Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Everolimus

Proprietary Product Name: Afinitor

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

14 March 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviation	Meaning
RAD001	Everolimus
%Red	Percentage reduction from Baseline in average weekly seizure frequency during the Core phase Maintenance period
SFB	Average weekly seizure frequency in the 8 week Baseline phase
SFM	Average weekly seizure frequency in the Core phase Maintenance period
TSC	Tuberous sclerosis complex
TN-C_{min}	Time normalised C_{min}

1. Introduction

1.1. Submission type

This is a full application to extend the indications of Afinitor (everolimus) and to update the Clinical Trials section of the Product Information.

1.2. Drug class and therapeutic indication

Everolimus is a signal transduction inhibitor targeting mTOR (mammalian target of rapamycin), or more specifically, mTORC1 (mammalian 'target of rapamycin' complex 1). mTOR is a key serine-threonine kinase playing a central role in the regulation of cell growth, proliferation and survival.

Everolimus exerts its activity through high affinity interaction with the intracellular receptor protein FKBP12.

Everolimus is an inhibitor of the growth and proliferation of tumour cells, endothelial cells, fibroblasts and blood vessel-associated smooth muscle cells.

In a mouse neuronal model of TSC in which TSC1 is ablated in most neurons during cortical development, everolimus was shown to markedly improve survival and neurological function following repeated intraperitoneal administration.[1]

Current Indications are:

> *Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not candidates for curative surgical resection.*
>
> *Patients with tuberous sclerosis complex (TSC) who have renal angiomyolipoma not requiring immediate surgery.*
>
> *Postmenopausal women with hormone receptor-positive, HER2 negative advanced breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole.*
>
> *Progressive, unresectable or metastatic, well or moderately differentiated neuroendocrine tumours (NETs) of pancreatic origin.*
>
> *Progressive, unresectable or metastatic, well-differentiated, non-functional neuroendocrine tumours (NET) of gastrointestinal or lung origin in adults.*
>
> *Advanced renal cell carcinoma after failure of treatment with sorafenib or sunitinib.*

The sponsor proposes to add the Indication:

> *Adjunctive treatment of patients aged 2years and older with TSC[2] and refractory seizures.*

[1] All from current PI

[2] Tuberous sclerosis complex the abbreviation is defined in the preceding Indication: patients with tuberous sclerosis complex (TSC) who have renal angiomyolipoma not requiring immediate surgery.

1.3. Dosage forms and strengths

Table 1: Dosage forms and strengths

			AUST R
Afinitor everolimus	tablets	2.5mg	177648
		5mg	154661
		10mg	154663
	dispersible tablets	2mg	200203
		3mg	200204
		5mg	200205

It is noted that the PI contains:

> Relative bioavailability of dispersible tablets
>
> The $AUC_{0-\infty}$ of the Afinitor Dispersible Tablets when administered as a suspension in water was equivalent to that of Afinitor Tablets (85% to 91% of that associated with Afinitor Tablets). The predicted trough concentrations of everolimus at steady state after daily administration were similar for both dosage forms. The C_{max} of everolimus associated with the Afinitor Dispersible Tablets was, however, somewhat lower (64% to 80% relative to that associated with Afinitor Tablets).

1.4. Dosage and administration

The dosage and administration section runs to 7 pages.

Afinitor should be administered orally once daily at the same time every day (preferably in the morning), either consistently with or consistently without food (see Pharmacokinetics). Afinitor is available in two formulations: tablets (Afinitor Tablets) and dispersible tablets (Afinitor Dispersible Tablets).

The changes proposed to dosage and Administration in the PI mostly relate to the proposed new indication. However there are some changes made to dosage Table 16/22 not in the annotated copy.

1.5. Proposed changes to the product documentation

The sponsor also proposes for the following sections:

- changes to the Mechanism of Action
- adding to the Exposure-response relationships under Pharmacodynamic properties
- adding to the Paediatrics Pharmacokinetics
- adding Tuberous sclerosis complex (TSC) with refractory seizures to Clinical Trials
- adding to the Precautions Hepatic Impairment
- amending the Precautions Paediatric use
- adding to the Interactions with Other Medicines - Agents whose plasma concentration may be altered by everolimus
- updating the Adverse Effects.

1.6. Background

Everolimus was initially developed for the prophylaxis of organ transplant rejection. It was first registered in Australia in 2009 for treatment of advanced renal cell carcinoma. Everolimus has multiple indications with the most recent extension for the treatment of progressive, unresectable or metastatic, well-differentiated, non-functional neuroendocrine tumours (NET) of gastrointestinal or lung origin. That submission (PM-2015-03569-1-4) was approved on 13 January 2017.

Of particular note for paediatric use:

- Everolimus is not recommended for use in paediatric cancer patients.
- Everolimus is not recommended for use in paediatric patients with TSC who have renal angiomyolipoma in the absence of SEGA.
- Everolimus has not been studied in paediatric patients < 1 year of age with TSC who have sub ependymal giant cell astrocytoma (SEGA).
- Dosing recommendations for paediatric patients with TSC who have SEGA are consistent with those for the corresponding adult population with the exception of those patients with hepatic impairment. Everolimus is not recommended for patients < 18 years of age with TSC who have SEGA and hepatic impairment.

This submission represents that first proposed use of everolimus for a non-oncology indication. Additionally it is proposed for use in a paediatric population.

About 85% of children and adolescents with TSC have neurological manifestations including epilepsy, cognitive impairment and behavioural problems, whereas a subset of affected adults have no signs of cerebral manifestations and have a normal mental status. Brain lesions mainly consist of cortical tubers, subependymal nodules and subependymal giant-cell astrocytomas, whose growth is a fearful complication.[3]

1.7. Information on the condition being treated

Tuberous sclerosis complex has a prevalence approaching 1 in 6000 live births. It is an autosomal dominant genetic condition involving the tuberous sclerosis 1 gene (TSC1) and/or the tuberous sclerosis 2 gene (TSC2), mutations of which are found in 80% to 85% of patients.

Products from these two genes form a tumour suppressor complex. When either TSC1 or TSC2 are deficient, mammalian target of rapamycin complex 1 (mTORC1) is upregulated leading to abnormal cellular growth, proliferation, and protein synthesis. This results in a variety of benign tumours, or hamartomas, in multiple organ systems: lesions in the kidney, brain, skin, lung, heart, and eye.

Up to 20% of hamartomas in the brain (usually subependymal nodules) demonstrate progressive growth becoming subependymal giant-cell astrocytomas (SEGAs). As they enlarge, symptoms of increased intracranial pressure, new neurologic deficits, or deterioration of seizure control may be observed.

Development can occur of early-onset epilepsy and other neuro-psychiatric problems such as developmental delay, mental retardation, and autism.

In patients with TSC, the mechanisms causing epilepsy are not entirely understood; dysregulation of development and maintenance of cortical structure and function because of

[3] Pirson Y. Tuberous sclerosis complex-associated kidney angiomyolipoma: from contemplation to action. *Nephrol Dial Transpla*nt 2013; 28: 1680-1685.

mTOR dependent processes may play a role in the development of epilepsy and neuropsychiatric disorders.

1.7.1. Seizures

Up to 90% of individuals with TSC are affected by a variety of seizure types of epilepsy, typically occurring in the first year of life (with 82% before 3 years of age); however, up to 12% of adult patients with TSC develop epilepsy as adults.

Patients with seizure onset before the age of 4 years, particularly when the seizures are frequent or refractory, have a substantially increased risk of subsequent mental retardation or autism.

1.8. Current treatment options and clinical rationale

SEGA are seen more frequently in childhood and adolescence; however, they have been reported in patients in their 30s and 40s. Historically, surgical resection has been used as standard of care to treat patients with TSC with SEGA. Despite its chances for success, a considerable level of risk of peri-and post-operative complications exists for such patients.

Seizures in patients with TSC ('TSC-seizures') may be controlled by medication such as antiepileptic drugs (AEDs) or methods such as epilepsy surgery, vagal nerve stimulator or ketogenic diet.

However seizures associated with TSC are poorly controlled by AEDs or epilepsy surgery, vagal nerve stimulation (VNS) or ketogenic diet and up to 60% of patients with TSC associated epilepsy fail to demonstrate improvement in seizure frequency with available therapies.

2. Clinical rationale

Pre-clinical results established the critical role of mTOR in TSC -related seizures and underlying epileptogenesis mechanisms and suggested inhibiting mTOR is a promising mechanism-based seizure reduction and antiepileptogenic therapy for treating TSC related epilepsy. On the basis of these pre-clinical results and preliminary clinical efficacy data, the sponsor initiated a Phase III study to investigate the safety and efficacy of everolimus in patients with TSC and refractory seizures.

2.1. Regulatory history

2.1.1. Australian regulatory history

First registered 6 August 2009.

2.1.2. Orphan drug designation

TGA orphan designation of TSC was obtained on 26 July 2010.

2.1.3. Related submissions

These studies were submitted with the most recent submission PM-2015-03569-1-4 and previously submitted to TGA:

- Study M2302; patients with TSC who have angiomyolipoma, previously submitted in Submission No: PM-2012-0193 1-3-4
- Study M2301; patients with TSC who have SEGA, previously submitted in Submission No: PM-2012-01931-3-4

- Study C2485; patients with TSC who have SEGA, initially submitted in Submission No: PM-2010-03193-3-4 and updated data submitted in Submission No: PM-2012-01931-3-4.

2.1.4. Overseas regulatory history

A similar application was submitted in EU, Canada and Switzerland for the TSC seizures application. No approvals of the proposed indication have been granted to date.

2.2. Guidance

CHMP/EWP/566/98 Rev.2/Corr Guideline on Clinical Investigation of Medicinal Products in the Treatment of Epileptic Disorders Effective: 17 December 2010.

CPMP/EWP/2330/99 Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study Effective: 27 March 2002 TGA annotation: Sponsors are reminded that they should submit all available new safety data that are relevant to the intended treatment population.

CPMP/EWP/908/99 Points to Consider on Multiplicity Issues in Clinical Trials.

CPMP/ICH/375/95 ICH Topic E 1 Note for Guidance on Population Exposure: The Extent of Population Exposure to Assess Clinical Safety.

Note for Guidance on Clinical Safety Data Management Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95) Annotated with TGA Comments.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- Comparative BA and Bioequivalence (BE) Study Reports
  - Study X2111: A randomised, open label, two way crossover study investigating the bioequivalence of everolimus (RAD001) 2 x 5 mg dispersible tablets in suspension and 5 x 2 mg dispersible tablets in suspension, in healthy male subjects
- Pharmacokinetic Study Reports
  - Study M2301: M2301 PK Expert Report A randomised, double blind, placebo controlled study of everolimus in the treatment of patients with subependymal giant cell astrocytomas (SEGA) associated with tuberous sclerosis complex (TSC)
- Population pharmacokinetic analyses.
  - Study M2301: Population pharmacokinetics of everolimus in the treatment of patients with subependymal giant cell astrocytomas associated with tuberous sclerosis complex 5 year update (Modelling Report)
- Efficacy/safety studies.
  - Study M2304: Parts 1 2 and 3; A three arm, randomised, double blind, placebo controlled study of the efficacy and safety of two trough ranges of everolimus as adjunctive therapy in patients with tuberous sclerosis complex (TSC) who have refractory partial onset seizures.

The submission also contained: Clinical Overview, Summary of Clinical Pharmacology Studies Summary of Clinical Efficacy, Summary of Clinical Safety Synopses of Individual Studies and literature references.

3.2. Paediatric data

The EMA approved deferral to the Paediatric Investigation Plan (PIP) was to be completed by March 2020.

3.3. Good clinical practice

All studies were conducted in full compliance with current Good Clinical Practice.

4. Pharmacokinetics

New clinical pharmacology information from three studies, including data in patients with refractory TSC seizures from the pivotal Phase III study M2304 and the 5 year updated data in patients with TSC who have SEGA from previously reported studies (Study C2485 and Study M2301).

Comment: Justification for the inclusion of Study X2111 could not be found, reference to the study was found only in Table 3-1 Everolimus pharmacokinetic comparison between oncology patients and healthy subjects, but of this table the sponsor, just above the table, said:

No new information was added to Table 3-1 since the last sNDA/type II variation application (Afinitor neuroendocrine tumour of GI or lung origin submission).

Reviewing submission 2015-03569 the study was not included in that dossier. The study report was dated 22-May-2013.

The Study was not reviewed.

4.1. Studies providing pharmacokinetic information

Table 2: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in healthy adults	Bioequivalence; Single dose	X2111	*
Population PK analyses	Target population§	M2301	*
PK interactions	Antiepileptic drugs	M2304	

* Indicates the primary PK aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

4.2. Summary of pharmacokinetics

4.2.1. Population pharmacokinetics

4.2.1.1. PopPK analysis Study M2301

Population pharmacokinetics of everolimus in the treatment of patients with sub-ependymal giant cell astrocytomas associated with tuberous sclerosis complex; 5 year update.

This was a 5 year update of the previous model based on 3 year data up to 11 January 2013. Study M2301 consisted of a double blind randomised phase and an extension phase, in which treatment was expected to run 4 years after the last patient was randomised. Patients were

allowed to crossover from placebo to everolimus at SEGA progression or after the unblinding of the investigator on 13 May 2011.

The analysis population included 111 patients who ranged from age 1.0 to 27.4 years at the start of everolimus. This included the 78 patients in the previous analysis randomised to everolimus plus 33 new patients randomised to placebo who switched to everolimus and contributed PK samples. They contributed 2580 everolimus blood concentrations to the PopPK analysis.

The previous PopPK model (based on data cut-off date 11 January 2013) was a two compartment model with first order input (rate constant KA), apparent clearances (CL/F and Q/F), and apparent volumes (V2/F and V3/F). The typical values of some of the PK parameters depended on body surface area (BSA, m^2) and an indicator for the presence or absence of CYP3A4 or PgP inducers.

The previous PK model parameter estimates were updated with the 5 year data set and then compared with those existing from the 3 year data.

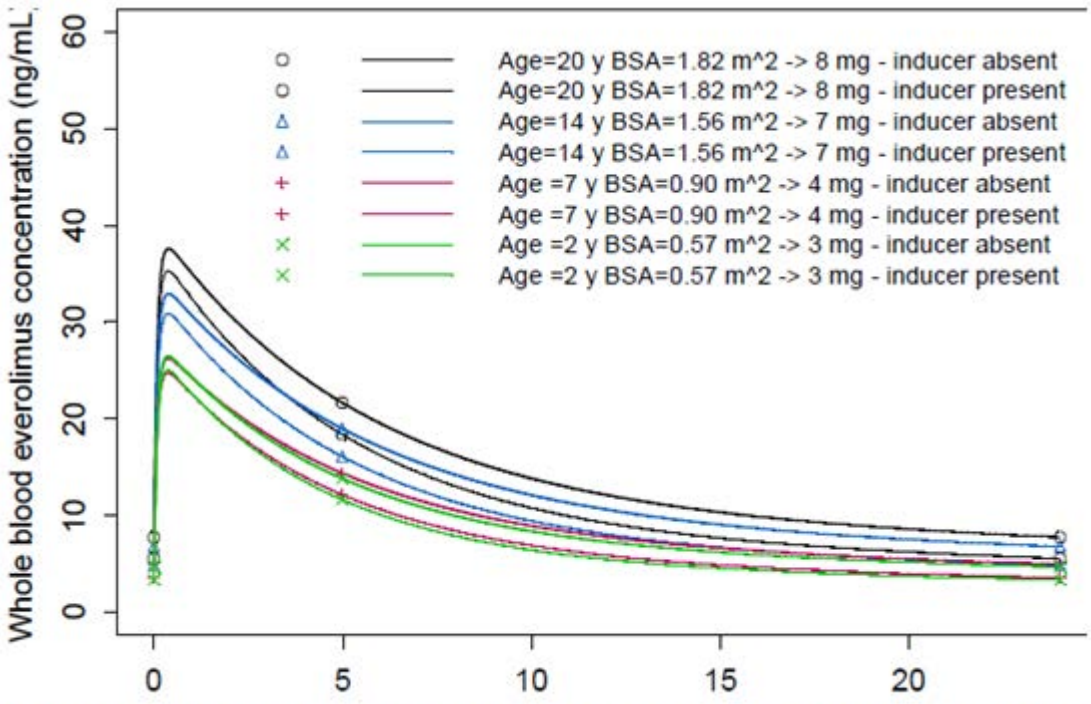
Since the use of additional covariates showed larger % error in predictions of trough levels, the 5 year model with no additional covariates (to those of the existing 3 year model) was adopted.

Typical steady state trough level was predicted to be near the midpoint of the target range of 5 to 15 ng/mL for an adult on a 4.5 mg/m^2 dose with absence of CYP3A4 or PgP enzyme inducers. The presence of inducer was associated with numerically greater decrease in trough levels for adults compared to children. Typical steady state trough levels are predicted to be near the lower limit of the target range for a child or anyone with presence of CYP3A4 or PgP enzyme inducers.

Thus: Children or anyone with presence of inducers may need a dose increase from 4.5 mg/m^2 to maintain steady state trough levels within the target range

Steady state C_{min} based on a higher starting dose was simulated for children 1 year to less than 3 years to deliver typical initial steady state C_{min} higher than 5 ng/mL across the BSA range observed in the trial at time of first everolimus dose (0.42 m^2 to 0.74m^2). A higher starting dose of 7 mg/m^2 based on the dispersible tablet or the regular tablet is suggested for children 1 to < 3 years to help minimize blood draws in these youngest children by reducing the number of dose titrations to attain the C_{min} within the target range of 5 to 15 ng/mL. See Figure 1.

Figure 1: Typical steady state concentration time profiles by BSA and absence/presence of inducer based on a dose of 4.5 mg/m²



Ages and BSA shown are median values in the age groups ≥18 y, 10 to <18 y, 3 to < 10 y, and 1 to < 3y.Source: Figure 6-1

4.2.2. Pharmacokinetic interactions Study M2304

Table 3: Concomitant antiepileptic therapy; Study M2304 Core phase (Safety Set)

	Everolimus		Placebo
	LT target of 3-7 ng/mL	HT target of 9-15 ng/mL	
	N=117	N=130	N=119
Concomitant antiepileptic therapy	**n (%)**	**n (%)**	**n (%)**
Vagal nerve stimulation treatment	**13 (11.1)**	**11 (8.5)**	**10 (8.4)**
Ketogenic diet treatment	**1 (0.9)**	**2 (1.5)**	**4 (3.4)**
Any background AEDs	**117 (100.0)**	**130 (100.0)**	**119 (100.0)**
Same AED regimen as used in Baseline phase	**113 (96.6)**	**123 (94.6)**	**118 (99.2)**
Number of AEDs in the regimen			
1	7 (6.0)	17 (13.1)	15 (12.6)
2	53 (45.3)	56 (43.1)	41 (34.5)
3	57 (48.7)	56 (43.1)	62 (52.1)
>3	0	1 (0.8)	1 (0.8)
Longest interruption in any AED			
1-3 days	1 (0.9)	3 (2.3)	0
4-7 days	0	0	0
>7 days	2 (1.7)	2 (1.5)	1 (0.8)
Change in dose in any AED or new AED started			
No	113 (96.6)	123 (94.6)	118 (99.2)
Yes	4 (3.4)	7 (5.4)	1 (0.8)
Compliant patient during Core phase [a]	**112 (95.7)**	**121 (93.1)**	**116 (97.5)**

AED(s) = antiepileptic drug(s) Source: [Study M2304-Table 14.3-1.6] Table 1-23

[a] Compliant patient = taking the same AED regimen of 1 to 3 AEDs as was used in the Baseline phase, without any interruption of any AED of more than 7 days and without any AED dose change or new AED started

In Study 2304 the concentration levels of 12 commonly prescribed AEDs were assessed:

- Inducers of CYP3A4: carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone, clobazam, topiramate
- Substrates of CYP3A4: clonazepam, diazepam, felbamate, zonisamide
- Not substrate or inducer of CYP3A4: valproic acid.

The impact of everolimus on the exposure of the AEDs was assessed via linear mixed models to compare the exposure of the AEDs before and after the administration of everolimus.

Separately for each AED, a linear mixed model was fitted to the log transformed concentrations, and included period (before and after everolimus administration) as a fixed effect and patient as a random effect. Geometric mean ratios of the concentrations with and without everolimus (as reference) and the 90% CIs were calculated from the model.

The above analyses were repeated considering patients exposed to only one of the 12 AEDs of interest to investigate any potential confounding effect. Model based analysis was performed on those AEDs taken by a minimum of 6 patients with valid concentrations for both everolimus and the corresponding AED.

Results of the statistical analysis

Treatment with everolimus was associated with minor increases in the concentrations of:

- Carbamazepine (geometric mean ratio of AED concentrations was 1.108 (90% CI: 1.016, 1.208))
- Clobazam (geometric mean ratio 1.093 (90% CI: 1.037, 1.153))
- Metabolite of clobazam (N-desmethylclobazam) (geometric mean ratio 1.071 (90% CI: 1.017, 1.127)).

'The increases in the pre-dose concentrations of these AEDs may not be clinically significant although dose adjustment for carbamazepine, a drug with a narrow therapeutic index, may be considered. Everolimus had no impact on the other AEDs evaluated in the study.'[4]

Table 4: Impact of everolimus on AED concentrations; Study M2304 Core phase Safety Set (Confirmed PK Sample Set)

Antiepileptic drug	N	n	Geometric mean AED concentration (ng/mL) Pre-everolimus	Post-everolimus	Ratio (post/pre) of geometric mean (90% CI)
Valproic acid	86	307	67.48	64.93	0.962 (0.913, 1.014)
Carbamazepine	34	121	5658.92	6269.86	1.108 (1.016, 1.208)
Clobazam	37	120	150.99	165.06	1.093 (1.037, 1.153)
N-desmethylclobazam	37	120	1368.01	1465.13	1.071 (1.017, 1.127)
Topiramate	34	118	4864.35	4781.95	0.983 (0.872, 1.108)
TRI477	31	104	65.61	71.24	1.086 (0.913, 1.291)
TRI476	31	103	1.34	1.60	1.194 (0.936, 1.523)
Clonazepam	17	64	13.67	14.55	1.065 (0.974, 1.163)
Zonisamide	12	43	16185.93	16639.57	1.028 (0.971, 1.089)
Phenobarbital	11	30	20524.35	19647.83	0.957 (0.886, 1.034)
Phenytoin	7	27	8205.57	8369.59	1.020 (0.874, 1.190)

N = Number of patients; n = Number of samples Source: Table 14.2-6.26 Table 11-38

[4] Interim Clinical Study Report

5. Pharmacodynamics

5.1. Exposure efficacy relationship

In study M2304, the relationship between everolimus exposure and the two primary efficacy endpoints of response rate and percentage change from Baseline in seizure frequency was investigated. No significant difference in response rate or seizure frequency reduction in relation to C_{min} level was shown.

Table 5: Response rate and percentage reduction from Baseline in seizure frequency by TN-C_{min}; Safety Set Study M2304 Core phase (Confirmed PK Sample Set)

	<3 ng/mL N=14	3-7 ng/mL N=147	>7-<9 ng/mL N=52	9-15 ng/mL N=30	>15 ng/mL N=2
Response rate (%)	14.3	29.9	44.2	50.0	50.0
95% CI [a]	1.8, 42.8	22.7, 38.0	30.5, 58.7	31.3, 68.7	1.3, 98.7
Median percentage reduction from Baseline	20.55	35.56	39.72	47.69	61.56
95% CI [b]	-8.45, 35.39	24.43, 41.88	28.02, 62.79	36.46, 66.32	42.73, 80.38

[a] Exact 95% CI obtained using Clopper-Pearson method
[b] 95% CI of the median based on bootstrap percentiles

Source: Table 14.2-6.21 and Table 14.2-6.23 Table 11-37
C_{min},TN = time-normalized minimum concentration

For response rate, logistic regression was used to model the probability of response. The model included terms for time normalised C_{min} (log transformed) in the Maintenance period of the Core phase (defined as from Study Day 43 until the last day of study medication in the Core phase), and Baseline seizure frequency. The model was stratified by age subgroup and adjusted for additional risk factors if appropriate.

The conditional logistic regression analysis for the probability of seizure response versus time normalised C_{min} (TN-C_{min}) stratified by age subgroup indicated that a 2 fold increase in TN-C_{min} was associated with a 2.17 fold increase (95% CI: 1.339, 3.524) in the odds for a response. In addition to TN-C_{min}, baseline seizure frequency was also a significant factor in the seizure response with an Odds Ratio of 0.978 (95% CI: 0.959, 0.998).

Table 6: Relationship for a 2 fold increase in everolimus exposure, between response rate and time normalised everolimus concentration at trough (TN-C_{min}) Study M2304 Core phase Safety Set (Confirmed PK Sample Set*)

Parameter[a]	Odds ratio[b]	95% CI
Log(C_{min},TN) across maintenance period of Core phase(ng/mL)	2.172	1.339, 3.524
Baseline seizure frequency (seizures per week)	0.978	0.959, 0.998

[a] Results from a logistic regression model: response (yes/no) as dependent variable, Log(C_{min},TN) across maintenance period of Core phase (ng/mL) and baseline seizure frequency (seizures per week) as continuous covariates, stratified by age subgroup at randomization. Source: Table 14.2-6.11
[b] Odds ratio is given for a 2-fold increase in everolimus exposure.
* Number of patients = 245, Number of samples = 245

C_{min},TN = time-normalized concentration at trough

A linear regression model was used to characterise the impact of exposure on the post Baseline average weekly seizure frequency. The model includes Baseline seizure frequency and TN-C_{min} in the Maintenance period of the Core phase, both in log scale as covariates. Moreover, an additional linear mixed model with repeated measurements was used to link the post Baseline average weekly seizure frequency to the TN-C_{min} in defined time intervals during the Core phase. The model was adjusted by the Baseline seizure frequency. The linear regression model

predicting the log of absolute seizure frequency during the Maintenance period of the Core phase indicated that for a 2 fold increase in TN-C_{min} there was a statistically significant 28% reduction (95% CI: 12%, 42%) in seizure frequency. Baseline seizure frequency and TN-C_{min} were both significant factors.

Table 7: Relationship between % reduction from baseline in seizure frequency and time normalised everolimus concentration at trough; Study M2304 Core phase Safety Set (Confirmed PK Sample Set)

Effect	Estimate [95% CI]	Standard error	Degrees of freedom	t value	Pr > |t|
Intercept	0.307 [-0.292; 0.906]	0.3041	231	1.010	0.314
Log(C_{min},TN)	-0.480 [-0.780; -0.179]	0.1525	231	-3.146	0.002
Log(Baseline seizure frequency)	0.974 [0.849; 1.100]	0.0638	231	15.282	< 0.001
Fold change for a 2-fold change C_{min} increase[a]	0.717 [0.582; 0.883]				

Results from a linear regression model: log of seizure frequency as dependent variable, Log(C+,TN) across maintenance period of Core phase (ng/mL) and baseline seizure frequency (seizures per week log transformed) as fixed effect continuous covariates.
[a] The fold change in seizure frequency for 2 fold C_{min} increase is calculated as exp(Log-C_{min}*log(2)) and the 95% CI is calculated in the same way. Number of patients = 234, Number of samples = 234 Source: Table 14.2-6.13
Since the analysis is performed on log scale, patient records with 0 seizures are not included in the analysis

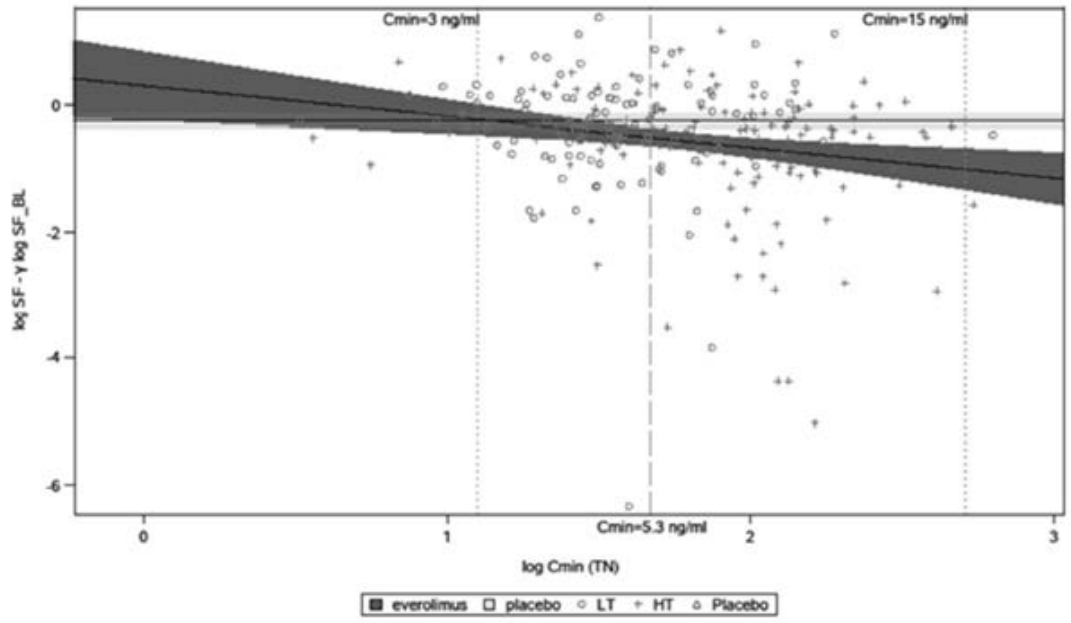
5.2. Minimum efficacious concentration

To find the lowest exposure (as TN-C_{min}) for which the 95% CIs of predicted change from baseline seizure frequency are not overlapping between everolimus and placebo, first a multiplicative linear regression model of seizure frequency predicted by TN-C_{min} was fit on everolimus data from the Maintenance phase of the Core phase.

Predictions were made for the adjusted 'log fold change in seizure frequency from baseline' across the observed range of TN-C_{min} values during the Core phase.

The 'log fold change in seizure frequency from baseline' and its 95% CIs were computed for both everolimus and placebo across the range of observed TN-C_{min} values. The lowest TN-C_{min} for which these CIs were not overlapping was then determined and considered as an estimate of the minimum efficacious concentration.

Figure 2: Relationship between percent reduction from baseline in seizure frequency and TN-C_{min} during Maintenance period of the Core phase Study M2304



Source: [SCP-Appendix 1-Figure 7-1] Figure 2-13 Summary of Clinical Pharmacology

Table 8: Baseline adjusted change of seizure frequency by TN-C_{min} during the Maintenance phase of the Core phase

	Fold change from Baseline in SF
At 3.0 ng/mL	0.803 [0.638; 1.010]
At 5.0 ng/mL	0.628 [0.550; 0.717]
At 5.2 ng/mL	0.617 [0.542; 0.702]
At 5.3 ng/mL	0.611 [0.537; 0.695]

6. Dosage selection for the pivotal studies

The PI proposed target C_{min} exposure range is 5 to 15 ng/mL and it is based on data of seizure response and overall safety observable across this range.

Starting dose was derived from the patient's age and concomitant use of CYP3A4/ P-glycoprotein (PgP) inducers.

It was based on the patients' body surface area (BSA) and on previously submitted results in Study C2485 and Study M2301 involving largely paediatric, TSC patients with SEGA lesions.

Table 9: Study M2304 Starting dose

Age	Not receiving CYP3A4/PgP inducer	Receiving CYP3A4/PgP inducer
Patients <10 years	6.0 mg/m²/day	9.0 mg/m²/day
Patients 10 to 18 years	5.0 mg/m²/day	8.0 mg/m²/day
Patients ≥ 18 years	3.0 mg/m²/day	5.0 mg/m²/day

7. Clinical efficacy

7.1. Study M2304

An Interim Clinical Study Report was submitted.

This interim CSR summarises all patient data during the Baseline and Core phases as well as partial Extension phase data, as of the 2 October 2015 data cut-off date.

Study M2304 A three arm, randomised, double blind, placebo controlled study of the efficacy and safety of two trough ranges of everolimus as adjunctive therapy in patients with tuberous sclerosis complex (TSC) who have refractory partial onset seizures

7.1.1. Study design, objectives, locations and dates

This randomised, double blind, placebo controlled study consisted of three phases:

- Baseline phase: From Screening Week 8 (V1) to randomisation visit at Week 0 (V2)
- Core phase: Double blind, placebo controlled, from randomisation at Week 0 (V2) to Week 18 (V11).
- Extension phase: From Week 18 (V11) until 48 weeks after the last patient has completed the Core phase, with all patients receiving everolimus at entry with blinding of the original randomisation arm maintained

During the Baseline phase, patients were to complete a seizure diary for a total of ≥ 8 weeks, which was considered long enough to provide reliable data on the Baseline seizure frequency of patients taking 1 to 3 AEDs.

During the Core phase patients received either:

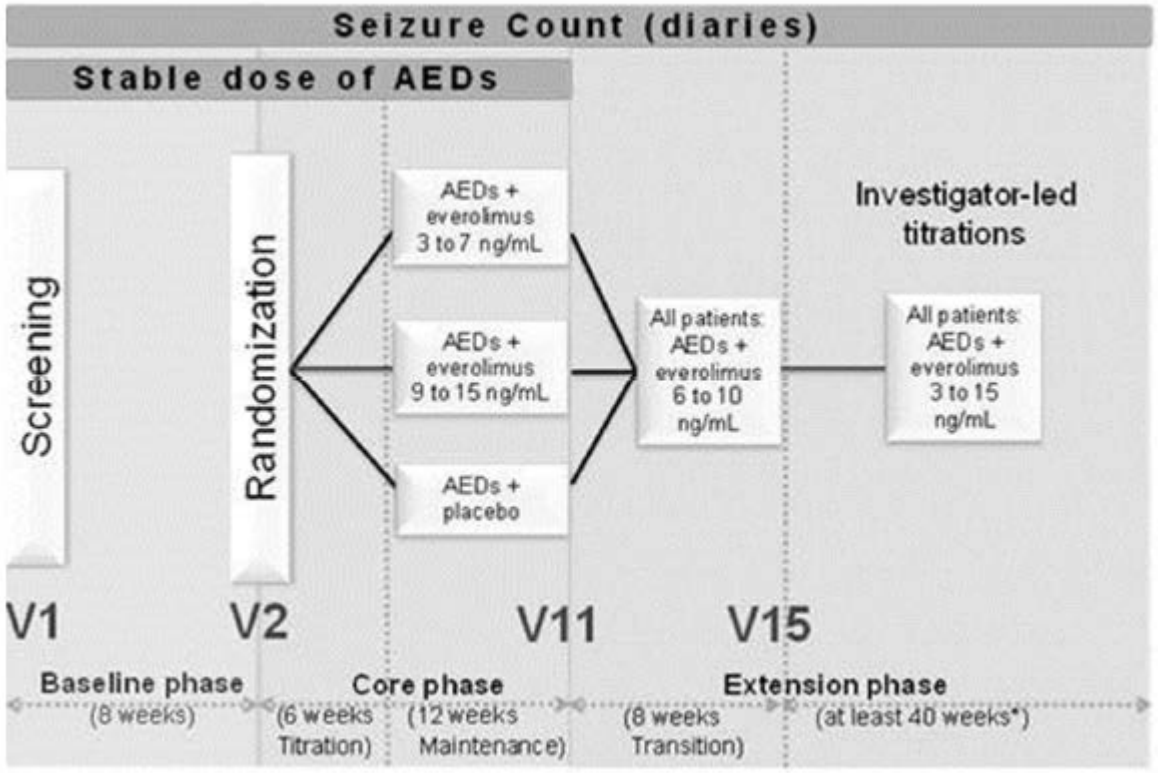
- Placebo or
- everolimus with titration to achieve a trough range of 3 to 7 ng/mL, or
- everolimus with titration to achieve a trough range of 9 to 15 ng/mL.

Patients entered the Core phase starting with a 6 week Titration period during which up to 3 dose adjustments could be made to reach the targeted everolimus trough range. This was followed by a Maintenance period of 12 weeks duration.

The Extension phase, in which all patients received everolimus, included an initial 8 weeks Transition period to bring patients to the common 6 to 10 ng/mL trough range followed by the Titration period with the option for Investigators to control everolimus dosing targeting the broad 3 to 15 ng/mL range.

The study formulation used was the tablets for oral suspension (dispersible tablets).

Figure 3: Study design



Source: Figure 9-1 AEDs = antiepileptic drugs

7.1.1.1. Objectives

Primary

To compare the reduction in frequency of TSC seizures on each of two trough ranges of everolimus (3 to 7 ng/mL and 9 to 15 ng/mL) versus placebo in patients with TSC who are taking one to three antiepileptic drugs (AEDs).

Secondary Objectives

There were multiple Secondary Objectives

1. To compare each of the two everolimus trough ranges versus placebo with respect to:
   a. Ability to completely suppress TSC seizures
   b. Proportion of patients with ≥ 25% reduction from Baseline in average weekly frequency of TSC seizures
   c. Distribution of reduction from Baseline in seizure Frequency
   d. Seizure free days
   e. Treatment duration
   f. Quality of life (QoL).
2. To assess everolimus in relation to neurocognitive, neurobehavioral, and neurodevelopmental measures using the Vineland Adaptive Behaviour Scales-II and the Wechsler Non-Verbal Scale of Ability.
3. To assess the relationship between everolimus concentration and efficacy/safety endpoints.

4. To evaluate the impact of everolimus on the pre-dose exposure of AEDs.
5. To evaluate the effect of the two everolimus trough ranges on long term seizure reduction.
6. To evaluate the safety and tolerability of each everolimus trough range in the study population.
7. To evaluate the impact of everolimus on the risk of suicidality using the Columbia Suicide Severity Rating Scale (C-SSRS).

Exploratory objectives

There were another 4 exploratory objectives.

7.1.1.2. Locations and date

The study was conducted in multiple countries in Europe, Asia, North America and Russia and in multiple centres including 3 in Australia.

The study commenced 29 April 2013 and the cut-off date for this report was 2 October 2015.

7.1.2. Protocol amendments after trial start

14 March 2014

The second Protocol amendment included:

- Among the Inclusion criteria the definition of TSC seizures was modified to include sensory seizures as the sole seizure type if confirmed to be partial onset by ictal EEG.
- To the Exclusion criteria there was one added in relation to patients on a ketogenic diet (defined as < 40 g of carbohydrate/day).
- Allowing investigator discretion to manage everolimus titrations in the Extension phase.
- The Safety Population in the original protocol was planned to be defined using actual C_{min} values; however, that approach was subsequently recognized to be inappropriate.

7.1.3. Inclusion criteria

There were multiple inclusion criteria including age 2 to 65 years old (except in Europe where the minimum age was 1 year) with a clinically definitive diagnosis of TSC and treatment resistant epilepsy with ≥ 16 reported quantifiable seizures (with no continuous 21 day Seizure free period) during the 8 week Baseline phase.

Patients eligible for inclusion in this study have to meet all of the following criteria:

1. Male or female between the ages of 2 and 65 years (except in Europe where the minimum age will be 1 at the request of the EMA). (A minimum number of paediatric patients will be randomised in the following age groups: 1 to <6 years (40 patients), 6 to < 12 years (40 patients), and 12 to < 18 years (40 patients).)
2. Clinically definite diagnosis of TSC (modified Gomez criteria)
3. Diagnosis of partial onset epilepsy according to the classification of the International League Against Epilepsy (Commission on Classification and Terminology of the International League Against Epilepsy, 1989) and revised in 2009 (Berg 2010). This classification is further modified for the purpose of capturing clinical details, and defines partial onset seizures in patients with TSC on the basis of the pathophysiology of TSC as either:
    - any seizure that has been definitively shown to be partial onset on ictal EEG, or
    - any probable seizure with motor signs (non-sensory) that has not been documented to be a primary generalised seizure on ictal EEG.

4. Uncontrolled partial onset seizures; must meet the following:
    a. At least 16 reported quantifiable (no cluster or innumerable seizures) partial onset seizures (as defined in Inclusion Criteria 3) over the Baseline period (56 days, 8 weeks) with no continuous 21 day seizure free period between Visit 1 (Screening Visit) and Visit 2 (Randomization visit), as per data captured in daily seizure diaries.
    b. Prior history of failure to control partial onset seizures despite having been treated with two or more sequential regimens of single or combined antiepileptic drugs
    c. Prior or concurrent use of vagal nerve stimulator (VNS) is allowed. If the patient is using VNS, device stimulator parameters must remain constant throughout the study.
    d. Prior epilepsy surgery is allowed if performed at least 12 months before study entry.
5. Must be receiving one, two, or three AEDs at a stable dose for at least 4 weeks at the start of the 8 week prospective Baseline phase, remain on the same regimen throughout the Baseline phase, and intend to continue the same regimen throughout the 18 week double blind Core phase (rescue medications are permitted). No more than one of these can be a strong CYP3A4 inducer (for example, Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin, Primidone)
6. If female of child bearing potential, documentation of negative pregnancy test at time of informed consent. Females of child bearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and for 8 weeks after stopping treatment. Highly effective contraception is defined as either:
    - Total abstinence: When this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (for example, calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not acceptable methods of contraception)
    - Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male partner sterilization, at least 6 months prior to screening visit, (with the appropriate post vasectomy documentation of the absence of sperm in the ejaculate). (For female subjects on the study, the vasectomized male partner should be the sole partner for that subject).
    - Use of a combination of any two of the following (a+b or a+c or b+c):
        a. Use of oral, injected or implanted hormonal methods of contraception
        b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
        c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository In case of use of oral contraception women should have been stable on the oral agent before taking study treatment for at least 3 months.
7. Sexually active males must use a condom during intercourse while taking study drug, and for 8 weeks after stopping study treatment. They should not father a child during this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
8. Hepatic, renal and blood laboratory values within the following range at screening:
    - AST and ALT levels < 2.5 x ULN

- serum bilirubin < 1.5 x ULN (this limit does not apply to patients with an elevated indirect bilirubin, if they have Gilbert's Syndrome),
- serum creatinine < 1.5 x ULN,
- haemoglobin ≥ 9 g/dL,
- platelets ≥ 80,000/mm^3,
- absolute neutrophil count ≥ 1,000/mm^3

9. Written informed consent: Subjects or their legal guardians must have the ability to comprehend the informed consent form and be willing to provide informed consent. For subjects who are too young or unable to comprehend the written consent, a legal guardian who is able to describe and provide an understanding of the informed consent to the subject must sign the consent form on behalf of the subject. In all cases, the informed consent process will follow the local rules and regulations.
10. Patient or caregiver must be able to reliably record seizures and keep a daily diary and recall adverse events.

7.1.4. Exclusion criteria

There were multiple exclusion criteria including weight less than 12 kg, an episode of status epilepticus in the last year and a history of seizure clusters.

Patients eligible for this study must not meet any of the following criteria:

1. Patients with seizures secondary to metabolic, toxic, infectious or psychogenic disorder or drug abuse or current seizures related to an acute medical illness.
2. Presence of only non-motor partial seizures (Criteria Not Applicable per Amendment 2)
3. Patients with TSC who have SEGA in need of immediate surgical intervention.
4. Patients under 2 years of age with untreated infantile spasms.
5. Within 52 weeks prior to study entry, an episode of status epilepticus, defined as:
    a. in adults and children 5 years and older ; continuous or intermittent, convulsive seizures lasting more than 10 minutes and requiring additional medical intervention such as with rescue medication not commonly used in the home (that is, a convulsive seizure or series of convulsive seizures not within the patient's typical seizure pattern and management)
    b. in children less than 5 years of age; continuous or intermittent, convulsive seizures lasting more than 10 minutes and requiring significant additional medical intervention such as hospitalization (note: It is recognised that some young patients may be sent for emergency care despite having experienced a seizure within their typical seizure pattern and management. Only the more severe episodes of prolonged convulsive seizures in such patient, such as those leading to hospitalisation, would qualify as status epilepticus).
6. Patients with history of seizure clusters (where individual seizures cannot be accurately counted according to the judgment of the investigator) occurring within 26 weeks prior to study entry.
7. Patients who require rescue medication during the Baseline phase for more than 6 days.
8. Patients with non TSC related progressive encephalopathy.
9. Patients who weigh less than 12 kg.

10. Patients with coexisting malignancies within the 3 years prior to randomisation, except for adequately treated carcinoma of the cervix or basal or squamous cell carcinomas of the skin.
11. Patients with any severe and/or uncontrolled medical conditions at randomisation such as:
    a. Symptomatic congestive heart failure of New York Heart Association Class III or IV, history of left ventricular ejection fraction (LVEF) < 50%, QTc interval > 460 ms, congenital QT syndrome, unstable angina pectoris, myocardial infarction within 6 months of study entry, serious uncontrolled cardiac arrhythmia or any other clinically significant cardiac disease
    b. Significant symptomatic deterioration of lung function. If clinically indicated, pulmonary function tests including measures of predicted lung volumes, DLco, O_2 saturation at rest on room air should be considered to exclude restrictive pulmonary disease, pneumonitis or pulmonary infiltrates
    c. Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of everolimus (for example, ulcerative disease, malabsorption syndrome or small bowel resection)
    d. liver disease such as cirrhosis, decompensated liver disease, and chronic hepatitis (that is quantifiable HBV-DNA and/or positive HbsAg, quantifiable HCV-RNA)
    e. Uncontrolled diabetes as defined by fasting serum glucose > 1.5 x ULN
    f. Active skin, mucosa, ocular or GI disorders of Grade > 1
    g. Active (acute or chronic) or uncontrolled severe infections
    h. A known history of HIV seropositivity or other active viral infections.
12. Patients with an active, bleeding diathesis.
13. Patient with uncontrolled hyperlipidaemia: fasting serum cholesterol > 300 mg/dL

    or >7.75 mmol/L AND fasting triglycerides > 2.5 x ULN.
14. Patients who have had a major surgery or significant traumatic injury within 4 weeks of study entry. Patients who have not recovered from the side effects of any major surgery (defined as requiring general anaesthesia), or patients that may require major surgery during the course of the study.
15. Patients with a prior history of organ transplant.
16. Patients receiving more than 3 antiepileptic drugs at any time in the baseline phase or at randomisation or who change the dose of the AEDs during 4 weeks before screening or during the baseline period.
17. Patients being treated with felbamate, unless treatment has been continuous for ≥ 1 year.
18. Patients currently receiving anticancer therapies or who have received anticancer therapies within 4 weeks of study entry (including chemotherapy, radiation therapy, antibody based therapy, etcetera).
19. Prior treatment with any investigational drug within the preceding 4 weeks prior to study entry.
20. Patients receiving chronic, systemic treatment with corticosteroids or another immunosuppressive agent at study entry. Topical or inhaled corticosteroids are allowed.
21. Patients who have received prior treatment with a systemic mTOR inhibitor (sirolimus, temsirolimus, everolimus) within 24 months of study entry. Patients who have received

prior treatment with a topical mTOR inhibitor (sirolimus, temsirolimus, everolimus) within 4 weeks of study entry.

22. Patients with a known hypersensitivity to everolimus or other rapamycin-analogues (sirolimus, temsirolimus) or to its excipients.
23. Patients with a history of non-compliance to medical regimens or who are considered potentially unreliable or will not be able to complete the entire study.
24. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
25. Patients with a Score of 4 or 5 on the Suicidal Ideation item within 2 years of Screening, or any 'yes' on the Suicidal Behaviour item of the Columbia-Suicide Severity Rating Scale at Screening or Baseline who upon follow up with a healthcare professional are found to be severely depressed or suicidal.
26. Maintenance of a diet consisting of < 40 g of carbohydrate per day within 3 months of screening

7.1.5. Efficacy variables and outcomes

The endpoints were multiple including differing Primary endpoints for the EMA and FDA. The EMA primary variable was the response rate[5] while that for the FDA was the percentage reduction in seizure frequency.

Comment: Given that the TGA has adopted EMA guidelines this evaluator proposes to use the response rate as the primary variable. The protocol indicates that the statistical analysis was not to be set up for co-primary endpoints.[6]

Seizure frequency was determined using counts of seizures, based on seizure diaries that were completed by the patient or caregiver throughout the trial.

During the Baseline phase (and if new seizures occurred during the study) the Investigator reviewed the known seizure types of each patient with the Epilepsy Study Consortium.[7] Only events thought to have a high probability of being seizures with approval from the Epilepsy Study Consortium and agreement from the Investigator were entered into the eCRF and counted as partial onset seizures and generalised onset seizures as shown in Figure 4.

[5] Response rate is the percentage of responders in a treatment group

[6] Protocol;each Agency will use their preferred variable as the primary variable, with the other (non-primary) variable being used in a supportive analysis. As each Agency will only use their preferred primary variable to make a decision on the primary objective, the full alpha level can be used for each Agency's primary variable, without correction for multiplicity.

[7] The ESC is an independent group of Scientific Investigators from academic medical research, dedicated to accelerating the development of new therapies in epilepsy to improve patient care.

Figure 4: Definitions of seizures

1. Average weekly seizure frequency in the 8 week Baseline phase (SFB)

$$= \frac{7 \times \text{no. seizures recorded over the Baseline phase}}{\text{No. of non-missing seizure diary days in the Baseline phase}}$$

2. Average weekly seizure frequency in the Core phase Maintenance period (SFM):

a. If patient does not discontinue during the 6 week Titration period,

$$SFM = \frac{7 \times \text{no. seizures recorded during the Core phase Maintenance period}}{\text{No. of non-missing seizure diary days in the Core phase Maintenance period}}$$

b. Otherwise,

$$SFM = \frac{7 \times \text{no. of seizures recorded during the Core phase Titration period}}{\text{No. of non-missing seizure diary days in the Core phase. Titration period}}$$

3. Percentage reduction from Baseline in average weekly seizure frequency during the Core phase Maintenance period (%Red)

$$\%Red = 100 \times (SFB - SFM) \div SFB$$

A responder was a patient with ≥ 50% reduction from Baseline in average weekly seizure frequency during the Maintenance period of the Core phase, that is when %reduction ≥ 50.[8]

Table 10: Study objectives

Objective	Endpoint
Primary To compare the reduction in frequency of TSC seizures on each of two trough ranges of everolimus (3-7 ng/mL and 9-15 ng/mL) versus placebo in patients with TSC who are taking one to three antiepileptic drugs (AEDs)	EMA: Response rate, where response means at least a 50% reduction from Baseline in TSC seizure frequency during Maintenance period of the Core phase FDA: Percentage reduction from Baseline in partial onset seizure frequency during Maintenance period of the Core phase
Supportive As above	
Secondary To compare each of the two everolimus trough ranges versus placebo with respect to: (1) Ability to completely suppress TSC seizures (2) Proportion of patients with ≥ 25% reduction from Baseline in average weekly frequency of TSC seizures (3) Distribution of reduction from Baseline in seizure frequency	(1) Seizure-free rate, where seizure-free means a 100% reduction in TSC seizure frequency during Maintenance period of the Core phase (2) Proportion of patients with at least a 25% reduction from Baseline in TSC seizure frequency during Maintenance period of the Core phase (3) Categorical variable of six levels of reduction from Baseline in TSC seizure frequency during Maintenance period of the Core phase (≤ -25% (exacerbation); >-25% to

[8] where a patient discontinued the trial without completing the patient seizure diary, then the %Red was assigned as equal to 0 and this patient was considered as a non-responder.

(4) Seizure-free days (5) Treatment duration (6) Quality of life (QoL) To assess everolimus in relation to neurocognitive, neurobehavioral, and neurodevelopmental measures using the Vineland Adaptive Behavior Scales-II and the Wechsler Non-Verbal Scale of Ability To assess the relationship between everolimus concentration and efficacy/safety endpoints To evaluate the impact of everolimus on the pre-dose exposure of AEDs To evaluate the effect of the two everolimus trough ranges on long-term seizure reduction To evaluate the safety and tolerability of each everolimus trough range in the study population To evaluate the impact of everolimus on the risk of suicidality using the Columbia Suicide Severity Rating Scale (C-SSRS)	< 25% (no change); ≥ 25% to <50%; ≥ 50% to <75%; ≥ 75% to <100%; 100% (seizure-freedom)) (4) Frequency of seizure-free days during Maintenance period of the Core phase (5) Time from randomisation until treatment discontinuation in the Core phase (6) Overall QoL global scores from the 3 age-specific questionnaires Change from Baseline of sub-test scores Percentage reduction in seizure frequency/frequency of selected adverse events (AEs) Pre-dose concentrations of AEDs at Baseline (AEDs alone) and at post-Baseline (AEDs plus everolimus) 50% response rate, percent reduction from Baseline, and seizure free-days in TSC seizure by time interval over the Extension phase Frequency of AEs/abnormal laboratory values Frequency C-SSRS outcomes, frequency of serious adverse events (SAEs) referring to a positive suicidal evaluation
Exploratory Explore the relationship between patient age and reduction from Baseline in TSC seizure frequency Compare each of the two everolimus trough ranges versus placebo with respect to reduction from Baseline in seizure frequency for each of three TSC seizure types (type IA, type IB, type IC) Compare each of the two everolimus trough ranges versus placebo with respect to reduction from Baseline in seizure frequency for all types of seizures grouped (I, II) Explore relationship between TSC1/TSC2 mutation status and reduction from Baseline in TSC seizure frequency	Response rate and percentage reduction in TSC seizure frequency during Maintenance period of Core phase Response rate and percentage reduction in seizure frequency during Maintenance period of Core phase Response rate and percentage reduction in seizure frequency during Maintenance period of Core phase Response rate and percentage reduction in TSC seizure frequency during Maintenance period of Core phase

7.1.6. Randomisation

At the end of the Baseline phase, patients who met the eligibility criteria were randomised in an approximate ratio of 1:1:1 to receive treatment A, B or C.

Randomisation was stratified by age group:

- 1 to < 6 years
- 6 to < 12 years

- 12 to < 18 years
- ≥ 18 years

Due to a mistake in the titration recommendations discovered early in the trial, preventing dose titrations despite C_{min} values outside the targeted trough range, it was decided to increase the sample size in the everolimus 9 to 15 ng/mL arm by 10 patients, that is 125 patients in total.

This sample size increase of 10 patients was made by inserting a number of blocks with randomisation ratio of 1:2:1 in favour of the everolimus 9 to 15 ng/mL arm, with the planned sample size becoming 355 patients (115 patients in the everolimus 3 to 7 ng/mL arm, 125 patients in the everolimus 9 to 15 ng/mL arm, and 115 in the placebo arm; overall randomisation ratio of 1:1.09:1).

7.1.7. Blinding methods

During the initial titration period of the Base phase dose was titrated via Interactive Response Technology (IRT) in a blinded fashion until each patient reached their assigned target trough range.

Patients on placebo had random increases and decreases in the number of tablets taken to simulate titration and to maintain the blind. Patients in the low trough group also had random increases and decreases in placebo tablets to simulate titration for the high trough group.

During the extension phase, placebo dose changes were possible at the start of dose transition. Starting at the visit at which everolimus concentrations were disclosed, placebo tablets were no longer dispensed.

7.1.8. Analysis populations

Full Analysis Set (FAS) comprised all patients to whom study treatment was assigned by randomisation.

Pharmacokinetic analyses were performed on the Confirmed PK Sample Set from all everolimus-treated patients in the Safety Set and Long-term Evaluation Safety Set, which was defined as follows:

> C_{min} collected prior to dose administration on the same treatment day and 20 to 28 hours after the previous dose, at steady state, and with no evidence of vomiting within 4 hours of the previous dose.

The Long-term Evaluation (LTE) Sets (Efficacy and Safety) comprise all patient data on everolimus in the study during the Core phase and Extension phase. Each LTE set consists of all patients who received at least one dose of everolimus and had at least one efficacy/safety assessment.

7.1.9. Sample size

The sample size calculation was based exclusively on response rate, the primary endpoint used by the EMA, but it was also expected to provide sufficient patients for the power of the FDA primary endpoint, percentage reduction in seizure frequency.

It was assumed that response rates would be 15% in the placebo arm and 35% in each of the two everolimus arms. That is, there was no a priori strong expectation that the higher targeted trough everolimus arm 9 to 15 ng/mL would deliver a higher response rate than the lower targeted trough everolimus arm 3 to 7 ng/mL, as better efficacy may be mitigated by worse tolerability. For this reason, the testing strategy was to simultaneously compare each pairwise comparison, splitting the significance level, rather than testing hierarchically starting with the higher trough arm for example. It was determined that a sample size of 355 patients would ensure 90% power for each of the primary comparisons of each everolimus arm versus placebo,

assuming one-sided 1.25% significance levels for each Cochran-Mantel-Haenszelchi-square test, and assuming balanced randomisation (that is 115 patients per randomisation arm).

Due to a mistake in the titration recommendations it was decided to increase the sample size in the everolimus 9 to 15 ng/mL arm by 10 patients, that is 125 patients in total in that arm.

7.1.10. Statistical methods

7.1.10.1. Primary endpoint

Response rate was compared between each everolimus arm versus the placebo arm in the Full Analysis Set using Cochran-Mantel-Haenszel (CMH) chi-square tests stratified by age subgroup. The Bonferroni-Holm procedure was used to ensure an overall family-wise Type I error rate of 2.5% one-sided. Response rates were provided with exact 95% CIs, and the odds ratio for each everolimus arm versus placebo was obtained from logistic regression models stratified by age subgroup.

Each Agency will use their preferred variable as the primary variable, with the other (non-primary) variable being used in a supportive analysis. As each Agency will only use their preferred primary variable to make a decision on the primary objective, the full alpha level can be used for each Agency's primary variable, without correction for multiplicity.

Comment: Given that the TGA has adopted EMA guidelines this evaluator proposes to use the response rate as the primary variable. The protocol indicates as above that the statistical analysis was not to be set up for co-primary endpoints.

Statistical analysis methods of the multiple supportive and secondary endpoints are described below.

FDA primary endpoint Percentage reduction in seizure frequency was compared between each everolimus arm vs. the placebo arm in the Full Analysis Set using rank analysis of covariance (ANCOVA), with Baseline average weekly seizure frequency as a covariate, and stratified by age subgroup. The Bonferroni-Holm procedure was used as a multiplicity correction to ensure an overall family wise Type I error rate of 2.5% one-sided. The median percentage reduction from Baseline is presented for each treatment group, along with 95% bootstrap CIs.

1. The seizure-free rates for each treatment arm in the FAS are presented along with exact 95% CIs, and the odds ratio for each everolimus arm versus placebo was derived from logistic regression models stratified by age subgroup.
2. The proportions of patients with at least 25% reduction in seizure frequency are presented in each treatment arm along with exact 95% CIs, and odds ratios for each everolimus arm versus placebo (plus Wald 95% CI) from logistic regression models stratified by age subgroup.
3. The distribution of reduction from Baseline in seizure frequency was categorised into six levels using the variable percentage reduction (%Red), the proportions of patients in each category are presented for each treatment arm.
4. The change from Baseline in frequency of seizure-free days per 28 days was summarised by treatment arm (mean, SD, range). Mean differences between each everolimus arm and the placebo arm in change from Baseline in frequency of seizure-free days are presented, along with the 95% CI.
5. Times from randomisation to treatment discontinuation in each arm are presented descriptively in the Full Analysis Set using Kaplan-Meier curves, from which summary statistics were determined. These statistics were given as point estimates with 95% CIs. The hazard ratio (and two-sided 95% CI) for each everolimus arm versus placebo was obtained from a Cox proportional hazards model stratified by age subgroup.

6. A long term evaluation of efficacy over the Extension phase for percentage reduction from Baseline in TSC seizure frequency, response rate and seizure free days, was computed by time interval using the LTE Efficacy Set.
7. Change from Baseline to the end of the Core phase in the overall quality-of-life scores are analysed using an ANCOVA model including terms for treatment and Baseline overall quality of life score. The differences in least square means between each everolimus arm and placebo, and the corresponding two-sided 95% CI, are presented.

7.1.11. Participant flow

Table 11: Patient disposition; Full Analysis Set

	Everolimus				Placebo	
	LT target of 3-7 ng/mL		HT target of 9-15 ng/mL			
Disposition	N=117		N=130		N=119	
Reason	n (%)		n (%)		n (%)	
Patients randomized						
Treated	117	(100.0)	130	(100.0)	119	(100.0)
Patients treated: Core phase						
Treatment ongoing [a] in Core phase	0		0		0	
End of treatment	117	(100.0)	130	(100.0)	119	(100.0)
Discontinued in Titration period	3	(2.6)	5	(3.8)	1	(0.8)
Discontinued in Maintenance period	4	(3.4)	3	(2.3)	4	(3.4)
Completed Core phase	110	(94.0)	122	(93.8)	114	(95.8)
Primary reason for end of treatment in Core phase						
Adverse event(s)	5 [b]	(4.3)	4	(3.1)	2	(1.7)
Lack of efficacy	0		2	(1.5)	2	(1.7)
Subject withdrew consent	2	(1.7)	1	(0.8)	1	(0.8)
Protocol deviation	0		1	(0.8)	0	
Patients treated: Extension phase [c]						
Patients entering Extension phase [d]	110	(94.0)	118	(90.8)	114	(95.8)
Treatment ongoing [a] in Extension phase	90	(76.9)	102	(78.5)	100	(84.0)
End of treatment	20	(17.1)	16	(12.3)	14	(11.8)
Discontinued in Extension phase	20	(17.1)	16	(12.3)	14	(11.8)
Completed Extension phase	0		0		0	
Primary reason for end of treatment in Extension phase						
Adverse event(s)	11	(9.4)	7	(5.4)	8	(6.7)	26	(7.1)
Subject withdrew consent	4	(3.4)	6	(4.6)	5	(4.2)	15	(4.1)
Lack of efficacy	3	(2.6)	2	(1.5)	1	(0.8)	6	(1.6)
Protocol deviation	2	(1.7)	1	(0.8)	0		3	(0.8)

[a] Patients ongoing at the time of the data cut-off of 02-Oct-2015 Source: Table 14.1-1.1 Table 10-1

[b] An apparent discrepancy is evident between the 5 patients in the everolimus LT arm who discontinued treatment in the Core phase as the result of an AE and the 6 patients from the LT group reported in the table displaying AEs leading to discontinuation in the Safety Set. This is attributed to Patient No. 0903/00004 who experienced intermittent diarrhoea commencing during the Core phase (and was thus captured in the AE table for the Safety Set) but which led to discontinuation only in the Extension phase, and as a result was not reported in this patient disposition table as an AE leading to discontinuation from the Core phase of the study.

[c] All patients in the Extension phase were treated with everolimus; the placebo column refers to patients originally randomized to placebo and subsequently crossed over to everolimus therapy in the Extension phase

[d] None of the patients had completed the Extension phase at the time of the data cut-off of 02-Oct-2015. In the everolimus 9-15 ng/mL arm, 3 patients completed the Core phase but did not enter the Extension phase and 1 patient completed the Core phase on the day of the data cut-off and entered the Extension phase on the following day (03-Oct-2015). All other patients who completed the Core phase entered the Extension phase.

Core phase is 18 weeks in duration and consists of 6-week Titration period followed by 12-week Maintenance period
Extension phase starts immediately after Core phase and lasts until 48 weeks after last patient completes Core phase

Table 12: Analysis sets by stratum

	Everolimus		Placebo
	LT target of 3-7 ng/mL	HT target of 9-15 ng/mL	
Analysis set	N=117	N=130	N=119
Randomization stratum	n (%)	n (%)	n (%)
Full Analysis Set	**117 (100.0)**	**130 (100.0)**	**119 (100.0)**
Age <6 years	34 (29.1)	36 (27.7)	34 (28.6)
Age 6 to <12 years	36 (30.8)	40 (30.8)	37 (31.1)
Age 12 to <18 years	26 (22.2)	31 (23.8)	26 (21.8)
Age ≥ 18 years	21 (17.9)	23 (17.7)	22 (18.5)
Safety Set	**117 (100.0)**	**130 (100.0)**	**119 (100.0)**
Age <6 years	34 (29.1)	36 (27.7)	34 (28.6)
Age 6 to <12 years	36 (30.8)	40 (30.8)	37 (31.1)
Age 12 to <18 years	26 (22.2)	31 (23.8)	26 (21.8)
Age ≥ 18 years	21 (17.9)	23 (17.7)	22 (18.5)
Per-protocol Set	**110 (94.0)**	**118 (90.8)**	**111 (93.3)**
Age <6 years	31 (26.5)	33 (25.4)	33 (27.7)
Age 6 to <12 years	34 (29.1)	36 (27.7)	35 (29.4)
Age 12 to <18 years	24 (20.5)	30 (23.1)	23 (19.3)
Age ≥ 18 years	21 (17.9)	19 (14.6)	20 (16.8)
Long-term Evaluation Efficacy Set	**117 (100.0)**	**130 (100.0)**	**114 (100.0)**
Age <6 years	34 (29.1)	36 (27.7)	32 (28.1)
Age 6 to <12 years	36 (30.8)	40 (30.8)	37 (32.5)
Age 12 to <18 years	26 (22.2)	31 (23.8)	24 (21.1)
Age ≥ 18 years	21 (17.9)	23 (17.7)	21 (18.4)
Long-term Evaluation Safety Set	**117 (100.0)**	**130 (100.0)**	**110 (96.5)**
Age <6 years	34 (29.1)	36 (27.7)	32 (28.1)
Age 6 to <12 years	36 (30.8)	40 (30.8)	36 (31.6)
Age 12 to <18 years	26 (22.2)	31 (23.8)	23 (20.2)
Age ≥ 18 years	21 (17.9)	23 (17.7)	19 (16.7)

Full Analysis Set includes all randomized patients **Safety Set** includes all patients who received at least one dose of study drug and had at least one valid post-Baseline safety evaluation **Per-protocol Set** includes all Full Analysis Set patients who were compliant with requirements of the protocol, who were evaluable for efficacy and has completed a minimum exposure requirement **Long-term Evaluation Efficacy Set** includes all patients who received at least one dose of everolimus and had at least one valid post-**Baseline efficacy evaluation Long-term Evaluation Safety Set** includes all patients who received at least one dose of everolimus and had at least one valid post-Baseline safety evaluation Source: Tables 11-1 & 2

7.1.12. Major protocol violations/deviations

Table 13: Protocol deviations; Full Analysis Set

	Everolimus				Placebo		All patients	
	LT target of 3-7 ng/mL		HT target of 9-15 ng/mL					
	N=117		N=130		N=119		N=366	
Protocol deviation	n (%)		n (%)		n (%)		n (%)	
Any major protocol deviation (excluded from Per-protocol Set)	**6**	**(5.1)**	**12**	**(9.2)**	**7**	**(5.9)**	**25**	**(6.8)**
Change in dose or in number of concomitant AEDs during Core phase or interruption >7 days	2	(1.7)	5	(3.8)	2	(1.7)	9	(2.5)
Did not receive 1-3 AEDs at same dose from 4 weeks prior to Screening visit to Baseline visit	1	(0.9)	3	(2.3)	2	(1.7)	6	(1.6)
Received topical mTOR inhibitor within 4 weeks of study entry	2	(1.7)	1	(0.8)	1	(0.8)	4	(1.1)
<16 quantifiable TSC seizures reported during Baseline phase	1	(0.9)	2	(1.5)	1	(0.8)	4	(1.1)
Continuous seizure-free interval of ≥ 21 days during Baseline phase	2	(1.7)	1	(0.8)	0		3	(0.8)
Seizure diary less than 50% complete	0		1	(0.8)	2	(1.7)	3	(0.8)
Baseline seizure diary less than 8 weeks in duration	0		1	(0.8)	0		1	(0.3)

AEDs = antiepileptic drugs; mTOR = mammalian target of rapamycin
A patient may have multiple protocol deviations

Source: Table 14.1-1.2 Table 10-2

7.1.13. Baseline data

Table 14: Demographic characteristics at Baseline; Full Analysis Set

	Everolimus		Placebo
	LT target of 3-7 ng/mL	HT target of 9-15 ng/mL	
Demographic variable	N=117	N=130	N=119
Age (years)			
Mean (standard deviation)	12.57 (10.087)	12.85 (10.010)	12.39 (9.430)
Median	9.72	10.08	10.34
Min, Max	2.2, 56.3	2.3, 50.5	2.2, 52.0
Age category (years) – n (%)			
<6 [a]	33 (28.2)	37 (28.5)	34 (28.6)
6 to <12	37 (31.6)	39 (30.0)	37 (31.1)
12 to <18	26 (22.2)	31 (23.8)	25 (21.0)
18 to <65	21 (17.9)	23 (17.7)	23 (19.3)
Gender – n (%)			
Male	64 (54.7)	65 (50.0)	61 (51.3)
Female	53 (45.3)	65 (50.0)	58 (48.7)
Weight (kg)			
Mean (standard deviation)	38.69 (22.802)	40.75 (27.267)	40.50 (24.923)
Median	31.20	30.70	33.00
Min, Max	12.0, 126.2	12.2, 147.9	12.5, 104.0
Body surface area (m^2)			
Mean (standard deviation)	1.18 (0.437)	1.20 (0.501)	1.20 (0.476)
Median	1.09	1.09	1.10
Min, Max	0.5, 2.4	0.5, 2.6	0.5, 2.2
Body mass index (kg/m^2)			
Mean (standard deviation)	19.29 (5.283)	19.56 (6.233)	19.78 (5.484)
Median	17.50	17.30	18.00
Min, Max	13.0, 44.1	10.8, 48.9	10.7, 36.4

[a] Eligible patients were aged ≥ 2 years, except in Europe where the minimum age was 1 year

Table 15: Tuberous Sclerosis Complex diagnosis; Full Analysis Set

	Everolimus		Placebo
	LT target of 3-7 ng/mL	HT target of 9-15 ng/mL	
	N=117	N=130	N=119
	n (%)	n (%)	n (%)
TSC diagnosis per modified Gomez criteria [a]			
≥ 2 major features	117 (100.0)	130 (100.0)	119 (100.0)
1 major feature and ≥ 2 minor features	0	0	0
Major features			
Cortical tuber	103 (88.0)	117 (90.0)	115 (96.6)
Hypomelanotic macules (≥ 3)	97 (82.9)	105 (80.8)	104 (87.4)
Subependymal nodule	87 (74.4)	109 (83.8)	106 (89.1)
Facial angiofibromas or forehead plaque	79 (67.5)	93 (71.5)	78 (65.5)
Renal angiomyolipoma	49 (41.9)	56 (43.1)	47 (39.5)
Cardiac rhabdomyoma, single or multiple	42 (35.9)	56 (43.1)	52 (43.7)
Shagreen patch (connective tissue nevus)	34 (29.1)	50 (38.5)	44 (37.0)
Multiple retinal nodular hamartomas	20 (17.1)	23 (17.7)	30 (25.2)
Subependymal giant cell astrocytoma	20 (17.1)	23 (17.7)	20 (16.8)
Nontraumatic ungual or periungual fibroma	15 (12.8)	26 (20.0)	16 (13.4)
Lymphangioleiomyomatosis	1 (0.9)	2 (1.5)	3 (2.5)
Minor features			
Multiple renal cysts	26 (22.2)	24 (18.5)	25 (21.0)
Cerebral white matter radial migration lines	26 (22.2)	20 (15.4)	21 (17.6)
'Confetti' skin lesions	11 (9.4)	13 (10.0)	12 (10.1)
Multiple, randomly distributed pits in dental enamel	5 (4.3)	15 (11.5)	12 (10.1)
Gingival fibromas	5 (4.3)	9 (6.9)	6 (5.0)
Nonrenal harmatoma	1 (0.9)	7 (5.4)	2 (1.7)
Retinal achromic patch	2 (1.7)	4 (3.1)	1 (0.8)
Bone cysts	1 (0.9)	3 (2.3)	1 (0.8)
Hamartomatous rectal polyps	0	2 (1.5)	0

[a] The co-occurrence of 'cortical tuber' and 'cerebral white matter radial migration lines' is considered as one major feature. In patients with the 2 major features of 'lymphangioleiomyomatosis' and 'renal angiomyolipoma', a further feature must be identified to assign TSC diagnosis. TSC = tuberous sclerosis complex Source: Table 14.1-3.3 Table 11-4

Table 16: Epilepsy background and seizure history; Full Analysis Set

	Everolimus		Placebo
	LT target of 3-7 ng/mL	HT target of 9-15 ng/mL	
Demographic variable	**N=117**	**N=130**	**N=119**
Time from initial diagnosis of TSC seizures until randomization (years)			
n	117	129	119
Mean (SD)	10.6 (9.51)	11.5 (9.65)	11.2 (8.89)
Median	7.4	8.7	9.0
Min, Max	0.3, 51.4	0.7, 50.5	1.2, 50.7
Time category (years)			
<2	6 (5.1)	6 (4.6)	5 (4.2)
2 to <4	21 (17.9)	22 (16.9)	18 (15.1)
4 to <6	16 (13.7)	18 (13.8)	18 (15.1)
≥ 6	74 (63.2)	83 (63.8)	78 (65.5)
Missing	0	1 (0.8)	0
Seizure history			
Complex partial seizure [a]	96 (82.1)	112 (86.2)	93 (78.2)
Predominantly stare and facial automatisms (atypical absence-like)	49 (41.9)	57 (43.8)	42 (35.3)
Predominantly stare (typical absence-like)	31 (26.5)	31 (23.8)	22 (18.5)
Not otherwise specified	51 (43.6)	62 (47.7)	59 (49.6)
Secondarily generalized seizure [b]	84 (71.8)	90 (69.2)	75 (63.0)
Tonic-clonic	56 (47.9)	57 (43.8)	54 (45.4)
Tonic	43 (36.8)	45 (34.6)	32 (26.9)
Myoclonic	12 (10.3)	11 (8.5)	18 (15.1)
Atonic	12 (10.3)	12 (9.2)	15 (12.6)
Clonic	8 (6.8)	7 (5.4)	7 (5.9)
Not otherwise specified	7 (6.0)	4 (3.1)	3 (2.5)
Simple partial seizure	44 (37.6)	54 (41.5)	51 (42.9)
Status epilepticus	11 (9.4)	26 (20.0)	19 (16.0)
Within 52 weeks of screening	0	1 (0.8)	0
Generalized onset seizure [c]	14 (12.0)	14 (10.8)	15 (12.6)
Tonic	7 (6.0)	7 (5.4)	6 (5.0)
Tonic-clonic	5 (4.3)	6 (4.6)	3 (2.5)
Atonic	3 (2.6)	4 (3.1)	5 (4.2)
Myoclonic	2 (1.7)	5 (3.8)	5 (4.2)
Absence	2 (1.7)	4 (3.1)	2 (1.7)
Not otherwise specified	1 (0.9)	0	2 (1.7)
Other [d]	30 (25.6)	37 (28.5)	35 (29.4)

[a] Modified to include what would be described as absence seizures of generalized onset in patients without TSC
[b] Modified to include what would be described as generalized onset in patients without TSC
[c] EEG confirmation of generalized onset
[d] Unclassifiable or infantile spasms or epileptic spasms

Source: Table 14.1-3.2 Table 11-5

Table 17: Prior antiepileptic therapy before the Baseline phase; Full Analysis Set

	Everolimus		Placebo
	LT target of 3-7 ng/mL	HT target of 9-15 ng/mL	
	N=117	N=130	N=119
Prior antiepileptic therapy	n (%)	n (%)	n (%)
Prior epilepsy surgery	**22 (18.8)**	**28 (21.5)**	**17 (14.3)**
Prior vagal nerve stimulation	**16 (13.7)**	**14 (10.8)**	**14 (11.8)**
Prior ketogenic diet treatment	**7 (6.0)**	**18 (13.8)**	**14 (11.8)**
Number of AEDs failed prior to study start [a]			
<2	0	0	0
2	4 (3.4)	8 (6.2)	5 (4.2)
3	15 (12.8)	9 (6.9)	13 (10.9)
4	22 (18.8)	27 (20.8)	16 (13.4)
5	22 (18.8)	25 (19.2)	22 (18.5)
6	10 (8.5)	17 (13.1)	10 (8.4)
>6	44 (37.6)	44 (33.8)	53 (44.5)

[a] Prior to study start = before the Screening visit AEDs = antiepileptic drugs Source: Table 14.1-3.6c Table 11-7

Table 18: Antiepileptic therapy during the Baseline phase; Full Analysis Set

	Everolimus		Placebo
	LT target of 3-7 ng/mL	HT target of 9-15 ng/mL	
	N=117	N=130	N=119
Antiepileptic therapy	n (%)	n (%)	n (%)
Vagal nerve stimulation	**13 (11.1)**	**11 (8.5)**	**10 (8.4)**
Ketogenic diet treatment	**1 (0.9)**	**2 (1.5)**	**4 (3.4)**
Any background AEDs	**117 (100.0)**	**130 (100.0)**	**119 (100.0)**
Number of AEDs in the regimen			
1	7 (6.0)	18 (13.8)	15 (12.6)
2	55 (47.0)	55 (42.3)	41 (34.5)
3	55 (47.0)	56 (43.1)	62 (52.1)
>3	0	1 (0.8)	1 (0.8)
Start date ≥ 4 weeks prior to Screening	**116 (99.1)**	**128 (98.5)**	**118 (99.2)**
Longest interruption in any AED			
1-3 days	0	0	0
4-7 days	0	0	0
>7 days	0	0	0
Change in dose in any AED or new AED started			
No	116 (99.1)	124 (95.4)	118 (99.2)
Yes	1 (0.9)	6 (4.6)	1 (0.8)
Compliant patient during Baseline phase [a]	**115 (98.3)**	**122 (93.8)**	**116 (97.5)**

[a] Compliant patient = taking the same AED regimen of 1 to 3 AEDs from at least 4 weeks prior to Screening until the Baseline visit, without any AED dose change or new AED started, and without interruption of any AED of more than 7 days during the 8-week Baseline phase Source: Table 14.1-3.7 Table 11-8

7.1.14. Results for the primary efficacy outcome (EMA)

Comment: Given that the TGA has adopted EMA guidelines this evaluator proposes to use the response rate as the primary variable. The protocol indicates that the statistical analysis was not to be set up for co-primary endpoints.[9]

7.1.14.1. Seizure Frequency Response Rate

Response rates were 28.2% (95% CI: 20.3, 37.3) and 40.0% (95% CI: 31.5, 49.0) for the everolimus low trough range and high trough range arms compared with 15.1% (95% CI: 9.2, 22.8) for the placebo arm, thus although the high trough range results are clearly superior to those of placebo, the 95% CIs for the low trough range and placebo overlap. However the Odds Ratios 95% CIs for both active arms compared to placebo are both above 1.0.

The sensitivity analyses support these observations.

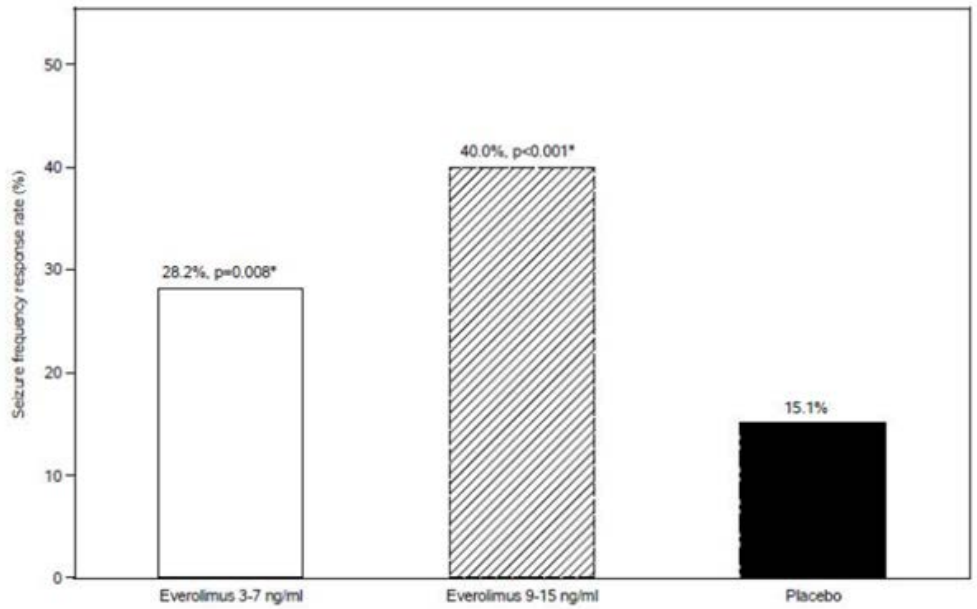
Table 19: Seizure frequency response rate; Full Analysis Set

	Everolimus		Placebo
	LT target of 3-7 ng/mL	HT target of 9-15 ng/mL	
Statistic	**N=117**	**N=130**	**N=119**
Responders – n (%)	**33 (28.2)**	**52 (40.0)**	**18 (15.1)**
Response rate 95% CI [a]	20.3, 37.3	31.5, 49.0	9.2, 22.8
Odds ratio (versus placebo) [b]	**2.21**	**3.93**	
95% CI	1.16, 4.20	2.10, 7.32	
p-value (versus placebo) [c]	0.008	<0.001	
Statistically significant per Bonferroni-Holm procedure [d]	Yes	Yes	
Non-responders – n (%)	84 (71.8)	78 (60.0)	101 (84.9)

[a] Exact 95% CI obtained using Clopper-Pearson method
[b] Odds ratio and its 95% CI obtained using logistic regression stratified by age subgroup. Odds ratio >1 favours everolimus arm.
[c] p-values computed from the Cochran-Mantel-Haenszel test stratified by age subgroup
[d] Family-wise error rate of 2.5% one-sided Source: Table 11-9

[9] Protocol; each Agency will use their preferred variable as the primary variable, with the other (non-primary) variable being used in a supportive analysis. As each Agency will only use their preferred primary variable to make a decision on the primary objective, the full alpha level can be used for each Agency's primary variable, without correction for multiplicity. Similar statement in SAP (Interim CSR)

Figure 5: Seizure frequency response rate; Full Analysis Set



* Statistically significant difference vs. placebo, based on Cochran-Mantel-Haenszel tests stratified by age subgroup and a Bonferroni-Holm procedure to ensure a family-wise Type I error rate of 2.5% one-sided Source: Figure 14.2-1.1 Figure 11-1

7.1.15. Results for other efficacy outcomes

7.1.15.1. Percentage Reduction from Baseline in Seizure Frequency

The median percent reduction in weekly seizure frequency was 29.3% (95% CI: 18.8, 41.9) and 39.6% (95% CI: 35.0, 48.7) for the everolimus low trough range and high trough range arms, respectively, compared with 14.9% (95% CI: 0.1, 21.7) for the placebo arm, thus although the high trough range results are clearly superior to those of placebo, the 95% CIs for the low trough range and placebo overlap. However the 95% CIs for the difference from placebo are all above 0.

Table 20: Percentage reduction from Baseline in weekly seizure frequency; Full Analysis Set

	Everolimus		Placebo
Seizure frequency (seizures per week)	LT target of 3-7 ng/mL N=117	HT target of 9-15 ng/mL N=130	N=119
Baseline			
n	117	130	119
Mean (standard deviation)	16.35 (23.945)	17.37 (26.058)	17.47 (25.861)
Median	8.63	9.45	10.50
Min, Max	1.4, 192.9	0.3, 218.4	1.3, 231.7
Core phase (Maintenance [a])			
n	117	130	118
Mean (standard deviation)	12.93 (23.703)	11.30 (19.984)	16.37 (25.323)
Median	6.83	4.91	8.53
Min, Max	0.0, 193.5	0.0, 133.7	0.0, 217.7
Change from Baseline to Core phase (Maintenance [a])			
n	117	130	118
Mean (standard deviation)	-3.42 (12.843)	-6.07 (12.422)	-1.18 (7.258)
Median	-2.13	-3.32	-1.00
Min, Max	-64.0, 84.1	-84.7, 36.5	-33.5, 21.7
Percentage reduction from Baseline to Core phase (Maintenance [a])			
n	117	130	119 [f]
Mean (standard deviation)	18.00 (62.853)	34.22 (51.857)	4.71 (54.115)
Median	29.29	39.55	14.86
Min, Max	-289.0, 100.0	-233.3, 100.0	-257.6, 100.0
95% CI of median [b]	18.82, 41.88	35.03, 48.74	0.11, 21.71
p-value for superiority versus placebo [c]	0.003	<0.001	
Statistically significant per Bonferroni-Holm procedure [d]	Yes	Yes	
Difference in median percentage reduction from Baseline between everolimus arms and placebo			
Median [e]	15.96	27.46	
95% CI of median [e]	1.98, 31.68	16.36, 43.36	

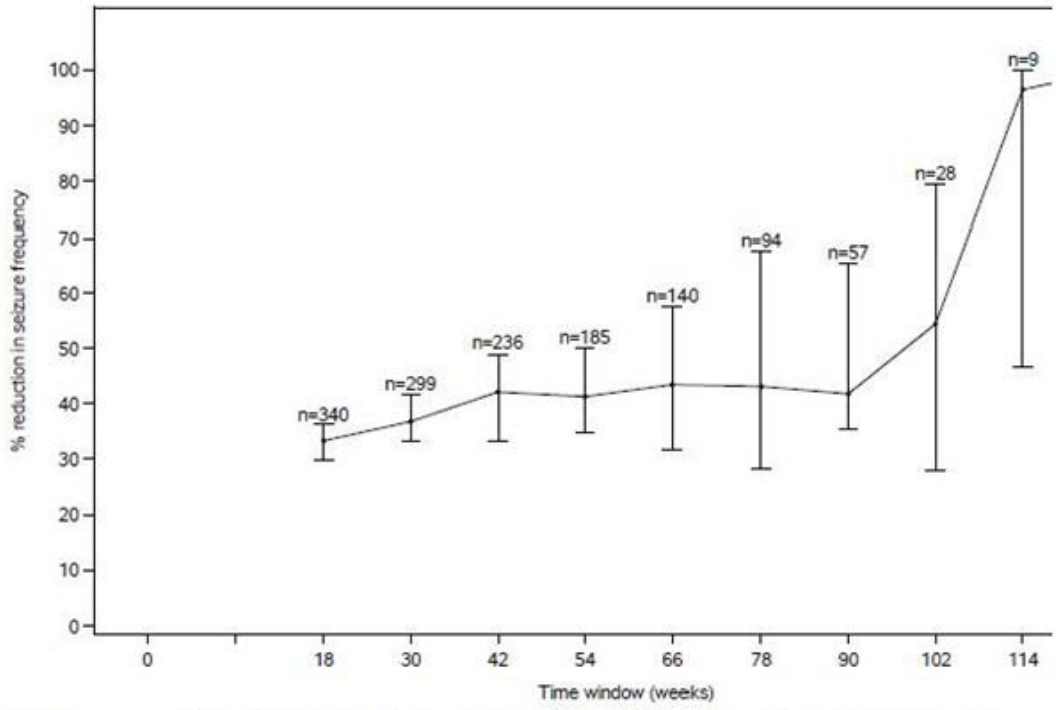
[a] If a patient discontinued before starting the Maintenance period, then the Titration period is used Source: Table 11-10
[b] 95% CI of the median based on bootstrap percentiles
[c] p-values obtained from rank ANCOVA with Baseline seizure frequency as covariate, stratified by age subgroup
[d] Family-wise error rate of 2.5% one-sided
[e] Results are based on stratified bootstrap methodology, stratified by age subgroup weighting by inverse variance. 95% CI of the median based on bootstrap percentiles.
[f] Note that one patient discontinued the Core phase without completing the patient seizure diary: the percentage reduction from baseline in seizure frequency was assigned as 0 (no change, as planned in the Statistical Analysis Plan)

Table 21: Secondary Endpoints

Endpoint		LT target of 3-7 ng/mL	HT target of 9-15 ng/mL	Placebo
		N = 117	N = 130	N = 118[b]
Seizure Free Rate		6/117 (5.1%)[a]	5/130 (3.8%)[a]	1/118 (0.8%)
≥ 25% reduction in seizure frequency		61/117 (52.1%)	91/130 (70.0%)	45/119 (37.8%)
Distribution of reduction from Baseline in seizure frequency	Category			
	100 Seizure-free	6 (5.1)	5 (3.8)	1 (0.8)
	≥ 75 to <100 75% responder	7 (6.0)	20 (15.4)	6 (5.0)
	≥ 50 to <75 50% responder	20 (17.1)	27 (20.8)	11 (9.2)
	≥ 25 to <50 25% responder	8 (23.9)	39 (30.0)	27 (22.7)
	>-25 to < 25 No change	41 (35.0)	24 (18.5)	49 (41.2)
	≤ -25 Exacerbation	15 (12.8)	15 (11.5)	24 (20.2)
Seizure Free Days Mean difference from baseline (SD)		2.95 (7.656)	5.76 (7.441)	1.58 (5.660)
Overall QoL score Mean difference from baseline (SD)		1.2 (10.52)	1.2 (7.91)	1.3 (8.91)

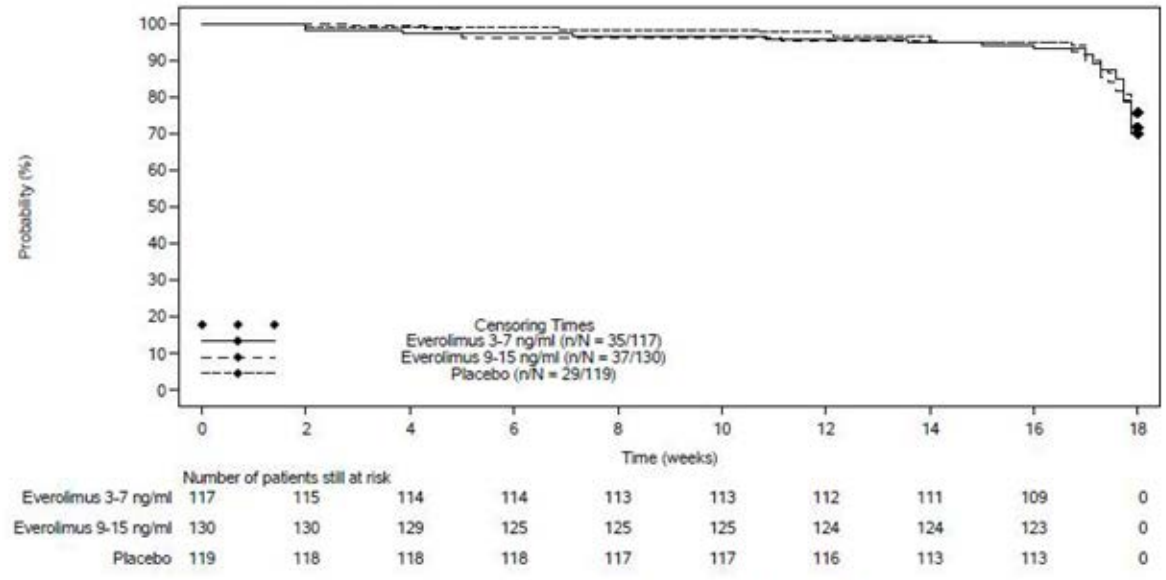
[a] vs. placebo Odds Ratio 95%CI lower bound < 1 [b] data on 1 patient missing

Figure 6: Percentage reduction in seizure frequency over time across all everolimus patients; Long-term Evaluation Efficacy Set



Vertical lines correspond to the 95% CI of the median based on bootstrap percentiles Source: Figure 14.2-1.5l Figure 11-7

Figure 7: Kaplan-Meier curves of time to treatment discontinuation; Full Analysis Set



For the purpose of this analysis, an event was defined as all patients who discontinued during the Core phase, plus patients whose last day of study treatment in the Core phase was before Study Day 126, where Study Day 1 was the date of randomization
Source: Figure 14.2-1.4 Figure 11-6

7.2. Evaluator's conclusions on clinical efficacy

The response rate in the Primary endpoint was 15.1% (95% CI: 9.2, 22.8) for the placebo arm, 28.2% (95% CI: 20.3, 37.3) for the C_{min} 3 to 7 ng/mL arm and 40.0% (95% CI: 31.5, 49.0) for the C_{min} 9 to 15 ng/mL arm. The 95%CIs for placebo and the 3 to 7 ng/mL arm overlap. However the Odds ratio 95%CIs do not include 1.0.

A similar result was seen for the supporting endpoint:

The median percent reduction in weekly seizure frequency was 29.3% (95% CI: 18.8, 41.9) and 39.6% (95% CI: 35.0, 48.7) for the everolimus low trough range and high trough range arms, respectively, compared with 14.9% (95% CI: 0.1, 21.7) for the placebo arm, thus although the high trough range results are clearly superior to those of placebo, the 95% CIs for the low trough range and placebo overlap. However the 95% CIs for the difference from placebo are all above 0.

The CPMP/EWP/2330/99 Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study has:

> Prerequisites for one pivotal study applications
>
> The degree of statistical significance. Statistical evidence considerably stronger than $p < 0.05$ is usually required, accompanied by precise estimates of treatment effects that is narrow confidence intervals. Tile required degree of significance will depend on factors such as the therapeutic indication, the primary endpoint, the amount of supportive data and whether the alternative analyses demonstrating consistency are pre-specified.

The proposed dosage is to maintain C_{min} at 5 to 15 ng/mL.

Then lower end of the range for C_{min} of the clearly significant result was 9ng/mL.

The recommended target C_{min} range is 5 to 15 ng/mL based on the following considerations:

> The time normalised C_{min} of 5.3ng/mL is the threshold concentration above which the 95% confidence interval of predicted change from baseline seizure frequency is not

overlapping with the 95% confidence interval of predicted change from baseline SF of placebo patients. This indicates a lower bound of the therapeutic range.

The modelling of efficacy to C_{min} (see Section 5 above) shows a relationship between C_{min} time normalised and a response.

For those subjects who would currently be eligible for everolimus treatment due to concurrent TSC-related conditions that is SEGA and renal angiomyolipoma, the 95% CIs for all 3 treatment groups overlapped, the numbers were small.

8. Clinical safety

The sponsor graded AEs severity in accordance with the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events.[10]

- Grade 1 Mild AE
- Grade 2 Moderate AE
- Grade 3 Severe AE
- Grade 4 Life-threatening or disabling AE
- Grade 5 Death related to AE

8.1. Patient exposure

8.1.1. Demographics

Whereas in Study M2304 the median age of patients was 10.1 years (min-max: 2.2 to 56.3 years) the previously existing study safety pool was 19.0 years (min-max: 1 to 61), reflecting a difference in Inclusion criteria in some of the previous studies. As a result there were a higher proportion of patients previously who were aged ≥ 18 years (54.2% versus 18.3% in Study M2304).

8.1.2. Exposure

The Summary of Clinical Safety is based on safety data from Study M2304 and three other studies that evaluated multi-year everolimus exposure in patients with TSC - completed Studies C2485, M2301, and M2302 (N=251).[11]

[10] https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf

[11] The sponsor defined them as:

- Old TSC Safety Pool including currently completed TSC Studies C2485, M2301, and M2302 (N=251), i.e. long-term exposure excluding Study M2304.
- New TSC Safety Pool including all available safety data from the Core and Extension phases of Study M2304 added to the 'Old TSC Safety Pool' (N=608), i.e. long-term exposure including Study M2304.

Table 22: Study sizes safety database

Studies	No. of patients who received everolimus
Study M2301-final analysis	111
Study M2302-final CSR	112
Study C2485-final analysis	28
Study M2304	357
Total	608

Table 23: Duration of exposure to everolimus; TSC pooled studies including M2304 (Long-term Evaluation Safety Set)

	All everolimus patients
Duration of exposure (months)	**N=608**
Exposure categories - n (%)	
<1	12 (2.0)
1 to <3	21 (3.5)
3 to <6	70 (11.5)
6 to <9	53 (8.7)
9 to <12	51 (8.4)
12 to <18	92 (15.1)
18 to <24	72 (11.8)
24 to <36	38 (6.3)
36 to <48	83 (13.7)
48 to <60	85 (14.0)
≥ 60	31 (5.1)
Duration of exposure	
n	608
Mean (standard deviation)	25.27 (19.8)
Median	18.25
Min-Max	0.1-83.2
Total patient-year exposure	**1280.60**

Data from Studies C2485, M2301, M2302, and M2304 are included in analysis
Source: Table 1-8

Table 24: Cumulative dose and dose intensity of study drug; Study M2304 Core phase (Safety Set)

	Everolimus		Placebo
	LT target of 3-7 ng/mL	HT target of 9-15 ng/mL	
	N=117	N=130	N=119
Cumulative dose (mg/m²)			
Mean (standard deviation)	714.81 (333.99)	1021.20 (534.75)	866.01 (402.21
Median	648.80	927.02	771.52
Min-Max	38.5 – 1810.4	58.7 – 2829.8	113.9 – 2124.5
Dose intensity (mg/m²/day)[a]			
Mean (standard deviation)	5.76 (2.49)	8.22 (4.13)	7.00 (3.15)
Median	5.18	7.49	6.12
Min-Max	1.3 – 14.5	1.4 – 24.4	2.4 – 17.7

[a] Dose intensity = cumulative dose (mg/m²)/duration of exposure (days) Source: [Study M2304-Table 14.3-1.2] Table 1-9

Table 25: Cumulative dose and dose intensity of study drug; Study M2304 Core and Extension phases (Long-term Evaluation Safety Set)

	Everolimus			
	LT target of 3-7 ng/mL	HT target of 9-15 ng/mL	Start Ext	All patients
	N=117	N=130	N=110	N=357
Cumulative dose (mg/m²)				
Mean (SD)	2383.60 (1656.79)	3394.91 (2317.51)	1980.03 (1680.09)	2627.51 (2017.18)
Median (range)	2028.63	2738.15	1590.72	2076.48
Min-Max	38.5 – 7866.3	58.7 – 10263.3	20.0 – 8260.4	20.0 – 10263.3
Dose intensity (mg/m²/day)[a]				
Mean (SD)	6.13 (2.98)	8.98 (4.44)	6.38 (2.54)	7.25 (3.71)
Median (range)	5.38	8.36	5.87	6.38
Min-Max	1.1 – 17.3	1.4 – 26.1	2.4 – 16.2	1.1 – 26.1

[a] Dose intensity = cumulative dose (mg/m²)/duration of exposure (days) Source: [Study M2304-Table 14.3-1.2l] Table 1-10
All patients received treatment with everolimus in the Extension phase; the 'Start ext' column refers to patients originally randomized to placebo and who subsequently crossed over to everolimus in the Extension phase

Table 26: Everolimus concentration at trough (C_{min}) by time window; Study M2304 Core phase (Safety Set; Confirmed PK Sample Set)

Cmin (ng/mL)	Week 1	Week 3	Week 5	Week 10	Week 14	Week 18
Everolimus LT target of 3-7 ng/mL						
n	92	94	103	101	100	95
Mean	6.83	5.94	5.42	5.34	5.96	5.67
SD	4.89	3.62	3.54	3.58	4.82	3.32
CV% mean	71.7	60.8	65.4	66.9	81.0	58.6
Geo-mean	5.68	5.09	4.68	4.51	5.00	5.01
CV% geo-mean	65.6	59.7	55.5	65.1	60.2	51.1
Median	5.58	5.13	4.40	4.39	4.75	5.05
Min, Max	1.35, 35.60	1.59, 19.20	1.31, 21.40	0.37, 25.80	1.07, 40.60	1.36, 25.30
Everolimus HT target of 9-15 ng/mL						
n	109	108	107	111	110	102
Mean	5.68	6.07	7.52	7.45	9.06	8.81
SD	2.45	3.19	6.51	3.75	12.65	4.55
CV% mean	43.1	52.6	86.6	50.3	139.7	51.7
Geo-mean	5.18	5.35	6.22	6.60	6.91	7.59
CV% geo-mean	45.5	54.8	63.8	53.8	71.3	65.2
Median	5.30	5.43	6.31	6.76	6.81	8.32
Min, Max	1.92, 15.20	0.99, 22.60	1.20, 55.80	1.34, 22.60	0.78, 125.0	0.77, 22.00

CV% = coefficient of variation (%) = SD/mean*100 Source: [Study M2304-Table 14.2-6.1] Table 1-13
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100

Table 27: Number of patients requiring study drug dose interruptions and/or reductions; Study M2304 Core and Extension phase (Long-term Evaluation Safety Set)

	Everolimus			
	LT target of 3-7 ng/mL	HT target of 9-15 ng/mL	Start Ext	All patients
	N=117	N=130	N=110	N=357
	n (%)	n (%)	n (%)	n (%)
Reductions/Interruptions				
Number of patients				
Without dose reduction/interruption	25 (21.4)	35 (26.9)	59 (53.6)	119 (33.3)
With at least one dose reduction/interruption	92 (78.6)	95 (73.1)	51 (46.4)	238 (66.7)
With only one dose reduction/interruption	35 (29.9)	27 (20.8)	28 (25.5)	90 (25.2)
With more than one dose reduction/ interruption	57 (48.7)	68 (52.3)	23 (20.9)	148 (41.5)
Number of patients with at least one dose reduction/interruption by reason				
As per protocol*	75 (64.1)	71 (54.6)	25 (22.7)	171 (47.9)
Adverse event	43 (36.8)	63 (48.5)	34 (30.9)	140 (39.2)
Dosing error	13 (11.1)	11 (8.5)	5 (4.5)	29 (8.1)
Dispensing error	1 (0.9)	2 (1.5)	0	3 (0.8)
Concomitant medication affecting drug exposure	1 (0.9)	0	1 (0.9)	2 (0.6)
Only Placebo tablets taken	0	1 (0.8)	0	1 (0.3)
Interruptions				
Number of patients				
Without dose interruption	81 (69.2)	69 (53.1)	79 (71.8)	229 (64.1)
With at least one dose interruption	36 (30.8)	61 (46.9)	31 (28.2)	128 (35.9)
With only one dose interruption	20 (17.1)	31 (23.8)	17 (15.5)	68 (19.0)
With more than one dose interruptions	16 (13.7)	30 (23.1)	14 (12.7)	60 (16.8)
Number of patients with at least one dose interruption by reason				
Adverse event	32 (27.4)	55 (42.3)	28 (25.5)	115 (32.2)
Dosing error	10 (8.5)	10 (7.7)	4 (3.6)	24 (6.7)
As per protocol	1 (0.9)	1 (0.8)	1 (0.9)	3 (0.8)
Dispensing error	1 (0.9)	2 (1.5)	0	3 (0.8)
Concomitant medication affecting drug exposure	1 (0.9)	0	1 (0.9)	2 (0.6)
Only Placebo tablets taken	0	1 (0.8)	0	1 (0.3)
Reductions				
Number of patients				
Without dose reduction	30 (25.6)	46 (35.4)	75 (68.2)	151 (42.3)
With at least one dose reduction	87 (74.4)	84 (64.6)	35 (31.8)	206 (57.7)
With only one dose reduction	45 (38.5)	45 (34.6)	28 (25.5)	118 (33.1)
With more than one dose reduction	42 (35.9)	39 (30.0)	7 (6.4)	88 (24.6)
Number of patients with at least one dose reduction by reason				
As per protocol	74 (63.2)	71 (54.6)	25 (22.7)	170 (47.6)
Adverse event	20 (17.1)	22 (16.9)	10 (9.1)	52 (14.6)
Dosing error	3 (2.6)	3 (2.3)	1 (0.9)	7 (2.0)

* As per protocol refers to the dose changes requested by the interactive response technology system in order to attain the target trough range. Source: Table 1-12

A patient with multiple occurrences of a reason for dose reduction or interruption is only counted once in that category

A patient with multiple reasons for dose reduction or interruption is only counted once in the total row

All patients received treatment with everolimus in the Extension phase; the 'Start ext' column refers to patients originally randomized to placebo and who subsequently crossed over to everolimus in the Extension phase

8.1.3. All adverse events (irrespective of relationship to study treatment)

Table 28: Summary of deaths and adverse events; TSC pooled studies excluding Study M2304 (Long-term Evaluation Safety Set)

Category	Everolimus N=251 n (%)
All deaths	**3 (1.2)**
On-treatment deaths[1]	3 (1.2)
Adverse events (AEs) [1]	**250 (99.6)**
AEs suspected to be drug-related	238 (94.8)
Grade 3/4 AEs	**138 (55.0)**
Suspected to be drug-related	86 (34.3)
Serious adverse events (SAEs)	**100 (39.8)**
Suspected to be drug-related	43 (17.1)
AEs leading to discontinuation	**21 (8.4)**
Suspected to be drug-related	16 (6.4)
Other significant AEs	**250 (99.6)**
AEs requiring dose interruption or reduction	192 (76.5)
AEs requiring additional therapy[3]	250 (99.6)

[1] Includes deaths up to 28 days after the last dose of study treatment in long-term evaluation phase
[2] Includes AEs occurring on or after the start of study treatment and no more than 28 days after the discontinuation of study treatment in long-term evaluation phase
[3] Additional therapy includes all non-drug therapy and concomitant medications. Source: [Appendix 1-Table 4.2-1l] Table 2-3

Table 29: Summary of adverse events; Study M2304 Core phase (Safety Set)

Category	Everolimus LT target of 3-7 ng/mL N=117	Everolimus HT target of 9-15 ng/mL N=130	Placebo N=119
Adverse events (AEs)[3]	**108 (92.3)**	**123 (94.6)**	**92 (77.3)**
AEs suspected to be drug-related	78 (66.7)	102 (78.5)	40 (33.6)
Grade 3-4 AEs	**21 (17.9)**	**31 (23.8)**	**13 (10.9)**
Suspected to be drug-related	16 (13.7)	19 (14.6)	7 (5.9)
Serious adverse events (SAEs)	**16 (13.7)**	**18 (13.8)**	**3 (2.5)**
Suspected to be drug-related	10 (8.5)	11 (8.5)	1 (0.8)
AEs leading to discontinuation	**6 (5.1)**	**4 (3.1)**	**2 (1.7)**
Suspected to be drug-related	6 (5.1)	3 (2.3)	2 (1.7)
Other significant AEs			
AEs requiring dose interruption or reduction	28 (23.9)	46 (35.4)	9 (7.6)
AEs requiring additional therapy[4]	94 (80.3)	112 (86.2)	63 (52.9)

[3] Only AEs occurring on or after the start of study treatment and no more than 30 days after the discontinuation of everolimus and before start of everolimus in the Extension phase are summarized Source: [Study M2304-Table 14.3.1-1.14] Table 2-1
[4] Additional therapy includes all non-drug therapy and concomitant medications.

Table 30: Summary of deaths and adverse events; Study M2304 Core and Extension phase (Long-term Evaluation Safety Set)

	Everolimus			
	LT target of 3-7 ng/mL N=117	HT target of 9-15 ng/mL N=130	Start Ext N=110	All patients N=357
Category	n (%)	n (%)	n (%)	n (%)
All deaths [1]	**0**	**1(0.8)**	**0**	**1(0.3)**
On-treatment deaths [2]	0	1(0.8)	0	1(0.3)
Adverse events (AEs) [3]	**115 (98.3)**	**128 (98.5)**	**101 (91.8)**	**344 (96.4)**
AEs suspected to be drug-related	94 (80.3)	114 (87.7)	74 (67.3)	282 (79.0)
Grade 3/4 AEs	**35 (29.9)**	**51 (39.2)**	**20 (18.2)**	**106 (29.7)**
Suspected to be drug-related	23 (19.7)	30 (23.1)	13 (11.8)	66 (18.5)
Serious adverse events (SAEs)	**30 (25.6)**	**34 (26.2)**	**18 (16.4)**	**82 (23.0)**
Suspected to be drug-related	17 (14.5)	18 (13.8)	8 (7.3)	43 (12.0)
AEs leading to discontinuation	**16 (13.7)**	**11 (8.5)**	**8 (7.3)**	**35 (9.8)**
Suspected to be drug-related	14 (12.0)	7 (5.4)	6 (5.5)	27 (7.6)
Other significant AEs				
AEs requiring dose interruption or reduction	46 (39.3)	65 (50.0)	37 (33.6)	148 (41.5)
AEs requiring additional therapy [4]	109 (93.2)	124 (95.4)	85 (77.3)	318 (89.1)

[1] Includes deaths on or after the start of everolimus Source: [Study M2304-Table 14.3.1-1.14l] Table 2-2
[2] Includes deaths on or after the start of everolimus and up to 30 days after the last dose of everolimus
[3] Only AEs occurring on or after the start of study treatment and no more than 30 days after the discontinuation of everolimus are summarized
[4] Additional therapy includes all non-drug therapy and concomitant medications
All patients received treatment with everolimus in the Extension phase; the 'Start ext' column refers to patients originally randomized to placebo and who subsequently crossed over to everolimus in the Extension phase

8.1.4. Treatment related adverse events (adverse drug reactions)

8.1.4.1. Main/pivotal study

Twenty-one patients from the everolimus treatment groups (10 (8.5%)) from the LT group and 11 (8.5%) from the HT group) experienced SAEs that were suspected by the Investigator to be related to study drug (Study M2304). The most commonly reported treatment-related SAEs were pneumonia (0.9% versus 2.3% versus 0% for the LT, HT, and placebo groups, respectively) and status epilepticus (1.7% versus 0.8% versus 0%).

Adverse events suspected to be related to everolimus were less frequently reported in the everolimus LT compared to the everolimus HT group (66.7% versus 78.5%). The most common AEs suspected to be related to everolimus where a higher proportion of everolimus-treated patients reported events (and where there was a ≥ 10% difference relative to placebo) included:

- Stomatitis (+20.5% and +27.4% for the LT and HT groups, respectively)
- Mouth ulceration (+19.7% and +15.0%)
- Aphthous ulcer (+2.6% and +11.4%)

The AEs suspected to be related to everolimus treatment are consistent with the known safety profile of everolimus.

As for overall AEs, the incidence of most of the emerging AEs suspected by the Investigators to be drug-related was high during the first 6 months of treatment, and consistently decreased thereafter. Reasons might include dropouts from AEs, recoding of events only once as well as increased tolerance.

Table 31: Adverse events with suspected relationship to study drug by preferred term (in at least 1% of patients in any group); Study M2304 Core phase (Safety Set)

	Everolimus		Placebo
	LT target of 3-7 ng/mL	HT target of 9-15 ng/mL	
	N=117	N=130	N=119
Preferred term	n (%)	n (%)	n (%)
Any AE suspected to be drug related	**78 (66.7)**	**102 (78.5)**	**40 (33.6)**
Stomatitis	28 (23.9)	40 (30.8)	4 (3.4)
Mouth ulceration	28 (23.9)	25 (19.2)	5 (4.2)
Aphthous ulcer	5 (4.3)	17 (13.1)	2 (1.7)
Diarrhoea	4 (3.4)	12 (9.2)	0
Rash	3 (2.6)	7 (5.4)	2 (1.7)
Acne	2 (1.7)	7 (5.4)	1 (0.8)
Hypertriglyceridaemia	5 (4.3)	6 (4.6)	0
Decreased appetite	4 (3.4)	6 (4.6)	4 (3.4)
Headache	1 (0.9)	5 (3.8)	1 (0.8)
Hypercholesterolaemia	3 (2.6)	4 (3.1)	0
Nasopharyngitis	3 (2.6)	4 (3.1)	0
Pyrexia	3 (2.6)	4 (3.1)	0
Blood cholesterol increased	2 (1.7)	4 (3.1)	0
Fatigue	2 (1.7)	4 (3.1)	3 (2.5)
Hyperlipidaemia	1 (0.9)	4 (3.1)	1 (0.8)
Pneumonia	1 (0.9)	4 (3.1)	0
Neutropenia	3 (2.6)	3 (2.3)	2 (1.7)
Blood triglycerides increased	2 (1.7)	3 (2.3)	1 (0.8)
Upper respiratory tract infection	2 (1.7)	3 (2.3)	1 (0.8)
Alopecia	1 (0.9)	3 (2.3)	1 (0.8)
Gastroenteritis	1 (0.9)	3 (2.3)	0
Nausea	0	3 (2.3)	4 (3.4)
Blood bicarbonate decreased	0	3 (2.3)	0
Menstruation irregular	2 (1.7)	2 (1.5)	1 (0.8)
Weight decreased	2 (1.7)	2 (1.5)	1 (0.8)
Somnolence	2 (1.7)	2 (1.5)	0
Neutrophil count decreased	1 (0.9)	2 (1.5)	1 (0.8)
Cough	1 (0.9)	2 (1.5)	0
Lip ulceration	1 (0.9)	2 (1.5)	0
Tongue ulceration	1 (0.9)	2 (1.5)	0
Urinary tract infection	1 (0.9)	2 (1.5)	0
Abdominal pain upper	0	2 (1.5)	2 (1.7)
Irritability	0	2 (1.5)	1 (0.8)
Rhinitis	0	2 (1.5)	1 (0.8)
Asthenia	0	2 (1.5)	0
Gingival bleeding	0	2 (1.5)	0
Hypernatraemia	0	2 (1.5)	0
Hypertrichosis	0	2 (1.5)	0
Proteinuria	0	2 (1.5)	0
Skin infection	0	2 (1.5)	0
Vomiting	4 (3.4)	1 (0.8)	4 (3.4)
Amenorrhoea	2 (1.7)	1 (0.8)	2 (1.7)
Oral herpes	2 (1.7)	1 (0.8)	0
Status epilepticus	2 (1.7)	1 (0.8)	0
Pharyngitis	2 (1.7)	0	1 (0.8)
Epistaxis	2 (1.7)	0	0
Hyperaemia	2 (1.7)	0	0
Blood creatinine increased	0	0	2 (1.7)
Constipation	0	0	2 (1.7)

Preferred terms are sorted in descending frequency, as reported in the everolimus 9-15ng/mL column
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment
Only includes AEs occurring on or after the start of study treatment and no more than 30 days after the discontinuation of study treatment and before start of everolimus in the Extension phase Source: [Study M2304-Table 14.3.1-1.2] Table 2-13

Table 32: AEs with suspected relationship to study drug, by preferred term and period of emergence (with a frequency of at least 2% in less than or equal to Month 6); Study M2304 Core and Extension phase (Long-term Evaluation Safety Set)

Preferred term	Months ≤ 6 N=357 n (%)	Months >6 to ≤ 12 N=288 n (%)	Months >12 to ≤ 24 N=180 n (%)	Months >24 to ≤ 36 N=20 n (%)
Any preferred term	**266 (74.5)**	**109 (37.8)**	**61 (33.9)**	**2 (10.0)**
Stomatitis	101 (28.3)	29 (10.1)	15 (8.3)	0
Mouth ulceration	70 (19.6)	21 (7.3)	10 (5.6)	0
Aphthous ulcer	32 (9.0)	7 (2.4)	0	1 (5.0)
Diarrhoea	21 (5.9)	5 (1.7)	3 (1.7)	0
Pyrexia	14 (3.9)	5 (1.7)	9 (5.0)	0
Decreased appetite	14 (3.9)	2 (0.7)	3 (1.7)	0
Blood cholesterol increased	11 (3.1)	2 (0.7)	4 (2.2)	0
Hypertriglyceridaemia	11 (3.1)	2 (0.7)	1 (0.6)	0
Acne	11 (3.1)	1 (0.3)	1 (0.6)	0
Rash	11 (3.1)	1 (0.3)	1 (0.6)	0
Pneumonia	10 (2.8)	5 (1.7)	2 (1.1)	0
Nasopharyngitis	10 (2.8)	3 (1.0)	3 (1.7)	0
Upper respiratory tract infection	9 (2.5)	10 (3.5)	6 (3.3)	0
Fatigue	9 (2.5)	0	0	0
Vomiting	8 (2.2)	3 (1.0)	2 (1.1)	0
Rhinitis	8 (2.2)	2 (0.7)	1 (0.6)	0
Weight decreased	8 (2.2)	1 (0.3)	2 (1.1)	0
Headache	8 (2.2)	1 (0.3)	0	0
Cough	7 (2.0)	4 (1.4)	2 (1.1)	0
Blood triglycerides increased	7 (2.0)	3 (1.0)	5 (2.8)	0
Hypercholesterolaemia	7 (2.0)	2 (0.7)	0	0

Preferred terms are sorted by descending frequency in the first 6-month period, and in case of ties by descending frequency in subsequent periods Source: [Appendix 1-Table 3.2-15l] Table 2-17
A patient with multiple occurrences of an AE is counted only once in the AE category
Only AEs occurring on or after the start of everolimus and no more than 30 days after the discontinuation of everolimus are summarized An AE is only counted in the time period in which it started.

The sponsor highlighted that considering the previous long-term exposure results (that is TSC studies excluding Study M2304), the incidence of most of the emerging AEs suspected by the Investigators to be drug-related was highest during the first 6 months of treatment, and consistently decreased thereafter. The incidence of emerging AEs decreased from 87.6% in the first 6 months to 36.8% for exposure beyond Month 48

Comparing with Study M2304:

- Under 6 Months, the overall incidence of emerging AEs was higher in the previous Pool versus Study M2304 (87.6% versus 74.5%), as were the incidences of stomatitis (+11.9%) and hypercholesterolemia (+9.5%). Other events were reported with a similar frequency between the two datasets.
- Between Months 6 to 12, the overall incidence of emerging AEs was higher in the previous Pool versus Study M2304 (53.1% versus 37.8%). The incidence of specific AEs was in general similar.
- Between Months 12 to 24 the overall incidence of emerging AEs was higher in the previous Pool versus Study M2304 (67.5% versus 33.9%). Stomatitis (7.9%) and mouth ulceration (5.0%) were both reported more frequently in the previous Pool.

8.1.5. Deaths

8.1.5.1. Integrated safety analyses

Three deaths were reported in the previous TSC Pool, none of which was considered to be related to everolimus:

- asphyxia (accidental strangulation)
- epilepsy (in the fifth year of the study)
- seizure disorder (complication of TSC).

8.1.5.2. Pivotal and/or main efficacy studies

One patient, initially randomised to the HT treatment group, died during the Extension phase of the study (9.5 months after start of therapy). Sudden unexpected death in epilepsy (SUDEP) was assessed as the cause of death (Study M2304); this was not suspected by the Investigator to be drug related.

8.1.6. Serious adverse events

Only pneumonia (4.8%) and seizures (3.4%) were reported as SAEs in more than 2% of patients in the long-term Study M2304 evaluation (Core and Extension phase combined).

Table 33: SAEs irrespective of causality by preferred term; Study M2304 Core phase (Safety Set) Everolimus

Preferred term	LT target of 3-7 ng/mL N=117 n (%)	HT target of 9-15 ng/mL N=130 n (%)	N=119 n (%)
Any SAE	**16 (13.7)**	**18 (13.8)**	**3 (2.5)**
Pneumonia	1 (0.9)	4 (3.1)	0
Status epilepticus	2 (1.7)	2 (1.5)	1 (0.8)
Headache	0	2 (1.5)	0
Seizure	2 (1.7)	1 (0.8)	0
Croup infectious	1 (0.9)	1 (0.8)	0
Gastroenteritis	1 (0.9)	1 (0.8)	0
Influenza	1 (0.9)	1 (0.8)	0
Stomatitis	1 (0.9)	1 (0.8)	0
Pneumonia viral	0	1 (0.8)	1 (0.8)
Humerus fracture	0	1 (0.8)	0
Bronchitis	0	1 (0.8)	0
Lung disorder	0	1 (0.8)	0
Mental status changes	0	1 (0.8)	0
Nausea	0	1 (0.8)	0
Osteomyelitis	0	1 (0.8)	0
Pyelonephritis	0	1 (0.8)	0
Skin infection	0	1 (0.8)	0
Vomiting	0	1 (0.8)	0
Mouth ulceration	2 (1.7)	0	0
Pharyngitis	2 (1.7)	0	0
Urinary tract infection	2 (1.7)	0	0
Aggression	1 (0.9)	0	0
Arthralgia	1 (0.9)	0	0
Blepharitis	1 (0.9)	0	0
Dacryocanaliculitis	1 (0.9)	0	0
Diarrhoea	1 (0.9)	0	0
Dyskinesia	1 (0.9)	0	0
Ear infection	1 (0.9)	0	0
Febrile convulsion	1 (0.9)	0	0
Meibomianitis	1 (0.9)	0	0
Menorrhagia	1 (0.9)	0	0
Pyrexia	1 (0.9)	0	0
Respiratory failure	1 (0.9)	0	0
Sinusitis	1 (0.9)	0	0
Upper limb fracture	0	0	1 (0.8)

Source: [Study M2304-Table 14.3.1-1.6] Table 2-20

Table 34: SAEs irrespective of causality by preferred term (with a frequency cut-off of 1%); TSC pooled studies excluding Study M2304

Preferred term	N=251 n (%)
Any preferred term	100 (39.8)
Pneumonia	21 (8.4)
Seizure	9 (3.6)
Epilepsy	8 (3.2)
Gastroenteritis	6 (2.4)
Cellulitis	5 (2.0)
Pyrexia	5 (2.0)
Urinary tract infection	4 (1.6)
Dehydration	4 (1.6)
Bronchitis	3 (1.2)
Gastroenteritis viral	3 (1.2)
Generalised tonic-clonic seizure	3 (1.2)
Status epilepticus	3 (1.2)
Pneumothorax	3 (1.2)

Preferred terms are sorted in descending frequency
A patient with multiple occurrences of an SAE under one treatment is counted only once in the SAE category for that treatment
Only includes SAEs occurring on or after the start of everolimus and no more than 28 days after the discontinuation of everolimus
Data from following trials are included in the analysis: C2485, M2301, and M2302
Source: [Appendix 1-Table 2.2-8l] Table 2-22

Table 35: SAEs irrespective of causality by preferred term (with a frequency cut-off of 1% in any everolimus patient group); Study M2304 Core and Extension phase

Preferred term	LT target of 3-7 ng/mL N=117 n (%)		HT target of 9-15 ng/mL N=130 n (%)		Start Ext N=110 n (%)		All patients N=357 n (%)	
Any serious adverse event	**30**	**(25.6)**	**34**	**(26.2)**	**18**	**(16.4)**	**82**	**(23.0)**
Pneumonia	6	(5.1)	8	(6.2)	3	(2.7)	17	(4.8)
Seizure	5	(4.3)	5	(3.8)	2	(1.8)	12	(3.4)
Gastroenteritis	2	(1.7)	3	(2.3)	1	(0.9)	6	(1.7)
Epilepsy	2	(1.7)	3	(2.3)	0		5	(1.4)
Status epilepticus	2	(1.7)	2	(1.5)	1	(0.9)	5	(1.4)
Pyrexia	2	(1.7)	1	(0.8)	1	(0.9)	4	(1.1)
Pyelonephritis	1	(0.9)	2	(1.5)	0		3	(0.8)
Bronchitis	1	(0.9)	1	(0.8)	1	(0.9)	3	(0.8)
Tonsillitis	0		1	(0.8)	2	(1.8)	3	(0.8)
Mouth ulceration	3	(2.6)	0		0		3	(0.8)
Pharyngitis	2	(1.7)	0		1	(0.9)	3	(0.8)
Headache	0		2	(1.5)	0		2	(0.6)
Urinary tract infection	2	(1.7)	0		0		2	(0.6)
Viral infection	0		0		2	(1.8)	2	(0.6)

Preferred terms are sorted in descending frequency, as reported in the all patients column
A patient with multiple occurrences of an SAE under one treatment is counted only once in the SAE category for that treatment
Only includes SAEs occurring on or after the start of everolimus and no more than 30 days after the discontinuation of everolimus
All patients received treatment with everolimus in the Extension phase; the 'Start ext' column refers to patients originally randomized to placebo and who subsequently crossed over to everolimus in the Extension phase
Source: [Study M2304-Table 14.3.1-1.6l] Table 2-21

8.1.7. Discontinuations due to adverse events

8.1.7.1. Main/pivotal studies

Of the 35 drug discontinuations, the most common AEs leading to study drug discontinuation were stomatitis (five patients), pneumonia (four patients), and pyrexia (two patients). The previous TSC database Pool only had one AE per term causing discontinuation.

Table 36: Adverse events leading to study drug discontinuation irrespective of causality by preferred term; Study M2304 Core phase (Safety Set)

	Everolimus		Placebo
	LT target of 3-7 ng/mL	HT target of 9-15 ng/mL	
	N=117	N=130	N=119
Preferred term	**n (%)**	**n (%)**	**n (%)**
Any AE leading to study drug discontinuation	**6 (5.1)**	**4 (3.1)**	**2 (1.7)**
Stomatitis	2 (1.7)	1 (0.8)	0
Mouth ulceration	0	1 (0.8)	0
Neutropenia	0	1 (0.8)	0
Pneumonia	0	1 (0.8)	0
Anxiety	1 (0.9)	0	0
Diarrhoea	1 (0.9)	0	0
Immunodeficiency	1 (0.9)	0	0
Pyrexia	1 (0.9)	0	0
Respiratory tract infection viral	0	0	1 (0.8)
Weight decreased	0	0	1 (0.8)

Preferred terms are presented in descending frequency, as reported in the Everolimus 9-15ng/ml column
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment
Only includes AEs occurring on or after the start of study treatment and no more than 30 days after the discontinuation of study treatment and before start of everolimus in the Extension phase Source: [Study M2304-Table 14.3.1-1.8] Table 2-23

Table 37: AEs leading to study drug discontinuation irrespective of causality by preferred term; Study M2304 Core and Extension phase (Long-term Evaluation Safety Set)

	Everolimus							
	LT target of 3-7 ng/mL		HT target of 9-15 ng/mL		Start Ext		All patients	
	N=117		N=130		N=110		N=357	
Preferred term	n (%)		n (%)		n (%)		n (%)	
Any AE leading to study drug discontinuation	**16**	**(13.7)**	**11**	**(8.5)**	**8**	**(7.3)**	**35**	**(9.8)**
Stomatitis	2	(1.7)	2	(1.5)	1	(0.9)	5	(1.4)
Pneumonia	2	(1.7)	1	(0.8)	1	(0.9)	4	(1.1)
Pyrexia	2	(1.7)	0		0		2	(0.6)
Abdominal pain	0		1	(0.8)	0		1	(0.3)
Blood cholesterol increased	0		1	(0.8)	0		1	(0.3)
Blood triglycerides increased	0		1	(0.8)	0		1	(0.3)
Confusional state	0		1	(0.8)	0		1	(0.3)
Epilepsy	0		1	(0.8)	0		1	(0.3)
Mouth ulceration	0		1	(0.8)	0		1	(0.3)
Neutropenia	0		1	(0.8)	0		1	(0.3)
Pneumonia viral	0		1	(0.8)	0		1	(0.3)
Respiratory failure	0		1	(0.8)	0		1	(0.3)
Acute kidney injury	1	(0.9)	0		0		1	(0.3)
Angioedema	1	(0.9)	0		0		1	(0.3)
Anxiety	1	(0.9)	0		0		1	(0.3)
Decreased appetite	1	(0.9)	0		0		1	(0.3)
Diarrhoea	1	(0.9)	0		0		1	(0.3)
Febrile convulsion	1	(0.9)	0		0		1	(0.3)
Hypertension	1	(0.9)	0		0		1	(0.3)
Immunodeficiency	1	(0.9)	0		0		1	(0.3)
Pneumonia mycoplasmal	1	(0.9)	0		0		1	(0.3)
Seizure	1	(0.9)	0		0		1	(0.3)
Upper respiratory tract infection	1	(0.9)	0		0		1	(0.3)
Cellulitis	0		0		1	(0.9)	1	(0.3)
Cognitive disorder	0		0		1	(0.9)	1	(0.3)
Malaise	0		0		1	(0.9)	1	(0.3)
Oedema peripheral	0		0		1	(0.9)	1	(0.3)
Staphylococcal skin infection	0		0		1	(0.9)	1	(0.3)
Status epilepticus	0		0		1	(0.9)	1	(0.3)

Preferred terms are sorted in descending frequency, as reported in the all patients column
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment
Only includes AEs occurring on or after the start of everolimus and no more than 30 days after the discontinuation of everolimus
All patients received treatment with everolimus in the Extension phase; the 'Start ext' column refers to patients originally randomized to placebo and who subsequently crossed over to everolimus in the Extension phase
Source: [Study M2304-Table 14.3.1-1.8l] Table 2-24

Table 38: AEs leading to study drug discontinuation irrespective of causality by preferred term; TSC pooled studies excluding Study M2304 (Long-term Evaluation Safety Set)

Preferred term	Everolimus N=251 n (%)
Any AE leading to study drug discontinuation	21 (8.4)
Acinetobacter bacteraemia	1 (0.4)
Aggression	1 (0.4)
Anaemia	1 (0.4)
Angioedema	1 (0.4)
Azoospermia	1 (0.4)
Blood alkaline phosphatase increased	1 (0.4)
Blood phosphorus decreased	1 (0.4)
Bronchospasm	1 (0.4)
Diarrhoea	1 (0.4)
Focal segmental glomerulosclerosis	1 (0.4)
Hypersensitivity	1 (0.4)
Localised oedema	1 (0.4)
Malaise	1 (0.4)
Nasal sinus cancer	1 (0.4)
Neurosurgery	1 (0.4)
Neutropenia	1 (0.4)
Pancreatic carcinoma	1 (0.4)
Pneumonia	1 (0.4)
Pneumothorax	1 (0.4)
Proteinuria	1 (0.4)
Rhabdomyolysis	1 (0.4)
Seizure	1 (0.4)
Sinusitis	1 (0.4)
Skin toxicity	1 (0.4)
Stomatitis	1 (0.4)
Viral infection	1 (0.4)

Preferred terms are presented alphabetically Source: [Appendix 1-Table 4.2-9l] Table 2-25
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category
Only includes AEs occurring on or after the start of study treatment and no more than 28 days after the discontinuation of everolimus Data from following trials are included in the analysis: C2485, M2301, and M2302

The overall profile of AEs leading to dose interruption or adjustment was similar to the previous Pool. The incidence of some AEs was higher in the previous TSC Safety Pool compared with Study M2304. Stomatitis (17.1%), upper respiratory tract infection (13.5%), pneumonia (12.7%), mouth ulceration (11.2%), and sinusitis (10.4%) were the most frequently occurring AEs that necessitated dose adjustment or study drug interruption in the previous Pool.

Table 39: AEs requiring dose adjustment or interruption, regardless of study drug relationship by primary system organ class, preferred term and treatment Study M2304 Core and Extension phase (Safety Set)

Preferred term	Everolimus N=251 n (%)
Any AE leading to study drug discontinuation	21 (8.4)
Acinetobacter bacteraemia	1 (0.4)
Aggression	1 (0.4)
Anaemia	1 (0.4)
Angioedema	1 (0.4)
Azoospermia	1 (0.4)
Blood alkaline phosphatase increased	1 (0.4)
Blood phosphorus decreased	1 (0.4)
Bronchospasm	1 (0.4)
Diarrhoea	1 (0.4)
Focal segmental glomerulosclerosis	1 (0.4)
Hypersensitivity	1 (0.4)
Localised oedema	1 (0.4)
Malaise	1 (0.4)
Nasal sinus cancer	1 (0.4)
Neurosurgery	1 (0.4)
Neutropenia	1 (0.4)
Pancreatic carcinoma	1 (0.4)
Pneumonia	1 (0.4)
Pneumothorax	1 (0.4)
Proteinuria	1 (0.4)
Rhabdomyolysis	1 (0.4)
Seizure	1 (0.4)
Sinusitis	1 (0.4)
Skin toxicity	1 (0.4)
Stomatitis	1 (0.4)
Viral infection	1 (0.4)

Preferred terms are presented alphabetically
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category
Only includes AEs occurring on or after the start of study treatment and no more than 28 days after the discontinuation of everolimus
Data from following trials are included in the analysis: C2485, M2301, and M2302
Source: [Appendix 1-Table 4.2-9l]

8.2. Evaluation of issues with possible regulatory impact

8.2.1. Infections

Study M2304 Core phase

Everolimus possesses immunosuppressive properties. In 54.7% and 64.6% of patients in the everolimus LT and HT treatment groups and 45.4% in the placebo group infections were diagnosed, especially upper respiratory infections (for example nasopharyngitis, upper respiratory tract infection). SAEs of infections were seen in 6.0% of patients in the everolimus LT group, 6.9% in the HT group, respectively relative to placebo, most commonly pneumonia but also including gastroenteritis and urinary tract infection. In the placebo group 0% had infections. Single cases of pneumonia in the everolimus HT group and viral respiratory tract infection in the placebo group led to treatment discontinuation.

8.2.2. Non-infectious pneumonitis

Study M2304 Core phase

One case of Grade 2 non-infectious pneumonitis was reported in the everolimus HT treatment group.

8.2.3. Stomatitis

8.2.3.1. Study M2304 Core phase

Stomatitis related events were more frequently reported in the everolimus treatment groups than with placebo (54.7%, 63.8%, and 9.2% in the everolimus LT, HT, and placebo groups, respectively). The most common AEs reported included:

- Stomatitis (28.2%, 30.8%, and 3.4% in the everolimus LT, HT, and placebo groups,
- Mouth ulceration (23.9%, 21.5%, and 4.2%)
- Aphthous ulcer (4.3%, 14.6%, and 1.7%).

Most cases were grade 1 or 2, and were suspected to be drug related in the majority of cases. Grade 3 events were reported in 3.4% and 3.8% of patients in the everolimus LT and HT groups, respectively. No grade 4 events were reported. These events tended to appear within the first 2 to 3 weeks of treatment.

8.2.4. Hypersensitivity (anaphylactic reaction)

Study M2304 Core phase

Across the three treatment groups (13.7% and 15.4% of patients in the everolimus LT and HT treatment groups compared with 6.7% in the placebo group) had hypersensitivity-related events.

One patient (0.9%) in the everolimus LT treatment group reported grade 3 urticaria requiring dose adjustment while a further three patients (one (0.9%) in everolimus LT group and 2 (1.5%) in everolimus HT group) experienced cases of grade 1/2 rash that necessitated dose adjustment. There were no cases of severe hypersensitivity or anaphylaxis.

One case of pharyngeal oedema in the everolimus LT treatment group was grade 2 in intensity.

8.2.5. Hepatic toxicity

The Clinical Study Report did not have a separate section on this.

The sponsor has proposed multiple hepatic impairment insertions in relation to which the sponsor has consistently referred to '2.7.2 Summary of Clinical Pharmacology'. The only relevant statement found therein is:

> Impaired hepatic function: No new information was generated in support of this indication.

In reviewing the summary results of the trial 23 to 25% had abnormal liver enzymes (Table 41) (2 at least were grade3/4 (Table 42)). One ADR of raised enzyme was reported (also 1 on placebo) raised ALT. Due to raised Alkaline phosphatase there was 1 discontinuation (Table 38), and 1 interruption or adjustment to dose (Table 39).

8.2.6. Renal toxicities

Study M2304 Core phase

Renal toxicities were reported 0.9% versus 3.8% versus 2.5% for the everolimus LT, HT, and placebo treatment groups, respectively, with 1 patient from the everolimus HT group experiencing a grade 3 elevation in blood creatinine (no action was taken and this event resolved after 23days).

8.2.7. Effects of everolimus on brain growth and development, particularly in patients under 3 years of age

Study M2304 Core phase

Five patients in the everolimus treatment groups (four (50.0%) in the LT and one patient (14.3%) in the HT group) experienced events. A single case (12.5%) of grade 4 status epilepticus was reported in a 2 year old patient in the everolimus LT group, which resolved after 16 days.

Table 40: Clinical impact of effects of everolimus on brain growth and development, particularly in patients under 3 years of age; Study M2304 Core phase (Safety Set)

	Everolimus		Placebo
	LT target of 3-7 ng/mL	HT target of 9-15 ng/mL	
	N=8	N=7	N=12
	n (%)	n (%)	n (%)
All effects on brain growth and development	**4 (50.0)**	**1 (14.3)**	**1 (8.3)**
Hemiparesis	0	1 (14.3)	0
Muscular weakness	1 (12.5)	0	0
Seizure	1 (12.5)	0	0
Sleep disorder	1 (12.5)	0	0
Status epilepticus	1 (12.5)	0	0
Insomnia	0	0	1 (8.3)
CTC grade 3/4 AEs	**1 (12.5)**	**0**	**0**
Status epilepticus	1 (12.5)	0	0
Suspected AEs	**2 (25.0)**	**0**	**1 (8.3)**
Sleep disorder	1 (12.5)	0	0
Status epilepticus	1 (12.5)	0	0
Insomnia	0	0	1 (8.3)
SAEs	**2 (25.0)**	**0**	**0**
Seizure	1 (12.5)	0	0
Status epilepticus	1 (12.5)	0	0
AE requiring dose adjustment	**1 (12.5)**	**0**	**0**
Status epilepticus	1 (12.5)	0	0

Preferred terms are sorted in descending frequency, as reported in the everolimus 9-15 ng/mL column
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment
A patient with multiple severity ratings for an AE while on a treatment is only counted under the maximum rating
Only includes AEs occurring on or after the start of study treatment and no more than 30 days after the discontinuation of study treatment and before start of everolimus in the Extension phase Source: [Study M2304-Table 14.3.1-1.12] Table 2-42

8.2.8. Female fertility (including secondary amenorrhea) in female patients aged 10 to 55 years

Study M2304 Core phase

The incidence of events related to female fertility (irregular menstruation and amenorrhoea) was similar across the three treatment groups.

8.2.9. Haemorrhages

Study M2304 Core phase

The incidence of haemorrhage was higher in the everolimus treatment groups (6.0% and 11.5% for LT and HT groups, respectively) compared to the placebo group (3.4%). About 50% of the grade 1/2 haemorrhage cases reported among the patients treated with everolimus were described as epistaxis. There was a single case (0.9%) of menorrhagia in the everolimus LT group (in a 44 year old patient) that fulfilled the criteria for an SAE; this event resolved after 26 days.

8.2.10. Haematology and haematological toxicity

Study M2304 Core phase

Haematology abnormalities that were more frequently reported in the everolimus treatment groups (with differences of ≥ 10% relative to placebo) included:

- Absolute neutrophils (hypo) (difference +2.1% and +14.2% for the everolimus LT and HT treatment groups, respectively)
- Absolute lymphocytes (hyper) (difference +15.6% and +1.7%).

All grade 3/4 cases resolved prior to the data cut-off date.

8.2.10.1. Cytopaenia

The incidence of Cytopaenia was similar across the three treatment groups (7.7%, 7.7%, and 7.6% for the everolimus LT, HT, and placebo treatment groups, respectively). The majority of the AEs in this category were neutropaenia, anaemia, and decreased neutrophil count.

8.2.11. Other laboratory tests

There were a higher incidence of Grade3/4 abnormal values for Potassium (hyper) (3.1% Study M2304 All patients versus 0.8% TSC Pool without M2304) and Sodium (hyper) ((4.2% versus 1.6%).

Among all abnormal clinical chemistry values in Study M2304 All patients results most had a similar or higher incidence than in the TSC Pool without M2304, except the liver enzymes, Phosphate (inorganic phosphorus) (hypo), Glucose (fasting) (hypo), Sodium (hypo) and Potassium (hypo). Magnesium (hyper) (40.9% Study M2304 All patients versus 3.6% TSC Pool without M2304) and Creatinine (hyper) (30.3% versus 12.0%) showed considerable differences.

Table 41: Abnormal Clinical Chemistry Values; Study M2304 Core and Extension phase and TSC pooled studies excluding Study M2304

Laboratory parameter	Study M2304				TSC Pool Without M2304
	LT target of 3-7 ng/mL	HT target of 9-15 ng/mL	Start Ext	All patients	
	N=117	N=130	N=110	N=357	
	All grades	All grades	All grades	All grades	N = 251
	n (%)	n (%)	n (%)	n (%)	n (%)
Cholesterol (total) (hyper)	108 (92.3)	113 (86.9)	96 (87.3)	317 (88.8)	220 (87.6)
Corrected calcium (hyper)	84 (71.8)	87 (66.9)	70 (63.6)	241 (67.5)	37 (14.7)
Triglycerides (hyper)	66 (56.4)	69 (53.1)	47 (42.7)	182 (51.0)	152 (60.6)
Magnesium (hyper)	55 (47.0)	49 (37.7)	42 (38.2)	146 (40.9)	9 (3.6)
Corrected calcium (hypo)	35 (29.9)	49 (37.7)	28 (25.5)	112 (31.4)	40 (15.9)
Creatinine (hyper)	35 (29.9)	45 (34.6)	28 (25.5)	108 (30.3)	30 (12.0)
Sodium (hyper)	40 (34.2)	43 (33.1)	24 (21.8)	107 (30.0)	29 (11.6)
Glucose (fasting) (hyper)	33 (28.2)	36 (27.7)	20 (18.2)	89 (24.9)	45 (17.9)[a]
Alkaline phosphatase, serum (hyper)	35 (29.9)	26 (20.0)	27 (24.5)	88 (24.6)	89 (35.5)
SGPT (ALT) (hyper)	27 (23.1)	36 (27.7)	20 (18.2)	83 (23.2)	98 (39.0)
SGOT (AST) (hyper)	26 (22.2)	34 (26.2)	22 (20.0)	82 (23.0)	123 (49.0)
Phosphate (inorganic phosphorus) (hypo)	17 (14.5)	27 (20.8)	14 (12.7)	58 (16.2)	83 (33.1)
Potassium (hyper)	24 (20.5)	17 (13.1)	6 (5.5)	47 (13.2)	18 (7.2)
Glucose (fasting) (hypo)	10 (8.5)	16 (12.3)	8 (7.3)	34 (9.5)	51 (20.3)[b]
Uric acid (hyper)	10 (8.5)	1 (8.5)	8 (7.3)	29 (8.1)	
Magnesium (hypo)	10 (8.5)	9 (6.9)	7 (6.4)	26 (7.3)	7 (2.8)
Sodium (hypo)	3 (2.6)	8 (6.2)	4 (3.6)	15 (4.2)	30 (12.0)
Creatinine clearance (hypo)	2 (1.7)	6 (4.6)	6 (5.5)	14 (3.9)	
Albumin (hypo)	5 (4.3)	6 (4.6)	1 (0.9)	12 (3.4)	12 (4.8)
Potassium (hypo)	2 (1.7)	5 (3.8)	1 (0.9)	8 (2.2)	44 (17.5)
Bicarbonate (hypo)					188 (74.9)
Fibrinogen (hypo)					110 (43.8)
Bilirubin (total) (hyper)					5 (2.0)

[a] Also Table 3.6 gives Glucose (hyper) 9 (3.6%)
[b] Also Table 3.6 gives Glucose (hypo) 12 (4.8%)

Source: Table3-5,3-6

Patients were counted only for the worst grade observed post-Baseline

Study M2304:

- Post-Baseline refers to values after the first dose of everolimus and no more than 30 days after the discontinuation of everolimus
- All patients received treatment with everolimus in the Extension phase; the 'Start ext' column refers to patients originally randomized to placebo and who subsequently crossed over to everolimus in the Extension phase

TSC Pool Post-Baseline refers to values after the first dose of study treatment and no more than 28 days after the discontinuation of everolimus. Data from following trials are included in the TSC Pool analysis: C2485, M2301, M2302

Table 42: Grade 3/4 Abnormal Clinical Chemistry Values; Study M2304 Core and Extension phase and TSC pooled studies excluding Study M2304

Laboratory parameter	studyM2304				TSC Pool Without M2304
	LT target of 3-7 ng/mL	HT target of 9-15 ng/mL	Start Ext	All patients	
	N=117	N=130	N=110	N=357	N=251
	n (%)	n (%)	n (%)	n (%)	n (%)
Cholesterol (total) (hyper)	1 (0.9)	1 (0.8)	1 (0.9)	3 (0.8)	2 (0.8)
Triglycerides (hyper)	5 (4.3)	5 (3.8)	1 (0.9)	11 (3.1)	5 (2.0)
Magnesium (hyper)	0	1 (0.8)	0	1 (0.3)	0
Corrected calcium (hypo)	6 (5.1)	1 (0.8)	1 (0.9)	8 (2.2)	2 (0.8)
Creatinine (hyper)	1 (0.9)	3 (2.3)	0	4 (1.1)	2 (0.8)
Sodium (hyper)	7 (6.0)	6 (4.6)	2 (1.8)	15 (4.2)	4 (1.6)
Glucose (fasting) (hyper)	0	0	0	0	1 (0.4)
Alkaline phosphatase, serum (hyper)	0	0	0	0	7 (2.8)
SGPT (ALT) (hyper)	0	2 (1.5)	0	2 (0.6)	1 (0.4)
SGOT (AST) (hyper)	0	1 (0.8)	0	1 (0.3)	3 (1.2)
Phosphate (inorganic phosphorus) (hypo)	1 (0.9)	5 (3.8)	2 (1.8)	8 (2.2)	12 (4.8)
Potassium (hyper)	8 (6.8)	2 (1.5)	1 (0.9)	11 (3.1)	2 (0.8)
Glucose (fasting) (hypo)	2 (1.7)	0	0	2 (0.6)	0
Uric acid (hyper)	1 (0.9)	1 (0.8)	0	2 (0.6)	
Magnesium (hypo)	1 (0.9)	1 (0.8)	0	2 (0.6)	0
Sodium (hypo)	1 (0.9)	3 (2.3)	0	4 (1.1)	4 (1.6)
Potassium (hypo)	0	0	0	0	1 (0.4)
Bicarbonate (hypo) 1					2 (0.8)
Fibrinogen (hypo)					10 (4.0)

[1] Also Table 3.6 gives Glucose (hyper) 0 Source: Table3-5,3-6
[2] Also Table 3.6 gives Glucose (hypo) 0
Patients were counted only for the worst grade observed post-Baseline
Study M2304:

- Post-Baseline refers to values after the first dose of everolimus and no more than 30 days after the discontinuation of everolimus
- All patients received treatment with everolimus in the Extension phase; the 'Start ext' column refers to patients originally randomized to placebo and who subsequently crossed over to everolimus in the Extension phase

TSC Pool Post-Baseline refers to values after the first dose of study treatment and no more than 28 days after the discontinuation of everolimus. Data from following trials are included in the TSC Pool analysis: C2485, M2301, M2302

8.2.12. Dyslipidaemia in paediatric population

Study M2304 Core phase

Dyslipidaemia related events occurred in 12.5% and 17.8% of paediatric patients in the everolimus LT and HT treatment groups compared with a 5.2% in the placebo group. Most cases were grade 1 or 2, and were suspected to be drug related in the majority of cases.

Table 43: Clinical impact of dyslipidaemia in paediatric population; Study M2304 Core phase (Safety Set)

	Everolimus				Placebo	
	LT target of 3-7 ng/mL		HT target of 9-15 ng/mL			
	N=96		N=107		N=97	
	n (%)		n (%)		n (%)	
All dyslipidaemia-related events	**12**	**(12.5)**	**19**	**(17.8)**	**5**	**(5.2)**
Hypertriglyceridaemia	6	(6.3)	8	(7.5)	2	(2.1)
Blood cholesterol increased	3	(3.1)	7	(6.5)	1	(1.0)
Hypercholesterolaemia	2	(2.1)	5	(4.7)	0	
Hyperlipidaemia	2	(2.1)	4	(3.7)	1	(1.0)
Low density lipoprotein increased	2	(2.1)	2	(1.9)	0	
Blood triglycerides increased	1	(1.0)	2	(1.9)	1	(1.0)
Lipids increased	0		1	(0.9)	0	
Dyslipidaemia	2	(2.1)	0		0	
CTC grade 3/4 AEs	**1**	**(1.0)**	**2**	**(1.9)**	**0**	
Blood cholesterol increased	0		1	(0.9)	0	
Blood triglycerides increased	0		1	(0.9)	0	
Hypertriglyceridaemia	1	(1.0)	0		0	
Suspected AEs	**8**	**(8.3)**	**12**	**(11.2)**	**2**	**(2.1)**
Hypertriglyceridaemia	5	(5.2)	6	(5.6)	0	
Hypercholesterolaemia	2	(2.1)	4	(3.7)	0	
Hyperlipidaemia	1	(1.0)	3	(2.8)	1	(1.0)
Blood triglycerides increased	1	(1.0)	2	(1.9)	1	(1.0)
Blood cholesterol increased	0		2	(1.9)	0	
Lipids increased	0		1	(0.9)	0	
Low density lipoprotein increased	0		1	(0.9)	0	
Dyslipidaemia	1	(1.0)	0		0	
AE requiring dose adjustment	**0**		**2**	**(1.9)**	**0**	
Hypertriglyceridaemia	0		1	(0.9)	0	
Lipids increased	0		1	(0.9)	0	

Percentages are calculated based on the number of patients aged < 18 years
Preferred terms are sorted in descending frequency, as reported in the everolimus 9-15ng/mL column
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment
A patient with multiple severity ratings for an AE while on a treatment is only counted under the maximum rating
Only includes AEs occurring on or after the start of study treatment and no more than 30 days after the discontinuation of study treatment and before start of everolimus in the Extension phase
Source: [Study M2304-Table 14.3.1-1.12 Table 2-39

8.2.13. Hyperglycaemia/new-onset diabetes mellitus

Study M2304 Core phase

One case of grade 1 hyperglycaemia was reported in a patient in the everolimus LT treatment group. No cases of new-onset diabetes mellitus were reported across the three treatment groups.

8.3. Vital signs and clinical examination findings

Study M2304 Core phase

8.3.1. Growth – height and weight

Standard deviation scores (SDS) for height, height velocity, body mass index, and weight velocity in patients aged < 18 years at study initiation were comparable both prior to and after starting treatment with everolimus. Based on N = 96 at week 72, 29 at 96 and 1 at 120 weeks

the proportions of patients with SDS values < 5th percentile or > 95th percentile on height, height velocity, body mass index, and weight velocity did not increase significantly after the start of everolimus therapy.

Table 44: Summary of growth data by time window; Study M2304 Core and Extension phase (Long-term Evaluation Safety Set)

Variable	Statistic	All everolimus patients					
		Baseline	Week 24	Week 48	Week 72	Week 96	Week 120
Height SDS	n	284	254	169	96	29	1
	Mean (SD)	0.946 (0.0564)	0.944 (0.0557)	0.944 (0.0536)	0.940 (0.0580)	0.921 (0.0465)	0.966 (NE)
	Median	0.948	0.946	0.943	0.940	0.930	0.966
	Min-Max	0.71-1.09	0.71-1.09	0.77-1.10	0.83-1.19	0.83-1.03	0.97-0.97
	Notably low, n (%)	0	0	0	0	0	0
	Notably high, n (%)	0	0	0	0	0	0
Height velocity SDS	n	173	258	171	97	29	1
	Mean (SD)	0.392 (4.0935)	-0.593 (3.1997)	-0.630 (3.1527)	-0.445 (5.5007)	-0.273 (2.1758)	-3.284 (NE)
	Median	0.064	-0.757	-0.947	-0.744	-0.250	-3.284
	Min-Max	-12.00-20.12	-16.30-15.87	-10.72-18.03	-12.78-46.56	-4.45-7.44	-3.28 - -3.28
	Notably low, n (%)	46 (26.6)	82 (31.8)	61 (35.7)	33 (34.0)	6 (20.7)	1 (100.0)
	Notably high, n (%)	44 (25.4)	41 (15.9)	30 (17.5)	11 (11.3)	3 (10.3)	0
BMI SDS	n	284	253	169	96	29	1
	Mean (SD)	1.097 (0.2323)	1.145 (0.5806)	1.125 (0.2548)	1.121 (0.2684)	1.184 (0.2253)	0.861 (NE)
	Median	1.115	1.116	1.141	1.112	1.187	0.861
	Min-Max	0.35-1.82	0.47-9.56	0.54-2.17	0.56-2.17	0.80-1.68	0.86-0.86
	Notably low, n (%)	0	0	0	0	0	0
	Notably high, n (%)	6 (2.1)	7 (2.8)	4 (2.4)	2 (2.1)	1 (3.4)	0
Weight velocity SDS	n	179	257	172	98	29	1
	Mean (SD)	-0.329 (1.9243)	-0.797 (1.8991)	-0.448 (1.9458)	-0.107 (1.9817)	-0.558 (1.0866)	1.347 (NE)
	Median	-0.482	-0.892	-0.550	-0.355	-0.542	1.347
	Min-Max	-6.29-5.92	-6.69-5.42	-7.79-9.43	-4.22-5.97	-3.01-2.11	1.35-1.35
	Notably low, n (%)	34 (19.0)	78 (30.4)	35 (20.3)	16 (16.3)	4 (13.8)	0
	Notably high, n (%)	24 (13.4)	28 (10.9)	18 (10.5)	10 (10.2)	1 (3.4)	0

SDS (standard deviation scores) for height and BMI (i.e. z-values) are obtained from the WHO Growth Charts, and SDS for height and weight velocity are obtained from Baumgartner et al 1986. Notably low and high are defined as values below the 5th percentile (SDS < -1.645) and above the 95th percentile (SDS >1.645), respectively Source: [Study M2304-Table 14.3-4.11] Table 4-1

8.3.1.1. Puberty

Overall, considering the patients at risk of delayed puberty at start date of everolimus, puberty appeared to be delayed for three patients (two females and one male). However, following a detailed medical review of these cases, there was no indication of delayed puberty for the two females.

8.3.1.2. Neuropsychological data

The sponsor attempted to collect information using the Vineland-II Adaptive Behaviour Composite Score and the Wechsler Nonverbal Composite Score, however most groups had data for less than 50% of subjects at Baseline, with even less at end of Core phase.

8.4. Other safety issues

The sponsor rather than use the trial report data proposes:

> In accordance with the Novartis Business Guidance, frequency category assessment of the identified ADRs in the updated TSC safety pool has been based upon overall incidence rates (all AEs irrespective of causality assessment) as opposed to those AEs reported as suspected by the investigators. In order to conduct an appropriate comparative analysis with the new safety data pool, the previous safety pool was updated according to the revised strategy.[12]

[12] CO Labelling change - Updated TSC Safety Pool page 9

The strategy applied for screening (detection) of AEs for ADR candidates and identification (causality assessment) of ADRs based on reported AEs:

1. Review of all AEs, irrespective of relationship to study medication, from Study M2304 was performed as follows:
    - Double blind phase: those reported at a higher frequency (≥ 1%) in the everolimus treated patients compared to placebo treated patients; and
    - Open label extension phase: those reported in ≥ 1% patients, overall.
2. Review of exposure adjusted data in everolimus treated patients double blind + open label phases of Study M2304 compared to the current TSC safety pool (Studies C2485/M2301/M2302): AEs were screened based upon absolute difference in incidence of ≥ 2%. The objective was to overcome any potential bias in frequency category assessment due to difference in exposure duration in the new study compared to the current safety pool.
3. The updated safety pool from TSC studies (including Study M2304) was compared to the current TSC safety pool, comparing rates of all AEs.
4. Any newly reported AE was medically assessed for identification as ADRs using standard Bradford-Hill criteria.
5. Final list of identified ADRs was cross-referenced with the ADR list from the current CDS to ascertain:
    - Potential change in frequency category of existing ADRs
    - Potential change in ADR definition (preferred term in the ADR table and footnote)
    - Potential addition of new ADRs (population specific or target indication specific)
    - Additional ADR assessment criteria:

        As an additional assessment criterion, all SAEs were also generally considered unless known to be associated with the patient's disease or noted as part of prior medical history.

Table 45: Adverse Reactions; Comparison of trial results versus sponsor proposed interpretation of results N = 608

	Long-term Evaluation Safety Set[a]	Updated TSC Safety Pool[b]
Preferred term	n (%)	n (%)
Stomatitis	232 (38.2)	410 (67.4)
Nasopharyngitis	56 (9.2)	168 (27.6)
Diarrhoea	51 (8.4)	152 (25.0)
Pyrexia	50 (8.2)	149 (24.5)
Upper respiratory tract infection	68 (11.2)	138 (22.7)
Vomiting		126 (20.7)
Cough	35 (5.8)	111 (18.3)
Headache		92 (15.1)
Amenorrhea*		32 (14.7)
Acne	52 (8.6)	85 (14.0)
Menstruation irregular*		29 (13.3)
Pneumonia	42 (6.9)	68 (11.2)
Sinusitis	34 (5.6)	66 (10.9)
Urinary tract infection		66 (10.9)
Fatigue	33 (5.4)	65 (10.7)
Hypercholesterolaemia	57 (9.4)	65 (10.7)
Decreased appetite	36 (5.9)	63 (10.4)
Mouth ulceration	141 (23.2)	
Aphthous ulcer	64 (10.5)	
Blood cholesterol increased	44 (7.2)	
Blood triglycerides increased	33 (5.4)	

[a] TSC pooled studies including M2304 2.7.4 Summary of Clinical Safety
[b] CO Labelling change - Updated TSC Safety Pool Listing is by most common in this set.
* N=218 (female between 10 to 55 years of age only)
Source: Table 2-16 Summary of Clinical Safety, Table 5-7 CO Labelling change -

CPMP/ICH/375/95 ICH Topic E 1 Note for Guidance on Population Exposure: The Extent of Population Exposure to Assess Clinical Safety:

> Regulatory standards for the safety evaluation of drugs should be based on previous experience with the occurrence and detection of adverse drug events (ADEs), statistical considerations of the probability of detecting specified frequencies of ADEs, and practical considerations.

The Form for Providing Product Information for a Restricted Medicine or Other Medicine in Relation to which The Secretary Requires Product Information to be Provided has:

ix) Adverse effects

Severity, clinical importance and frequency of adverse effects.

Note: For clarity and consistency, the following format is preferred:

1. A table of adverse events (not adverse reactions) at a cut-off of, for example, 1% comparing the frequency of adverse events (n(%) or (%)) on drug with placebo/active comparator (if studies support this comparison) (usually very common and common);
2. A line listing of adverse reactions that fall below the cut-off by System Organ Classes (SOC) using CIOMS3 frequencies (usually uncommon, rare); and
3. A post-marketing section of adverse reactions by system organ class using CIOMS frequencies (usually rare or very rare).

Note for Guidance on Clinical Safety Data Management Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95) Annotated with TGA Comments has:

2. Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established:

> all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

The phrase "responses to a medicinal products" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, that is, the relationship cannot be ruled out.

Regarding marketed medicinal products, a well-accepted definition of an adverse drug reaction in the post-marketing setting is found in WHO Technical Report 498 (1972) and reads as follows:

> A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.

The recent NHMC document Safety monitoring and reporting in clinical trials involving therapeutic goods[13] (November 2016) has the following in relation to ADRs:

> Adverse Reaction (AR)
>
> Any untoward and unintended response to an investigational medicinal product related to any dose administered.
>
> Comment: All adverse events judged by either the reporting investigator or the sponsor as having a reasonable possibility of a causal relationship to an investigational medicinal product would qualify as adverse reactions. The expression 'reasonable causal relationship' means to convey, in general, that there is evidence or argument to suggest a causal relationship.

Note:[14] The following are examples of types of evidence that would suggest a causal relationship between the investigational product and the adverse event:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (for example, angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (for example, tendon rupture).
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group

[13] https://www.nhmrc.gov.au/research/clinical-trials/nhmrc-clinical-trials-initiatives/promoting-consistency-in-safety-monitoring

[14] 'Selected examples taken from Extract from FDA Safety Reporting Guidance clarifying the types of evidence that would suggest a causal relationship between the investigational medicinal product and the adverse event.' Footnote from NHMRC document

Comment: The current and proposed PIs contain only a Table labelled:

> Adverse drug reactions from clinical trials in TSC reported at a higher rate in the Afinitor arm than in the placebo arm in TSC studies.
>
> Given that the definition includes both AEs considered related by the investigator or those considered related the sponsor, the decision process needs to be distinguished in the PI.
>
> The sponsor's approach seems broadly reasonable, although there are some pitfalls with unthinking application of exposure-adjusted incidence, for example anaphylaxis might be better analysed as a crude frequency. Other factors that are relevant might be captured under 'Bradford Hill criteria' but that's open to interpretation.

8.5. Safety in special populations

8.5.1. Age

The sponsor attempted to relate the incidence of AEs to age groups, especially < 3 years, but the numbers were small.

8.5.2. Gender

The incidence of most AEs was generally similar for both males and females, with the exception of vomiting (+10.7% higher in females relative to males).

Table 46: AEs irrespective of causality by gender (with a frequency cut-off of 10% in any group) (Long-term Evaluation Safety Set)

	All everolimus patients	
	Male N=184 n (%)	Female N=173 n (%)
Any preferred term	**177 (96.2)**	**167 (96.5)**
Stomatitis	60 (32.6)	57 (32.9)
Pyrexia	41 (22.3)	51 (29.5)
Diarrhoea	41 (22.3)	45 (26.0)
Nasopharyngitis	40 (21.7)	30 (17.3)
Mouth ulceration	40 (21.7)	39 (22.5)
Upper respiratory tract infection	35 (19.0)	30 (17.3)
Cough	24 (13.0)	26 (15.0)
Vomiting	24 (13.0)	41 (23.7)
Blood cholesterol increased	22 (12.0)	20 (11.6)
Aphthous ulcer	20 (10.9)	20 (11.6)
Headache	11 (6.0)	23 (13.3)

Preferred terms are sorted in descending frequency as reported in the male subgroup
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment
Only includes AEs occurring on or after the start of study treatment and no more than 30 days after the discontinuation of study treatment
Source: [Appendix 1-Table 3.2-2.4l] Table 5-5

8.5.3. Concomitant AEDs

The numbers of patients with only 1 concomitant AED were limited and therefore results for this subgrouping need to be interpreted with caution.

8.5.4. Adverse Reactions Comparison of Populations

Table 47: Adverse Reactions - Comparison of Study M2304 results, cross trial results and sponsor proposed interpretation of results N = 608

	Core and Extension Study M2304	Long-term Evaluation Safety Set[a]	Updated TSC Safety Pool[b]
Preferred term	n (%)	n (%)	n (%)
Stomatitis	112 (31.4)	232 (38.2)	410 (67.4)
Nasopharyngitis	11 (3.1)	56 (9.2)	168 (27.6)
Diarrhoea	27 (7.6)	51 (8.4)	152 (25.0)
Pyrexia	26 (7.3)	50 (8.2)	149 (24.5)
Upper respiratory tract infection	18 (5.0)	68 (11.2)	138 (22.7)
Vomiting	13 (3.6)		126 (20.7)
Cough	12 (3.4)	35 (5.8)	111 (18.3)
Headache	9 (2.5)		92 (15.1)
Amenorrhea*			32 (14.7)
Acne	12 (3.4)	52 (8.6)	85 (14.0)
Menstruation irregular*	8 (2.2)		29 (13.3)
Pneumonia	14 (3.9)	42 (6.9)	68 (11.2)
Sinusitis	5 (1.4)	34 (5.6)	66 (10.9)
Urinary tract infection	4 (1.1)		66 (10.9)
Fatigue	9 (2.5)	33 (5.4)	65 (10.7)
Hypercholesterolemia	9 (2.5)	57 (9.4)	65 (10.7)
Decreased appetite	18 (5.0)	36 (5.9)	63 (10.4)
Mouth ulceration	74 (20.7)	141 (23.2)	
Aphthous ulcer	36 (10.1)	64 (10.5)	
Blood cholesterol increased	15 (4.2)	44 (7.2)	
Blood triglycerides increased	13 (3.6)	33 (5.4)	

[a] TSC pooled studies including M2304 2.7.4 Summary of Clinical Safety
[b] CO Labelling change - Updated TSC Safety Pool Listing is by most common in this set.
* N=218 (female between 10 to 55 years of age only)
Source: Table 2-14, 2-16 Summary of Clinical Safety, Table 5-7 CO Labelling change -

8.6. Post marketing experience

At the time of the Summary of Clinical Safety the total worldwide cumulative market exposure to everolimus in the Oncology and TSC settings combined through 31 March 2015 was estimated to be 84021 patient-treatment-years.

The total cumulative worldwide patient exposure (until 31 March 2015) based on the worldwide sales of tablets sold per defined daily dose, has been estimated at 79056 patient-treatment years for the Oncology setting (Oncology PSUR 9; 18 May 2015) and 4965 patient-treatment years for the TSC setting (TSC PSUR 7; 19 May 2015).

8.7. Evaluator's overall conclusions on clinical safety

Comparing previous experience with Study M2304:

- Under 6 Months, the overall incidence of emerging AEs was higher in the previous Pool versus Study M2304 (87.6% versus 74.5%), as were the incidences of stomatitis (+11.9%) and hypercholesterolemia (+9.5%). Other events were reported with a similar frequency between the two datasets.
- Between Months 6 to 12, the overall incidence of emerging AEs was higher in the previous Pool versus Study M2304 (53.1% versus 37.8%). The incidence of specific AEs was in general similar.

- Between Months 12 to 24 the overall incidence of emerging AEs was higher in the previous Pool versus Study M2304 (67.5% versus 33.9%). Stomatitis (7.9%) and mouth ulceration (5.0%) were both reported more frequently in the previous pool.

There were some differences from the previous experience, the sponsor's explanation for these related to the difference in age composition with 2 of the earlier trials confined to adults.

There appeared to be no major difference from the previous safety experience of everolimus in TSC patients.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

Table 48: First round assessment of benefits

Indication	
Benefits	**Strengths and Uncertainties**
Up to 60% of patients with TSC associated epilepsy fail to demonstrate improvement in seizure frequency with available therapies. The response rate in the Primary endpoint was 15.1% for the placebo arm, 28.2% for the C_{min} 3 to 7 ng/mL arm and 40.0% for the C_{min} 9 to 15 ng/mL arm.	The 95% CIs for the C_{min} 9 to 15 ng/mL arm and placebo clearly separate. The 95%CIs for placebo and the 3 to 7 ng/mL arm overlap. However the Odds ratio 95%CIs do not include 1.0. By modelling the sponsor ascertained the lowest C_{min} at which the 95% CIs were still separated from placebo.

9.2. First round assessment of risks

Table 49: First round assessment of risks

Risks	Strengths and Uncertainties
Exposure is increased from previously recommended for TSC. The exact mechanism of action is unclear.	There are no major changes in adverse reactions from those already reported in other TSC trials. Regression analyses of the time to first event of stomatitis and infections and infestations versus TN-C_{min} indicated that 2 fold increases in TN-C_{min} were not associated with statistically significant increases in the risk of either of these events during the core phase (stomatitis: HR 1.092; 95% CI: 0.866, 1.376; infections and infestations: HR 1.060; 95% CI: 0.848, 1.325).

9.3. First round assessment of benefit-risk balance

The benefit-risk balance is considered favourable.

10. First round recommendation regarding authorisation

It is not recommended that the proposed indication everolimus be approved.

It is recommended that everolimus be approved subject to a satisfactory PI for the modified indication of:

> *Afinitor is indicated for the Adjunctive treatment of patients aged 2 years and older with TSC and **associated** refractory seizures.*

It was a requirement for inclusion in Study M2034 that patients have a 'Clinically definite diagnosis of TSC.' Refractory seizures alone (a possible interpretation), was not included in the submission. The additional insertion clarifies this.

11. Clinical questions

11.1. Hepatic toxicity

The Clinical Study Report did not have a separate section on this. The Summary of Clinical Safety had under 1.1.1Safety aspects of the product Additional known risks with everolimus therapy that require close monitoring and evaluation include: and safety in patients with hepatic impairment.

The sponsor has proposed multiple hepatic impairment insertions in relation to which the sponsor has consistently referred to 2.7.2 Summary of Clinical Pharmacology. The only relevant statement found therein is:

> 3.2.9 Impaired hepatic function: No new information was generated in support of this indication.

In the summary results of the trial 23 to 25% had abnormal liver enzymes (Table 41) (2 at least were grade3/4 (Table 42)). One ADR of raised enzyme was reported (also 1 on placebo) raised ALT. Due to raised Alkaline phosphatase there was 1 discontinuation (Table 38), and 1 interruption or adjustment to dose (Table 39).

1. Please review and comment.
2. Please justify the proposed insertions.

12. Second round evaluation of clinical data submitted in response to questions

There was no second round clinical evaluation. The response to the question raised is in the AusPAR document in the Delegates discussion.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au