performed, and age effects analysis have yet to be performed. In addition, no minimal clinically important differences were identified and, for the purposes of this review, QOLCE has not been assessed or validated in a population of patients with tuberous sclerosis complex (including those with subependymal giant cell astrocytomas).

APPENDIX 6: REVIEW OF PHARMACOLOGY: DRUG INTERACTIONS

Aim

To summarize the possible interactions between everolimus and other drugs that patients with TSC with a SEGA may be taking concomitantly.

Findings

CYP3A4 or P-glycoprotein (PgP) Inducers

Substances that are strong inducers of CYP3A4 or PgP, such as anticonvulsant drugs, may increase the metabolism or efflux of everolimus from intestinal cells, thereby decreasing the concentration of everolimus in the blood stream. According to the product monograph,[18] concomitant use of strong CYP3A4 or PgP inducers and everolimus should be avoided, but if they cannot, everolimus dosage may need to be increased. Ninety per cent of people with TSC experience seizures and, therefore, many patients who would receive everolimus for the treatment of TSC with SEGAs are likely to be taking concomitant seizure medication, such as carbamazepine, phenobarbital, or phenytoin, which are strong CYP3A4 inducers. Hence, there is potential for the need for higher dosing of everolimus in this patient population.

Other strong inducers of CYP3A4 or PgP include rifampicin, rifabutin, St. John's wort, corticosteroids (such as prednisone, dexamethasone, and prednisolone), and anti-HIV drugs (such as efavirenz and nevirapine).[18]

CYP3A4 or PgP Inhibitors

Strong inhibitors of CYP3A4 or PgP may increase concentrations of everolimus in the bloodstream and should also be avoided.[18] Strong CYP3A4 inhibitors decrease everolimus metabolism and strong PgP inhibitors may decrease efflux of everolimus from intestinal cells. These drugs include protease inhibitors (atazanavir, indinavir, nelfinavir, ritonavir, and saquinavir), some antibiotics (clarithromycin, telithromycin, and chloramphenicol), and some antifungals (ketoconazole, itraconazole, and nefazodone). Concomitant treatment with moderate inhibitors of CYP3A4 (including, but not limited to, erythromycin, verapamil, cyclosporine, fluconazole, diltiazem, amprenavir, fosamprenavir, or aprepitant) and moderate PgP inhibitors may require a dose reduction of everolimus and requires caution.[18]

CYP3A4 Substrates

Although studies have found no pharmacokinetic interactions between everolimus and HMG-CoA reductase inhibitors atorvastatin (a CYP3A4 substrate), pravastatin (a non-CYP3A4 substrate), and simvastatin (a CYP3A4 substrate), the everolimus dose examined was 2 mg, and not 10 mg, as is used in TSC trials.[18] Thus, there is the potential for interactions and caution should be exercised when prescribing statins and everolimus.

As everolimus has been shown to increase the concentration of midazolam, an orally administered CYP3A4 substrate, in healthy subjects, caution should also be exercised with the co-administration of everolimus and oral CYP3A4 substrates. Interactions between everolimus and non-orally administered CYP3A4 substrates have not been examined.[18]

As there are sex differences in the metabolism of CYP3A4 and the clearance of CYP3A4 substrates, it is possible that the likelihood of drug interactions may differ between men and women.[21]

Vaccines

As everolimus is an immunosuppressant, it may reduce the effectiveness of vaccinations given during everolimus treatment. Live vaccines should not be administered to patients taking everolimus.[18]

Conclusion

Caution should be taken when co-administering everolimus with CYP3A4 or PgP inducers, inhibitors, or substrates. Many patients who would receive everolimus for the treatment of TSC with SEGAs are likely to be taking concomitant seizure medication, such as carbamazepine, phenobarbital, or phenytoin, which are strong CYP3A4 inducers. Hence, there is potential for the need for higher dosing of everolimus in this patient population. As there are sex differences in the metabolism of CYP3A4 and the clearance of CYP3A4 substrates, it is possible that the likelihood of drug interaction may differ between men and women.[21] Everolimus may reduce the effectiveness of vaccines and patients taking everolimus should not receive live vaccines.[18]

APPENDIX 7: REVIEW OF TUBEROUS SCLEROSIS COMPLEX WITH SUBEPENDYMAL GIANT CELL ASTROCYTOMA

Aim

To summarize the natural history, diagnosis, characteristics, and genetics of tuberous sclerosis complex (TSC) with subependymal giant cell astrocytoma (SEGA).

Tuberous Sclerosis Complex and Subependymal Giant Cell Astrocytoma

TSC is a genetic disorder that has been identified in children, adults, and prenatally.[22,23] While TSC can be inherited in an autosomal dominant fashion, the majority of cases (approximately 80%) arise sporadically.[22] Typical characteristics associated with TSC include the development of noncancerous tumours (hamartomas) in numerous organs such as the brain, eyes, kidneys, heart, lung, skin, bone,[22,23] and blood vessels.[23] Disease incidence is estimated at 1:6,000[22,23] to 1:10,000[22] live births and it currently affects in the range of one[22] to 1.5[23] million people worldwide.

Diagnosis can occur at any age and is often difficult mainly due to both the range of clinical effects and the degree of severity associated with TSC. Severity can range from mild (undetected) to severe.[22,23] Early attempts at a diagnostic algorithm (1908) included Vogt's triad, whereby angiofibromas, mental retardation, and intractable epilepsy were necessary for TSC diagnosis.[23] The advent of more modern imaging technologies, such as magnetic resonance imaging and computed tomography, have allowed for further definitive diagnoses.[23] Clinical features of TSC are currently divided into major and minor categories to further aid in diagnosis. Definitive diagnosis is indicated with the presence of two major features or one major feature and two minor features.[23] Classification of major and minor clinical features is presented in Table 10.

TABLE 10: CLINICAL FEATURES OF TUBEROUS SCLEROSIS COMPLEX

Clinical Features[a]	Onset Age
Major Clinical Features	
Cardiac rhabdomyoma	Fetal period
Cortical tuber	
Retinal hamartoma	Infancy
Hypomelanotic macule	Infancy to childhood
Facial angiofibroma	Infancy to adulthood
Shagreen patch	Childhood
Renal angiomyolipoma	Childhood to adolescence
Subependymal nodule	
Subependymal giant cell tumour	
Lymphangiomyomatosis	Adolescence to adulthood
Ungual fibroma	
Minor Clinical Features	
Bone cysts	NS
Cerebral white-matter radial migration lines	
Confetti-like skin lesions	
Fibromas — gingival	
Hamartomatous rectal polyps	

Clinical Features[a]	Onset Age
Non-renal hamartoma	
Pits in dental enamel — multiple	
Renal cysts — multiple	
Retinal achromic patch	

NS = not specified.
[a] Source: Adapted from Kohrman, 2012.[23]

Genetics and Pathogenesis of Tuberous Sclerosis Complex

Mutations in the *TSC1* or *TSC2* genes lead to the development of TSC. Two-thirds of mutations in these genes occur in sporadic fashion, while one-third is inherited through autosomal dominance.[23] Interestingly, approximately 70% to 90% of patients exhibit *TSC1* or *TSC2* mutations, while 10% to 15% of those with a clinical TSC diagnosis have no identifiable mutation in these genes.[22] This leads to speculation regarding the possibility of mutations specific to promoter regions or introns,[23] unidentified gene loci, or the possibility of low-level somatic mosaicism.[22] The broad phenotypic expression associated with TSC is thought to be due to the hundreds of mutations possible in *TSC1* and *TSC2*.[23] The rate of *TSC2* mutations is higher than that of *TSC1* (five times more frequent[22]) and sporadic *TSC2* mutations are correlated with increased disease severity when compared with *TSC1* or inherited *TSC2* mutations.[23] Research has indicated that the proteins encoded by these two genes (hamartin and tuberin, respectively) must be functional and work together.[22,23] The hamartin-tuberin complex can have downstream effects on the mTOR protein (made up of the mTORC1 and mTOR2 complex proteins), which is a serine-threonine kinase involved in cell growth. Problems arise upon mutation leading to non-functional hamartin-tuberin, which in turn leads to unregulated downstream growth promotion signalling and the development of tumours.[22]

Neuropathologic Manifestations

Children present primarily with neurological manifestations such as brain dysplasias (cortical tubers), small subependymal nodules (SENs), and in some cases SEGAs.[23] Epilepsy, seizures, cognitive and behavioural disorders (such as attention deficit hyperactivity disorder and mood and anxiety disorders), and autism spectrum disorder are some of the neurological issues experienced by patients with TSC.[23] Epilepsy involves a lifetime risk of up to 90%, yet its exact source in TSC remain unknown.[23] Seizures and developmental delays are often associated with cortical tubers.[22] In addition, TSC patients can present with different seizure types, including infantile spasms, myoclonic, generalized tonic-clonic, and complex partial.[23] Approximately 50% of patients with TSC display cognitive and behavioural disorders and there is also an increased rate of mood and anxiety disorders associated with the adult TSC population.[23] In addition, up to 40% of TSC patients also meet the International Classification of Disease, 10th Edition criteria for autism spectrum disorder, which is comparatively more than that of the general population.[23]

With regard to non-neurological manifestations, more than 90% of TSC patients also experience cutaneous manifestations such as facial angiofibromas and periungual or mucosal tissue fibromas.[22,23] Angiomyolipomas, renal cysts, and renal cell carcinomas are all renal manifestations associated with TSC patients and occur at an incidence of 80%, 9% to 20%, and 2% to 3%, respectively.[22] In addition, a small percentage of patients can also develop early-onset autosomal polycystic kidney disease (PKD) caused by gene deletions in the TSC2 and PKD1 genes.[22,23] Between 50% and 60% of TSC patients develop cardiac rhabdomyomas and retinal hamartomas, while lymphangioleiomyomatosis (a tumour

predominantly affecting women that becomes symptomatic in adulthood[23]) appears to occur in around 40% of TSC patients.[22,23]

Cortical tubers have a prevalence rate of approximately 80% to 90% in patients with TSC and are firm tumours often found at the grey and white-matter junctions.[22,23] They consist of dysplastic neurons, white matter, giant glioneuronal cells, and exhibit disorganized cortical lamination.[22] SENS are prevalent in up to 90% of TSC patients, are found in the walls of the latter ventricles, and are generally asymptomatic.[22,23] About 5% to 20% of the time, SENs (typically at the level of the foramen of Monro) begin to grow at a faster rate and become SEGAs,[22,23] which are the most common type of brain tumours in the patient with TSC.[22] SEGAs are generally characterized as glioneuronal tumours that are slow but constant in growth once established.[22] This constant growth is thought to occur due to the up-regulation of many factors (which are assumed to be different from other brain tumours associated with TSC) , including both epidermal growth factors and epidermal growth factor receptor, both hepatocyte growth factor and hepatocyte growth factor receptor, and vascular endothelial growth factor.[22] While SEGAs occur in a small percentage of TSC patients, they are also responsible for up to 25% of the excess mortality associated with this disease.[22] SEGAs can remain asymptomatic until they grow large enough to cause obstruction, often leading to secondary hydrocephalus,[22] which requires a shunt to divert the built-up cerebrospinal fluid.[24] These shunts can lead to additional complications, including malfunction, infection, and even death associated with shunt failure.[24] Other symptoms associated with SEGAs include neurological deficits, sight impairments, endocrinopathies, and TSC-associated neuropsychiatric disorders (discussed previously).[22]

REFERENCES

1. [Pr]AFINITOR® (everolimus tablets): 2.5 mg, 5 mg and 10 mg; [Pr]AFINITOR® DISPERZ™ (everolimus tablets for oral suspension): 2 mg, 3 mg and 5 mg [product monograph]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2014 Nov 3.
2. CDR submission: [PR]Afinitor®, 2.5mg, 5mg and 10mg oral tablets. Company: Novartis Pharmaceuticals Canada Inc [**CONFIDENTIAL** manufacturer's submission]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2014.
3. Dixon BP, Hulbert JC, Bissler JJ. Tuberous sclerosis complex renal disease. Nephron Exp Nephrol [Internet]. 2011 [cited 2014 Nov 17];118(1):e15-e20. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2992644
4. Tuberous Sclerosis Alliance [Internet]. Silver Springs (MD): Tuberous Sclerosis Alliance; 2014. What is TSC?; [cited 2014 Nov 17]. Available from: http://www.tsalliance.org/pages.aspx?content=2
5. Owens J, Bodensteiner JB. Tuberous sclerosis complex: Management. 2014 Nov 5 [cited 2014 Nov 17]. In: UpToDate [Internet]. Waltham (MA): UpToDate; c2005 - . Available from: www.uptodate.com Subscription required.
6. Clinical Study Report: CRAD001M2301. A randomized, double-blind, placebo-controlled study of RAD001 in the treatment of patients with subependymal giant cell astrocytomas (SEGA) associated with tuberous sclerosis complex (TSC) [**CONFIDENTIAL** internal manufacturer's report]. Dorval (QC): Novartis; 2014 Sep 14.
7. Clinical Study Report: CRAD001C2485. Everolimus (RAD001) therapy of giant cell astrocytomas in patients with tuberous sclerosis complex [**CONFIDENTIAL** internal manufacturer's report]. Dorval (QC): Novartis; 2014.
8. Kingswood JC, Jozwiak S, Belousova ED, Frost MD, Kuperman RA, Bebin EM, et al. The effect of everolimus on renal angiomyolipoma in patients with tuberous sclerosis complex being treated for subependymal giant cell astrocytoma: subgroup results from the randomized, placebo-controlled, Phase 3 trial EXIST-1. Nephrol Dial Transplant. 2014 Jun;29(6):1203-10.
9. Franz DN, Belousova E, Sparagana S, Bebin EM, Frost M, Kuperman R, et al. Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial. The Lancet. 2013;381(9861):125-32.
10. Krueger DA, Care MM, Holland K, Agricola K, Tudor C, Mangeshkar P, et al. Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis. N Engl J Med. 2010;363:1801-11.
11. Krueger DA, Care MM, Agricola K, Tudor C, Mays M, Franz DN. Everolimus long-term safety and efficacy in subependymal giant cell astrocytoma. Neurology. 2013;80(6):574-80.
12. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical review(s). In: Afinitor Disperz (everolimus). Company: Novartis. Application no.:203985. Approval date: 29/06/2012 [Internet]. Rockville (MD): FDA; 2012 [cited 2014 Sep 19]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203985Orig1s000MedR.pdf

13. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Statistical review(s). In: Afinitor Disperz (everolimus). Company: Novartis. Application no.:203985. Approval date: 29/08/2012 [Internet]. Rockville (MD): FDA; 2012 [cited 2014 Sep 19]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203985Orig1s000StatR.pdf

14. Health Canada reviewer's report: Afinitor (everolimus) [**CONFIDENTIAL** internal report]. Ottawa: Therapeutics Products Directorate, Health Canada; 2011 May 24.

15. Sabaz M, Lawson JA, Cairns DR, Duchowny MS, Resnick TJ, Dean PM, et al. Validation of the quality of life in childhood epilepsy questionnaire in American epilepsy patients. Epilepsy Behav. 2003 Dec;4(6):680-91.

16. Aggarwal A, Datta V, Thakur LC. Quality of life in children with epilepsy. Indian Pediatr. 2011;48(11):893-6.

17. Krueger DA, Wilfong AA, Holland-Bouley K, Anderson AE, Agricola K, Tudor C, et al. Everolimus treatment of refractory epilepsy in tuberous sclerosis complex. Ann Neurol. 2013 Nov;74(5):679-87.

18. [Pr]AFINITOR® (everolimus tablets): 2.5 mg, 5 mg and 10 mg [product monograph]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2013.

19. Talarska D, Steinborn B, Michalak M. Cognitive functioning and behaviour of epileptic children in parents' assessment. Neurol Neurochir Pol. 2011 Sep;45(5):474-9.

20. Cowan J, Baker GA. A review of subjective impact measures for use with children and adolescents with epilepsy. Qual Life Res. 2004;13(8):1435-43.

21. Waxman DJ, Holloway MG. Sex differences in the expression of hepatic drug metabolizing enzymes. Mol Pharmacol [Internet]. 2009 Aug [cited 2014 Nov 17];76(2):215-28. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2713118

22. Franz DN. Pharmacologic management of tuberous sclerosis complex-associated subependymal giant cell astrocytomas. Expert Opinion on Orphan Drugs. 2014;2(1):53-66.

23. Kohrman MH. Emerging treatments in the management of tuberous sclerosis complex. Pediatr Neurol. 2012 May;46(5):267-75.

24. Gupta N, Park J, Solomon C, Kranz DA, Wrensch M, Wu YW. Long-term outcomes in patients with treated childhood hydrocephalus. J Neurosurg. 2007 May;106(5 Suppl):334-9.