15 December 2016
EMA/12340/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Votubia

International non-proprietary name: everolimus

Procedure No. EMEA/H/C/002311/II/0041

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

AE	Adverse event
AED	Anti-epileptic drug
AESI	Adverse event of special interest
ANCOVA	(Rank) Analysis of covariance
BSA	Body surface area
CHMP	Committee for medicinal products for human use
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel test
c_{min}	Trough concentration
CYP3A4	Cytochrome p450 3a4
EEG	Electroencephalography
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
F_{pen}	Penetration Factor
FAS	Full Analysis Set
FDA	Food and drug administration
GCP	Good clinical practice
HT	high trough range (target trough 9-15 ng/mL)
LT	low trough range (target trough 3-7 ng/mL)
ILAE	International League Against Epilepsy
MedDRA	Medical dictionary for regulatory activities
mTOR	Mammalian target of rapamycin
mTORC1	mTOR-raptor signal transduction complex
PBT	Persistence, bioaccumulation potential and toxicity
PD	Pharmacodynamics
PEC	Predicted Environmental Concentration
PgP	P-glycoprotein
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
POS	Partial onset seizures
PPS	Per Protocol Set
PT	Preferred Term
QoL	Quality of life
SAE	Serious adverse event
SEGA	Subependymal giant-cell astrocytoma
SOC	System organ class
TSC	Tuberous sclerosis complex
TSC1	Tuberous sclerosis 1 gene, code for hamartin
TSC2	Tuberous sclerosis 2 gene, code for tuberin
VNS	vagal nerve stimulation

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Ltd submitted to the European Medicines Agency on 30 May 2016 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of Indication to include adjunctive treatment of patients aged 2 years and older with refractory seizures associated with tuberous sclerosis complex (TSC) for Votubia 2 mg, 3 mg and 5 mg dispersible tablets. Sections 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated in parallel based on the results from the pivotal study. In addition, sections 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 are also updated for the 2.5 mg, 5 mg and 10 mg tablets to reflect on data relevant to these formulations.
The Package Leaflet is updated in accordance.
Furthermore, the PI is brought in line with the latest QRD template version 10.

The requested variation proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Votubia was designated as an orphan medicinal product EU/3/10/764 on 4 August 2010. Votubia was designated as an orphan medicinal product in the following indication: treatment of tuberous sclerosis.

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decision(s) P/0124/2016 on the agreement of a paediatric investigation plan (PIP).
At the time of submission of the application, the PIP P/0124/2016 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol assistance

The MAH received Protocol Assistance from the CHMP on 23 June 2011. The Protocol Assistance pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Harald Enzmann Co-Rapporteur: Greg Markey

Timetable	Actual dates
Submission date	30 May 2016
Start of procedure:	18 June 2016
CHMP Co-Rapporteur Assessment Report	11 August 2016
CHMP Rapporteur Assessment Report	15 August 2016
PRAC Rapporteur Assessment Report	11 August 2016
PRAC Outcome	2 September 2016
CHMP members comments	5 September 2016
Request for supplementary information (RSI)	15 September 2016
Joint CHMP Rapporteur Assessment Report	24 November 2016
PRAC Rapporteur Assessment Report	8 November 2016
PRAC members comments	23 November 2016
Updated PRAC Rapporteur Assessment Report	24 November 2016
PRAC Outcome	1 December 2016
CHMP members comments	5 December 2016
Updated CHMP Rapporteur Assessment Report	8 December 2016
Opinion	15 December 2016

2. Scientific discussion

2.1. Introduction

Votubia contains the active substance everolimus, a rapamycin derivative, which acts as selective inhibitor of the mammalian target of rapamycin (mTOR), a serine-threonine kinase within the mTOR-raptor signal transduction complex 1 (mTORC1) which is involved in the regulation of protein synthesis, cell growth, proliferation and survival. Due to its immunosuppressing activity, everolimus was initially developed to prevent allograft rejection following solid organ transplantation. It is approved under the tradenames Certican® and Zortress® in more than 80 countries worldwide for use in these indications. In the EU, everolimus is also approved under the tradename Afinitor® for the treatment of patients with advanced renal cell cancer, advanced neuroendocrine tumours, and hormone receptor-positive advanced breast cancer.

Votubia has been authorised in the EU/EEA through the centralised procedure by Commission Decision in September 2011 for treatment of renal angiomyolipoma and subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC). It is available as tablets (2.5, 5 and 10 mg) and dispersible tablets (2, 3 and 5 mg).

TSC is a rare and debilitating disease with a prevalence of approximately 1 in 6000 live births (Krueger and Franz, 2008). It is an autosomal dominant genetic condition involving the tuberous sclerosis 1 gene (TSC1*)* and/or the tuberous sclerosis 2 gene (TSC2*)*. Deficiency of either gene leads to upregulation of mTORC1 resulting in abnormal cellular growth, proliferation, and protein synthesis, which can cause a variety of benign tumours, or hamartomas, in multiple organ systems including lesions in the kidney, brain, skin, lung and heart. Skin lesions occur in nearly all patients and are key to the recognition and diagnosis of TSC. Hamartomas in the brain usually present themselves in the form of subependymal nodules. Up to 20% of patients with TSC demonstrate progressive growth of the subependymal nodules, such that it becomes Subependymal giant cell astrocytoma (SEGA), which represents a significant medical risk for the patients, including potential sudden death secondary to acute hydrocephalus (Adriaensen et al. 2009). The majority of patients with TSC also have numerous bilateral renal angiomyolipoma.

In addition to growth abnormalities, patients with TSC usually develop epilepsy and neuro-psychiatric problems such as developmental delay, mental retardation, and autism (Curatolo et al. 2002; Levine et al. 2006). Epilepsy has been reported in up to 90% of individuals with TSC (Wong 2010), with an onset usually in the first years of life (with 82% before 3 years of age). A variety of seizure types have been reported including infantile spasms, simple partial, complex partial and secondarily generalized tonic-clonic seizures, as well as absence, tonic, atonic, clonic, myoclonic and tonic-clonic generalized seizures (Holmes and Stafstrom 2007, Wong 2010). In a Massachusetts General Hospital retrospective study that included all children and adults with TSC seen between Jan-2002 and Oct-2008 (291 patients), the most common seizures observed were complex partial seizures (86.9%, including those with secondary generalization) and infantile spasms (46.4%). The vast majority of patients (93.2%) had evidence of at least one seizure phenotype with a clear focal onset (Chu-Shore et al. 2010). Furthermore, children with TSC often develop epileptic encephalopathies such as Lennox-Gastaut syndrome and 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 (Joinson et al. 2003; Bolton et l. 2002; Goh et al. 2005; Yates et al. 2011; Bolton et al. 2015).

Seizures associated with TSC are treated with antiepileptic drugs (AEDs) or methods such as epilepsy surgery, vagal nerve stimulator or ketogenic diet (Jobst 2009; Wong 2010). Other than for infantile

spasms in TSC for which vigabatrin is usually recommended as first line treatment (Tibussek et al. 2016, Krueger and Northrup 2013, Pellock et al. 2010), there is little evidence to guide effective anticonvulsant treatment. The published literature suggests that TSC-seizures may respond to one or several AEDs approved for the treatment of partial seizures, e.g. topiramate, lamotrigine, levetiracetam, oxcarbazepine, and clobazam (Franz et al. 2000; Franz et al. 2001; Collins et al. 2006; Jennesson et al 2013). The prevalence of medically refractory epilepsy in TSC even with adequate trials of currently available anticonvulsant medications has been reported as high as approximately 60% (Krueger and Northrup 2013, Jennesson et al. 2013, Chu-Shore et al. 2010).

Although the mechanisms causing epilepsy in TSC are not entirely understood, dysregulation of development and maintenance of cortical structure and function because of mTOR dependent processes may play a role in the development of epilepsy and neuropsychiatric disorders. While abnormal mTOR activity has been recognised to contribute to tumorigenesis in TSC, more recent data also implicate genetically driven, hyperactive mTOR signaling in epilepsy (Crino 2010; Wong 2010).

With the present application, the MAH seeks to extend the indication of Votubia (in TSC patients) as adjunctive treatment of patients aged 2 years and older with refractory seizures associated with TSC. The application is supported by one pivotal study (CRAD001M2304, hereafter referred to as study M2304 or EXIST-3), a double-blind, randomized, multi-center, Phase III trial evaluating the efficacy and safety of everolimus in patients (1 to 65 years in Europe, and 2 to 65 years for the rest of the world) who have refractory TSC -seizures while being on a stable regimen of 1 to 3 AEDs. This study was designed to compare the reduction in frequency of TSC-seizures for patients treated with everolimus titrated towards a target everolimus trough concentration of 3-7 ng/mL or 9-15 ng/mL, versus matching placebo.

Notably, given that seizures and SEGA occur in a widely overlapping (mainly but not exclusively paediatric) population, seizures have been recorded as secondary endpoints of both SEGA trials C2485 and M2301 mainly under the assumption that SEGA volume and seizure frequency are strongly correlated. When these data were previously assessed, some evidence of seizure reduction by everolimus could be derived from study C2485, whereas this could not be confirmed in trial M2301. Consequently, the current SEGA indication states that the evidence is based on analysis of change in SEGA volume and that further clinical benefit, such as improvement in disease-related symptoms, has not been demonstrated.

2.2. Non-clinical aspects

Apart from an updated environmental risk assessment (ERA), no new non-clinical data have been submitted to support this application, which was considered acceptable by the CHMP. Relevant data from the scientific literature supporting an effect of mTOR inhibitors in TSC-seizure control are summarised below.

2.2.1. Pharmacology

Primary pharmacodynamic studies

Besides non-clinical studies showing efficacy of everolimus in a variety of cancer models, several *in vitro* and *in vivo* tests support a role of mTOR in TSC-seizures and epileptogenesis.

Genetically modified mice with homozygous deletion of TSC1 (Uhlmann et al 2002, Fraser et al., 2004) or TSC2 (Way et al 2009) displayed seizure activity and early death. Early-treatment paradigms using mTOR inhibitors including rapamycin were shown to prevent early death, delay epileptogenesis and alter histopathologic phenotypes such as astrogliosis and neuronal enlargement (Zeng et al 2008; Meikle et al 2008; Goto et al 2011, Carson et al 2012; Way et al 2012). A causal association of hyperactive mTOR to

the acquired seizures was demonstrated.

Hyperactive mTOR pathway was also seen in multiple non-genetically defined epilepsy mouse models. However, unlike models with genetically defined mTOR hyperactivation, the causality of hyperactive mTOR pathway to the acquired seizures has not been established. mTOR inhibitors had antiepileptogenic activity in some but not all of these acquired seizure models.

Huang et al. (2010) showed that mTOR is hyperactive in rat brains with chronic spontaneous seizures. Inhibition of the mTOR pathway by rapamycin markedly reduces seizure activity, along with inhibition of mossy fiber sprouting. Zeng et al. (2008) also reported that mTOR signalling is increased in a mouse model of TSC and mTOR inhibition. The overexpression of mTOR however prevented development of epilepsy in this model. The authors further investigated the role of the mTOR pathway in the kainate model of epilepsy in male rats (Zeng et al., 2009), showing that the mTOR pathway is strongly activated with a biphasic time course after kainate-induced status epilepticus, and this mTOR activation could be blocked by rapamycin treatment. Furthermore, while not altering the acute characteristics of status epilepticus, rapamycin pre-treatment counteracted known effects of kainate status epilepticus on neuronal death, neurogenesis, and mossy fiber sprouting. Finally, both pre- and posttreatment with rapamycin significantly decreased the development of chronic epilepsy.

In other models, no convincing response to mTOR inhibition was shown, including experiments by Sliwa et al. (2011) to investigate if rapamycin post-treatment influences epileptogenesis in the amydgala stimulation model of temporal lobe epilepsy in rats and by Buckmaster and Lew (2011) of long-term systemic treatment with rapamycin, beginning one day after pilocarpine-induced status epilepticus in mice.

Several *in vitro* experiments further support the hypothesis that mTOR plays a central role in TSC-related seizures. Two *in vitro* neurophysiology studies by Daoud et al. (2007) and Ruegg et al. (2007) showed no pronounced acute action of rapamycin on neuronal firing or excitatory neurotransmission in hippocampal neurons. At doses supramaximal for the inhibition of mTOR pathway activity in cells (200 nM), rapamycin did not alter sodium or potassium currents recorded in cultured hippocampal neurons (Ruegg et al 2007). No consistent effect on synaptic events and firing frequency of neurons was seen. Daoud et al (2007) tested a high dose of rapamycin (250 nM) in ex vivo hippocampal brain slices from wild type animals. Rapamycin had no effect on evoked field excitatory postsynaptic potentials recorded in CA1 hippocampus in response to Schaffer collateral stimulation. Higher doses of 500 nM and above increased the amplitude of the field excitatory postsynaptic potential, but such an effect is not consistent with anti-seizure activity.

Bateup et al. (2013) used *in vitro* and *in vivo* approaches to compare neural network activity in cultured wild type and TSC1 knockout mouse hippocampal neurons using multi-electrode arrays. They found that loss of TSC1 results in hippocampal network hyperexcitability manifested by elevated spontaneous activity in dissociated cultures and increased seizure susceptibility *in vivo*. Prolonged high levels of network activity chronically engage activity-dependent homeostatic pathways that secondarily alter the biochemical, functional, and transcriptional state of neurons *in vitro*. The loss of inhibition and upregulation of network activity, as well as many of the pursuant secondary responses in TSC1 knockout neurons, could be reversed by treatment with 50 nM rapamycin. A prominent but slow, gradual reduction in firing frequency in TSC1 knockout neurons, but only a very modest effect on the firing rate of wild type neurons was observed. The time course was considered more consistent with a correction of the transcriptional or translational changes induced by mTOR hyperactivity and consequent cellular changes. The results support the idea that TSC is an mTOR-overactivation syndrome which can be normalized with rapamycin as inhibitor.

2.2.2. Ecotoxicity / environmental risk assessment

The MAH submitted an updated environmental risk assessment (ERA) for everolimus including Phase I and Phase II assessment in accordance with Guideline EMEA/CHMP/SWP/4447/00 corr 2. A daily dose of 20 mg everolimus was assumed as a worst case scenario.

Assessment of persistence, bioaccumulation potential and toxicity (PBT) for everolimus resulted in a n-octanol/water partition coefficient for everolimus of LogKow 4.0, which is below the threshold of 4.5 and thus no screening for PBT was needed.

Using the default fraction of market penetration (F_{pen}) of 1%, the predicted environmental concentration in surfacewater ($PEC_{surface\ water}$) was calculated at of 0.1µg/L which was above the action limit, thus requiring Phase II environmental fate and effect analysis. The Phase II Assessment Tier A took into account the marketing forecast figures for the five years following the submission of the present ERA. The forecasts included all indications treated with everolimus under the brand names of Afinitor®, Votubia® and Certican® and thus cover the overall possible release of everolimus into the environment after patients' use of these products. Based on these figures, a refined $PEC_{surfacewater}$ has been calculated at 0.27 ng/L. The $PEC_{groundwater}$ was calculated resulting in a value of 0.068 ng/L.

The results of additional tests of the physico-chemical properties and fate as well as Phase IIa and b studies are summarised in Table 1. Based on the results of these tests, everolimus is considered to constitute no significant risk to surface waters, sewage treatment plants, groundwater and sediments.

Table 1 – Summary of main study results

Substance (INN / Invented Name): everolimus			
CAS-number (if available): 159351-69-6			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD117	4.0	Potential PBT: N
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default	0.1	µg/L	> 0.01 threshold Y
$PEC_{surfacewater}$, refined	0.00027	µg/L	acceptable for risk assessment Phase II
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	Koc sludge : 1654-3294 L/kg Kd sludge: 470 – 1029 L/kg Koc soil: 50197->2348392 L/kg Kd (soils): 432 –> 36635 L/kg	

Ready Biodegradability Test	OECD 301	2% in 28d			Not biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ =0.29 resp. 0.35 d $DT_{50, sediment}$ =26.9 resp. 24.4 d $DT_{50, whole system}$ =3.1 resp. 2.0d % shifting to sediment = Yes: 25.6 resp. 17.7% (14d) Metabolite: M4 max. 28.6%, not identified, but DT_{50} calculated: $DT_{50 whole system}$: 2.5 resp. 5.1 d			
Phase IIa Effect Studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition (*Pseudokirchneriella subcapitata)*	OECD 201	NOEC	1.5	µg/L	
Daphnia sp. Reproduction *(Daphnia magna)*	OECD 211	NOEC	0.014	µg/L	
Fish, Early Life Stage Toxicity *(Brachydanio rerio)*	OECD 210	NOEC	2.1	µg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{50}	>1000	mg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	25-28	L/kg	5 % lipid
Sediment dwelling organism (*Chironomus riparius)*	OECD 218	NOEC	2.5	mg/kg	

2.2.3. Discussion on non-clinical aspects

No new non-clinical data have been submitted by the MAH, which was considered acceptable by the CHMP in light of the available data from previously conducted non-clinical studies with everolimus as well as from the scientific literature. Relevant pharmacology data from both animal models and *in vitro* tests support a central role of mTOR in TSC-associated seizures. However, the exact mechanism of action of mTOR inhibitors in the reduction of seizures associated with TSC was not fully elucidated at the time of this report.

Based on an updated ERA taking into account the proposed extended target population, the CHMP agreed that everolimus does not constitute a significant risk to surface waters, sewage treatment plants, groundwater and sediments.

2.2.4. Conclusion on the non-clinical aspects

The CHMP was of the view that the present application was acceptable from a non-clinical perspective. Furthermore, based on the updated ERA, everolimus is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

Good Clinical Practice (GCP)

The MAH confirmed that all clinical trials were performed in accordance with GCP.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 2 - Tabular overview of clinical studies

Study no.	Design	Population	Patients and treatments	Treatment duration	Endpoints
M2304 99 centers 25 countries	Multicenter, double-blind, randomized 1:1.09:1 ratio, stratification by age, parallel-group, Phase III Efficacy and safety	Male or female patients with confirmed TSC who have refractory partial-onset seizures on a stable dose of 1 to 3 AEDs, age 1 to 65 year-old*.	Total: 366 1-3 AEDs **+** Everolimus with titration to trough range of 3-7 ng/mL (N=117) (low trough, LT) **OR** Everolimus with titration to trough range of 9-15 ng/mL (N=130) (high trough, HT) **OR** Matching placebo (N=119)	Until 48 weeks after the last patient has completed the 18 weeks of the Core phase Analysis of primary endpoints were done during the 12-week maintenance phase	Primary: EMA: Response rate, where response means at least a 50% reduction from Baseline in protocol defined partial-onset seizure frequency. **OR** FDA: Percentage reduction from Baseline in protocol defined partial onset seizure frequency. Secondary & exploratory: Seizure free rate 25% reduction from Baseline in seizure frequency Treatment duration QoL Scores of the Vineland Adaptive Behavior Scales II and the Wechsler Non-Verbal Scale of Ability PK exposure response analysis Safety and tolerability

* The youngest patient enrolled in the study was 2.2 years at Baseline.
AEDs: antiepileptic drugs – **QoL**: quality of life
Source: [Study M2304]

2.3.2. Pharmacokinetics

The Pharmacokinetics (PK) of everolimus have previously been investigated in a comprehensive study programme including characterization of single-dose PK in healthy subjects, multiple-dose PK in oncology patients and transplant patients, mass balance (absorption, distribution, metabolism, excretion), drug-drug interactions, exposure-response relationships, bioequivalence and relative bioavailability of formulations, cardiac safety, food effects on drug absorption, PK in special populations (liver impairment, renal impairment, paediatric), and population PK in transplant and oncology patients. These data have been assessed during the review of the initial marketing authorisation application and subsequent post-authorisation procedures.

Data have shown that everolimus is primarily excreted through the fecal route (80%) while only a minor amount is excreted in urine (5%). Everolimus is primarily eliminated by metabolism via Cytochrome p450 (CYP) 3A4 and is a substrate for (PgP). Due to significant increases in exposure of everolimus, co-administration with strong CYP3A4 inhibitors should be avoided. If concomitant use of moderate inhibitors of CYP3A4/PgP is required, reducing the dose by 50% is recommended. If concomitant use of strong inducers of CYP3A4/PgP is required, higher or doubling of the dose is recommended.

To support the present application, additional data were presented from the pivotal study M2304, comparing the effect of everolimus and placebo as adjunctive therapy on seizure frequency in paediatric and adult patients who have refractory TSC-seizures and were already receiving 1 to 3 AEDs at Baseline (see section 2.4.2. for further details on the study methods). This study compared the reduction in frequency of TSC-seizures for patients treated with everolimus titrated toward low (3-7 ng/mL, LT) or high (9-15 ng/mL, HT) target pre-dose concentrations.

During the 6-week Titration period of the Core phase of the study, pre-dose PK blood samples for the determination of everolimus concentration in blood (c_{min}) were collected. Patients were expected to achieve the planned target trough range during this dose-titration period. After the completion of the Titration period, patients continued their current dose level during the 12-week Maintenance period. Pre-dose PK blood samples were to be collected every 4 weeks during the Maintenance period, with the potential for further titration during this time. In addition, pre-dose blood samples for everolimus concentration determination should have been collected 2 weeks after any everolimus dose adjustment, and after initiation or dose adjustment of a CYP3A4/PgP) inducer/inhibitor. Trough concentrations and dose-normalized c_{min} (ng/mL per mg dose and ng/mL per mg/m^2 dose) were summarized for each everolimus treatment arm by time window and by age subgroups (1 to <6, 6 to <12, 12 to <18, and ≥ 18 years old) and by the use of CYP3A4 inducer.

Furthermore, AED concentrations were measured as everolimus is metabolized by the CYP3A4 pathway in the liver, and to some extent in the intestinal wall, and since many of the concomitantly administered AEDs were also metabolized by the CYP3A4 pathway. The concentration levels of 12 commonly prescribed AEDs listed below 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.

Pre-dose blood samples were collected at Visits 1, 2, 3, and 5 for the measurement of AED concentration. Patients weighing 12 to 20 kg, due to their small blood volume, were not required to provide PK AED blood samples. Effect of everolimus on the exposure of AEDs was assessed by comparing the AED concentrations at Visits 1 and 2 (AEDs alone) and at Visits 3 and 5 (AEDs plus everolimus).

PK results of Study M2304

Pre- and inline-validations of the methods used to determine everolimus and AED plasma concentrations have shown adequate sensitivity, precision, accuracy and specificity to determine everolimus and the concomitant medications at the concentration levels expected in real samples.

Concentrations of everolimus from study M2304 were generally consistent with historical ranges in TSC population.

- Pre-dose everolimus concentration (c_{min})

The majority of patients randomized to the everolimus LT treatment group achieved the target c_{min} range of 3 to 7 ng/mL after the first starting dose at Week 1 and the median c_{min} was maintained within the target range during the entire Core phase. At Week 18, the everolimus LT group had a median c_{min} of 5.05 ng/mL.

The HT treatment group had similar c_{min} values as the LT group at Week 1 because the same starting doses were administered to both treatment arms. The mean and median c_{min} values for the HT group gradually increased from Week 1 to the end of the Core phase at Week 18 as a result of dose titrations. At Week 18, the median c_{min} for the HT group was 8.32 ng/mL. Approximately 60% of the patients in the HT group were below the lower limit of the target c_{min} range (9 ng/mL) at the end of the Core phase.

Table 3 – Trough Concentration of Everolimus by Time Window during the Core Phase of Study M2304 Safety Set – Confirmed PK Sample Set)

	Time window					
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
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100
Geo-mean = Geometric mean = exponential of the mean of the log transformed data

During the Extension phase, c_{min} for the LT arm remained within the 3-7 ng/mL range. For the HT arm, c_{min} values were maintained at the level attained by week 18 (end of Core phase) for the duration of the Extension phase.

Time-normalized c_{min} was an estimate of the daily trough concentrations for a patient averaged over a time interval Δt between consecutive assessment times (t1, t2). Median time-normalized c_{min} during the

Maintenance period of the Core phase was 4.65 for the LT and 7.27 for the HT group, respectively, with a considerable overlap of concentrations between the two groups.

Impact of age on everolimus pre-dose concentration

Patients aged ≥ 18 years tended to have lower median c_{min} values during the Core phase. At Week 1 of the Core phase in Study M2304 the median c_{min} for patients ≥ 18 years of age was below 5 ng/mL and was the lowest compared to patients of other age ranges. While starting doses were selected according to patient age, titration doses (2 or 4 mg, depending on the use of CYP3A4 inducers or inhibitors) were the same for all patients which led to lower mg/m^2 doses for older patients.

Impact of CYP3A4/PgP inducers/inhibitors on everolimus pre-dose concentration

In general, use of CYP3A4/PgP inducers during the Core phase was associated with lower concentrations, despite a higher start- and titration dose for patients receiving inducers. A linear mixed effect model indicated that c_{min} associated with the use of CYP3A4/PgP inducers was statistically lower than when inducers were not administered, with a geometric mean ratio of 0.455 (90% CI: 0.316, 0.656). Furthermore, c_{min} associated with the use of CYP3A4/PgP moderate and/or strong inhibitors was statistically higher than when inhibitors were not administered, with a geometric mean ratio of 2.371 (90% CI: 1.657, 3.392).

- Effect of everolimus on AED concentration

Treatment with everolimus was associated with minor increases (approximately 10%) in the concentrations of the following AEDs:

- Carbamazepine (geometric mean ratio post/pre everolimus: 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])

Everolimus had no impact on the other AEDs evaluated in the study.

2.3.3. Pharmacodynamics

Mechanism of action

Everolimus is a selective inhibitor of the serine-threonine kinase mTOR within the TORC1 complex, that acts as a nutrient sensor and monitor of the cellular metabolic state, regulating protein synthesis and ultimately cell growth and cell proliferation (including angiogenesis) and survival.

TSC is caused by mutations in either the TSC1 or TSC2 genes with consequent mTOR (mammalian target of rapamycin) hyper-activation within the mTORC1 complex, which obtains signals from many upstream inputs, and propagates the information via regulation of multiple downstream pathways. Up to 80 to 90% of individuals with TSC are affected by epilepsy (Wong 2010). Polymorphic seizures with focal onset are observed in most TSC patients. The onset of seizures typically occurs in the first year of life (with 82% before 3 years of age). Adults also remain at risk and up to 12% of patients with TSC develop epilepsy at their adult age, indicating that TSC patients are at an increased risk of epilepsy throughout their lifetimes (Chu-Shore et al. 2010). Seizures in TSC are presumed to originate within or close to the focal region of cortical abnormality (i.e. mainly cortical tubers) [Holmes and Stafstrom, 2007; Wong, 2008]. It is also discussed that mTOR dysregulation in neurons could directly influence a variety of downstream mechanisms of epileptogenesis (such as alterations in neurotransmitter receptor and ion channel expression and neuronal and synaptic organization).

In fact, human genetic data implicate genetically driven, hyperactive mTOR signaling in epilepsy [Crino 2010; Wong, 2010]. Mutations in upstream mTOR regulatory genes, including TSC1 and TSC2 have been associated with seizure disorders [Mirzaa and Poduri 2014]. Additionally, somatic mutations in mTOR itself have recently been identified in seizurogenic tissue in surgical resections from epilepsy patients with focal cortical dysplasia [Lim et al. 2015, Jansen et al. 2015]. These mTOR mutations have also been shown to increase mTOR pathway activity in cell lines and in primary rodent neurons [Mirzaa et al. 2016]. Introduction of these mTOR mutations into mouse cerebral cortex via in utero electroporation causes seizures, which can be reversed by treatment with the mTOR inhibitor rapamycin [Lim et al. 2015]. Overall, these data suggest that hyperactive mTOR function induces epilepsy, as occurs in patients with mutations in TSC1 or TSC2, and that mTOR inhibitors reduce seizure activity by inhibiting this hyperactive mTOR signalling.

The specific cellular mechanisms by which mTOR hyper-activation elicits epileptogenesis are less certain. Components of the mTOR signalling pathway are widely expressed in the nervous system and TSC proteins are also highly abundant in the adult central nervous system. It is also known that mTOR signalling is involved in regulating cell proliferation, autophagy, metabolism, synaptogenesis and growth of dendrites and axons, hence is important during brain development and in maintaining proper mature brain functions.

A general concept for epileptogenesis is that epilepsy results from an imbalance between excitatory and inhibitory forces in the brain. A defect in the involved mechanisms secondary to cellular changes induced by mTOR hyper-activation could disrupt this physiologic balance of the neurotransmitters and lead to epileptogenesis and seizure generation.

Primary and Secondary pharmacology

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. Response rate and percentage reduction in seizure frequency was analysed in the Maintenance period during the Core phase by time normalized c_{min} categories (<3, 3 to 7, >7 to <9, 9 to 15, and >15 ng/mL).

For response rate, logistic regression was used to model the probability of response. The model was stratified by age subgroup and adjusted for additional risk factors if appropriate.

A linear regression model was used to characterize the impact of exposure on the post-Baseline average weekly seizure frequency. The model includes Baseline seizure frequency and time-normalized 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 time-normalized c_{min} in defined time intervals during the Core phase. The model was adjusted by the Baseline seizure frequency. Other covariates were included if appropriate.

A trend indicative of better seizure frequency response/reduction was evident at higher time-normalized c_{min}. No definitive interpretation can be made for the >15 ng/mL group as there were only 2 patients included in this subgroup.

Table 4 – Response rate and percentage reduction from Baseline in seizure frequency by time-normalized c_{min} - Safety Set (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

Additional model-based analyses showed a strong, consistent, and highly statistically significant relationship between exposure and seizure frequency response or post-Baseline seizure frequency.

- Results of a conditional logistic regression analysis for the probability of seizure response versus time-normalized c_{min} stratified by age subgroup indicated that a 2-fold increase in time-normalized 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 time-normalized c_{min}, Baseline seizure frequency was also a significant factor (with an odds ratio of 0.978 [95% CI: 0.959, 0.998]).
- Results of a 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 time-normalized c_{min} there was a statistically significant 28% reduction (95% CI: 12%, 42%) in post-Baseline seizure frequency. Baseline seizure frequency and time-normalized c_{min} were both significant factors.
- Results of a 2-week interval, repeated-measure analysis of the relationship between seizure frequency and time-normalized c_{min} indicated that Baseline seizure frequency, duration of treatment, and time-normalized c_{min} were significant factors for post-Baseline seizure frequency.
- The use of CYP3A4/PgP inducers or inhibitors was not a significant factor in the post-Baseline seizure frequency-exposure analysis.

Finally, a model-based approach was used to determine the lowest time-normalized c_{min} concentration for which the response in seizure frequency (represented by fold change from Baseline in seizure frequency) was statistically different between everolimus and placebo. The results showed that a time-normalized c_{min} of 5.3 ng/mL is the lowest exposure for which the 95% CI of predicted change from Baseline seizure frequency (0.537; 0.695) is not overlapping with the 95% CI of predicted change from Baseline seizure frequency of placebo (0.696; 0.879), indicating a significant difference at that trough concentration.

2.3.4. Discussion on clinical pharmacology

The clinical pharmacology of everolimus has previously been assessed in the context of the initial marketing authorisation application of Votubia and subsequent post-authorisation procedures. This included studies in TSC patients in order to support the current indications of Votubia for the treatment of renal angiomyolipoma and SEGA associated (TSC). Additional supportive data for the present application were provided from the pivotal phase III trial M2304 in patients with refractory TSC seizures, which collected plasma concentrations of everolimus and concomitant AEDs.

As had already been found in earlier studies with everolimus, whereas the majority of patients randomized to the everolimus low trough range (target trough 3-7 ng/mL, LT) treatment group achieved the target c_{min} range of 3 to 7 ng/mL after the first starting dose at Week 1, it was difficult to reach the higher targeted trough concentration range of 9-15 ng/mL (HT group). Approximately 60% of the

patients in the HT group had plasma values below the lower limit of the target c_{min} range (9 ng/mL) at the end of the Core phase.

Patients aged ≥ 18 years tended to have lower median c_{min} values during the Core phase. While starting doses were selected according to patient age, titration doses (2 or 4 mg, depending on the use of CYP3A4 inducers or inhibitors) were the same for all patients which led to lower mg/m^2 doses in the older age range.

In general, use of CYP3A4/PgP inducers during the Core phase were associated with lower everolimus concentrations, despite a higher start- and titration dose for patients receiving inducers. Trough concentrations were approximately halved in patients taking CYP3A4/PgP inducers and doubled in patients taking CYP3A4/PgP inhibitors. This is in line with findings in previous studies.

Although not optimal, no further dose adjustment was considered necessary in case of concomitant use of CYP3A4/PgP inducers given the option of further dose titration until suitable everolimus trough concentrations are achieved. In case a strong inducer is added to an existing everolimus treatment regimen, checking the trough level 2 weeks after initiation of the inducer and assessing tolerability before increasing the dose is recommended. Similarly, monitoring of trough levels 2 weeks after discontinuation of an inducer and dose adjustment, if needed, is recommended.

With regards to concomitant use of CYP3A4/PgP inhibitors, halving the starting dose is recommended (when commencing everolimus therapy) or halving the current dose (during ongoing everolimus therapy) for patients who require addition of CYP3A4/PgP inhibitors to their current treatment regimen. This approach was considered appropriate by the CHMP.

Everolimus had no impact on the plasma concentrations of the majority of concomitant AEDs evaluated in the study. However, small increases of approximately 10% in the plasma concentrations (c_{min}) of carbamazepine, clobazam and the main metabolite of clobazam were observed. The CHMP agreed that these increases were likely not clinically relevant, but it was noted that only changes in c_{min} values were available although the majority of adverse events of AEDs would be presumed to correlate rather with $c_{max.}$ Relevant information was included in the Product Information. Dose adjustment for carbamazepine, a drug with a narrow therapeutic index, may be considered.

Exposure-response analyses showed a trend for better seizure frequency response/reduction at higher time-normalized c_{min}. A time-normalized c_{min} of 5.3 ng/mL was determined as minimum efficacious concentration.

No significant impact of age and use of CYP3A4/PgP inducers on the exposure-response relationship was seen, but the analyses revealed Baseline seizure frequency as a significant factor. However, the analysis with the most straightforward interpretation, the conditional logistic regression analysis for the probability of seizures response versus time-normalized c_{min} stratified by age, resulted in an odds ratio of 0.978 [95% CI: 0.959, 0.998], which was near 1 (see also discussion in section 2.4.4. in relation to clinical relevance).

As for the mechanism of action, everolimus is believed to exert its anti-seizure activity in TSC via mTOR inhibition. In TSC, epileptogenesis has been shown to be linked to the formation of cortical abnormality (i.e. mainly cortical tubers), however there is also evidence that dysregulation of the mTOR pathway may be involved. mTOR regulates protein synthesis and multiple downstream cellular functions that may influence neuronal excitability and epileptogenesis. Overactivation of mTOR results in neuronal dysplasia, aberrant axonogenesis and dendrite formation. However, the exact mechanism of action of mTOR inhibitors in the reduction of seizures associated with TSC is not fully elucidated, and everolimus may act via inhibition of mTOR induced epileptogenesis or via decrease of epileptic foci (e.g. via reduction in cortical tuber load).

2.3.5. Conclusions on clinical pharmacology

The CHMP concluded that the present application was adequately supported by clinical pharmacology data. Relevant information including dose adjustments in case of concomitant use of everolimus with CYP3A4/PgP inducers or inhibitors has been included in the product information.

2.4. Clinical efficacy

The efficacy of everolimus in the adjunctive treatment of paediatric and adult patients with refractory seizures associated with TSC has been investigated in a single, double-blind, randomized, placebo-controlled, Phase III trial (study M2304). To support the present application, interim data (cut-off date: 02 Oct 2015) were provided, which cover all patients having completed the double-blind Core phase of the study.

Supportive data were also presented from previous SEGA studies C2485 and M2301 as well as from the scientific literature.

2.4.1. Dose response study(ies)

No dedicated dose-response studies have been conducted in support of this application.

The selection of the starting dose of everolimus and target trough range for exposure of 3-15 ng/mL to be investigated in two separate dose range groups (LT group: 3-7 ng/mL and HT group: 9-15 ng/mL) in the pivotal study M2304 was based on the patients' body surface area (BSA) and on previously submitted results from study C2485 and M2301 involving largely paediatric TSC patients with SEGA lesions. According to the MAH, in study M2301, an everolimus trough (c_{min}) level of 3-15 ng/mL has shown superior efficacy versus placebo in patients with TSC who have SEGA, with an acceptable safety profile. In addition, there was a significant correlation between SEGA volume reduction and c_{min}. The dose range explored in study M2304 comprised the minimum and maximum target trough range approved for treatment of SEGA treatment (5-15 ng/ml).

2.4.2. Main study

Study CRAD001M2304: A three-arm, randomized, 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

2.4.2.1. Methods

Study M2304 was a three-arm, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of two trough ranges of everolimus given as adjunctive therapy in patients with refractory TSC seizures.

The study consisted of three phases (see also Figure 1):

- Baseline phase: 8 weeks.
- Core phase: 18 weeks (double-blind, placebo-controlled), consisting of a 6-week titration and 12 week maintenance period.
- Extension phase: At least 48 weeks (i.e. up until 48 weeks after the last patient had completed the Core phase), with all patients receiving everolimus, including a transition phase of 8 weeks.

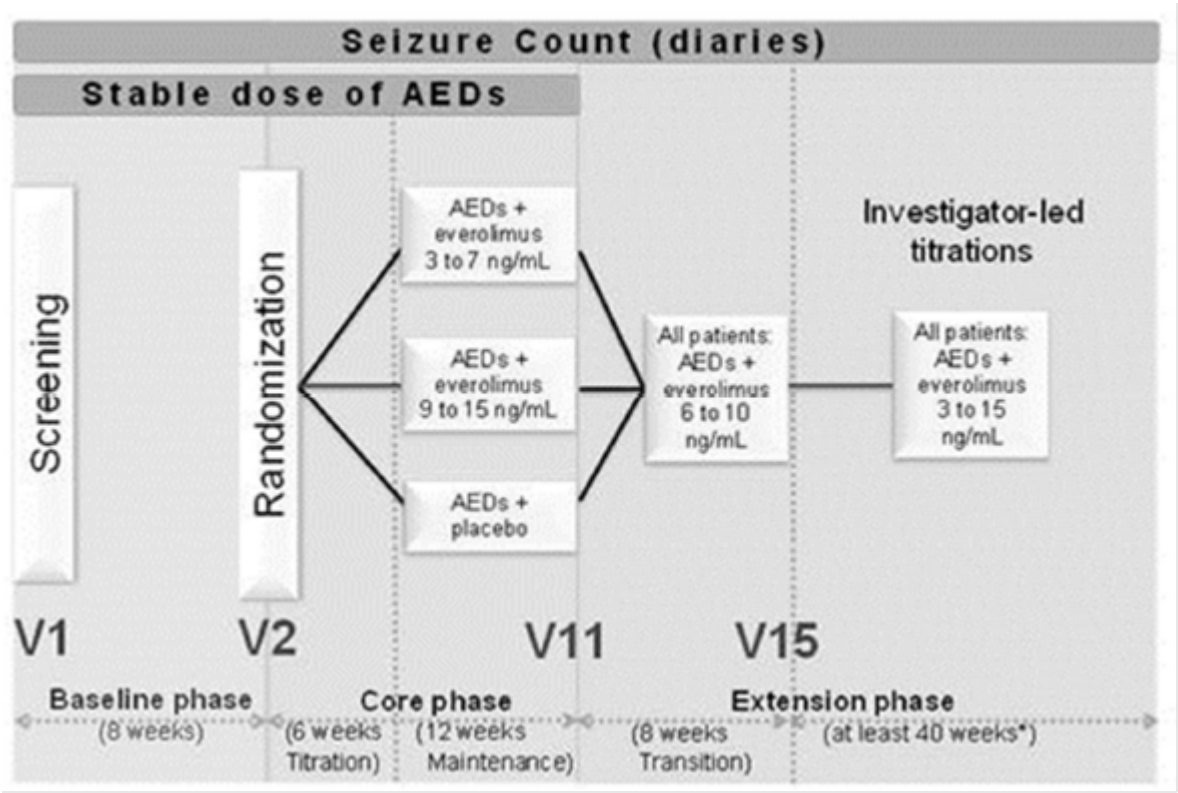

Figure 1 – Design of Study M2301

AEDs= antiepileptic drugs

Note: the figure presents the study schematic as of protocol amendment 2. Prior to amendment 2 the patients randomized to everolimus were to remain on their Core phase everolimus trough dose during the Extension phase, the patients randomized to placebo were to receive everolimus trough dose of 3 to 15 ng/mL during the Extension phase and there was no transition period.

Study participants

Key inclusion criteria:

- Male or female between the ages of 2 and 65 years (except in Europe where the minimum age was set to 1year at the request of the EMA).
- Clinically definite diagnosis of TSC according to modified Gomez criteria (Gomez 1999). *Note:* positive genetic test without definite diagnosis of TSC as per the modified Gomez criteria was not allowed.
- Diagnosis of partial-onset epilepsy according to the classification of the International League Against Epilepsy (Commission on Classification and Terminology of the ILAE, 1989) and revised in 2009 (Berg 2010). This classification was further modified for the purpose of capturing clinical details, and defines partial onset seizures (POS) 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 electroencephalogram (EEG), or
    - any probable seizure with motor signs (non-sensory) that has NOT been documented to be a primary generalized seizure on ictal EEG.

- Uncontrolled partial-onset seizures; must meet the following:
    - At least 16 reported quantifiable (no cluster or innumerable seizures) POS (as defined above) over the 8 week Baseline period with no continuous 21-day seizure-free period between Screening and Randomization visit, as per data captured in daily seizure diaries.
    - Prior history of failure to control POS despite having been treated with two or more sequential regimens of single or combined antiepileptic drugs.
    - 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.
    - Prior epilepsy surgery is allowed if performed at least 12 months before study entry.
- Must be receiving 1-3 AEDs at a stable dose for at least 4 weeks at the start of the 8-week 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 (e.g., carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone).

Key exclusion criteria:

- Patients with seizures secondary to metabolic, toxic, infectious or psychogenic disorder or drug abuse or current seizures related to an acute medical illness.
- Presence of only non-motor partial seizures (Criteria Not Applicable per Amendment 2)
- Patients with TSC who have SEGA in need of immediate surgical intervention.
- Patients under 2 years of age with untreated infantile spasms.
- Within 52 weeks prior to study entry, an episode of status epilepticus.
- 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.
- Patients who require rescue medication during the Baseline phase for more than 6 days.
- Patients with non-TSC related progressive encephalopathy.
- Patients who weigh less than 12 kg.
- Patients being treated with felbamate, unless treatment has been continuous for ≥ 1 year.
- 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.
- Patients with a Score of 4 or 5 on the Suicidal Ideation item within 2 years of Screening, or any “yes” on the Suicidal Behavior 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.
- Maintenance of a diet consisting of <40 g of carbohydrate per day within 3 months of screening.

Treatments

Patients received either everolimus or placebo orally once daily. Everolimus was supplied as 2mg dispersible tablets for oral suspension and respective placebo tablets for oral suspension (dispersible tablets) were used.

Patients receiving everolimus were allocated to one of two treatment arms with titration to an everolimus trough range of 3 to 7 ng/mL (LT-dose) and 9 to 15 ng/mL (HT-dose), respectively. Therapeutic drug monitoring of everolimus was used with a targeted trough concentration range in whole blood to determine the optimal therapeutic dose. To achieve the individual dose, patients may have received a combination of everolimus and placebo tablets (see Blinding below)

The starting dose was the same for the LT-dose and the HT-dose group and was determined based on the patient's age and concomitant use of enzyme inducers as presented in the following table:

Table 5 – Overview of Everolimus Starting Dose

Age	Not receiving CYP3A4/PgP inducer	Receiving CYP3A4/PgP inducer
Patients <10 years	6.0 mg/m^2/day	9.0 mg/m^2/day
Patients 10 to 18 years	5.0 mg/m^2/day	8.0 mg/m^2/day
Patients ≥ 18 years	3.0 mg/m^2/day	5.0 mg/m^2/day

CYP3A4 = cytochrome P450 3A4; PgP = P-glycoprotein.

During the Core phase 6-week Titration period, up to 3 dose adjustments could be made to reach the targeted everolimus trough range. Dose titration was performed via Interactive Response Technology in a blinded fashion by whole increments of 2 mg (patients not taking CYP3A4/PgP inducers) and 4 mg (patients taking CYP3A4/PgP inducers) until each patient reached their assigned target trough range.

Further titration was also allowed during the Maintenance phase, if necessary in order to reach the targeted trough range. For patients who did not tolerate the protocol-specified dosing schedule, dose adjustments or interruptions were permitted.

Concomitant treatment, AED therapy, and rescue medication

Patients were required to be taking 1 to 3 concomitant AEDs during the Baseline and Core phases of the study. The specific drugs and doses of these medications were to be stable 28 days prior to the Screening visit and throughout the Core phase of the study.

Rescue medication was permitted, but only for a period that did not exceed 6 cumulative days during the Baseline phase of the study and did not exceed 7 consecutive days or a total of 14 cumulative days during the Core phase of the study. Use of rescue medications for a longer duration was considered as treatment failure and the patient was to be discontinued from trial therapy. The choice of rescue medications (e.g., buccal midazolam, rectal diazepam and other benzodiazepines) to provide additional seizure control was to follow the local institution's practice.

Objectives

The primary objective was to compare the effect of each of two trough ranges of everolimus (3-7 ng/mL and 9-15 ng/mL) versus placebo in reducing TSC seizure frequency in patients with TSC who were taking one to three AEDs.

Secondary objectives included comparison of each of the two everolimus trough ranges versus placebo with respect to the ability to completely suppress TSC seizures, the proportion of patients with ≥ 25% reduction from Baseline in average weekly TSC seizure frequency, distribution of reduction from Baseline in seizure frequency, and seizure-free days. Furthermore to evaluate safety of each everolimus trough range in the study population, the relationship between everolimus concentration and efficacy/safety

endpoints, the impact of everolimus on pre-dose exposures of AEDs and the effect of the two everolimus trough concentrations on long-term seizure reduction.

Outcomes / endpoints

Two separate definitions of the primary efficacy endpoint were used. For the purpose of registering the present application in the EU, 50% response rate was used as the primary variable. Percentage reduction in seizure frequency [primary endpoint for the USA/ Food and Drug Administration (FDA)] was a secondary endpoint. Both outcome measures were based on calculation of average weekly seizure frequencies during Baseline and Maintenance period.

TSC seizures counted in this trial were defined as seizures with motor signs that have not been documented to be primary generalized seizures on EEG. Protocol Amendment 2 further extended this definition by including also the sensory seizures (without motor sign) confirmed to be partial-onset by ictal EEG.

The 50% response rate was defined as percentage of patients with a reduction from Baseline in TSC seizure frequency of at least 50% during the maintenance period of the Core phase of the study.

Secondary efficacy endpoints:

- Percentage reduction from Baseline in TSC seizure frequency during the maintenance period of the Core phase.
- Seizure-free rate, i.e. 100% reduction in TSC seizure frequency during maintenance period of the Core phase
- Proportion of patients with ≥ 25% reduction from Baseline in TSC seizures (maintenance period)
- Categorized reduction from Baseline in TSC seizure frequency:
    - exacerbation ≤ -25 %,
    - no change: > -25 % to < 25 %,
    - 25% response: ≥ 25% to < 50%,
    - 50% response: ≥ 50 % to < 75%,
    - 25% response: ≥ 75% to < 100%,
    - Seizure-freedom: 100%
- Frequency of seizure free days (per 28 days; maintenance period)
- Time from randomization to treatment discontinuation.
- Long-term evaluation of seizure frequency (TSC seizures): 50% response rate and percent reduction from Baseline, and seizure free-days in TSC seizure by time interval over the Extension phase.
- Change in quality of life (QoL) scores (Quality of Life in Childhood Epilepsy Questionnaire [Qolce] for patients ≤ 10 years, Quality of Life in Epilepsy Inventory for Adolescents-48 [Qolie-AD-48] for patients 11 to ≤ 17 years, Quality of Life in Epilepsy Inventory-31-Problems [Qolie-31-P] for patients ≥ 18 years).

Exploratory efficacy endpoints included subgroup analyses such as seizure frequency by age (1 to < 6 years, 6 to < 12 years, 12 to < 18 years, and ≥ 18 years) and seizure frequency by type of partial-onset and generalized onset seizure. For the latter, the 50% response rate and percentage reduction in weekly seizure frequency, were summarized by differences in each everolimus trough range and the placebo arm for three different types of POS [simple partial (IA), complex partial (IB), secondary generalized (IC)], for (focal or generalized onset) convulsive Grand mal seizures plus drop attacks (IC3-5+IID,IIE, IIF) as well

as for (focal onset) generalized tonic-clonic seizures (IC4) at Baseline separately. Furthermore, 50% response rate and percentage reduction in seizure frequency were recalculated for other seizure types namely, generalized onset seizures (seizure codes IIA1, IIA2, IIB, IIC, IID, IIE, IIF and IIG). Finally, seizure frequency by TSC1/TSC2 mutation status, by number of concomitant AEDs and in patients diagnosed with SEGA at Baseline were investigated.

Sample size

Assuming a 50% response rate of 15% in the placebo arm and 35% in each of the two everolimus arms, 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-Haenszel (CMH) chi-square test, and assuming balanced randomization (i.e. 115 patients per randomization arm).

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

Randomisation

Patients who fulfilled all inclusion/exclusion criteria were randomized via Interactive Response Technology to one of the 3 treatment arms in a 1:1:1 ratio in order to obtain 115 subjects in each treatment arm. When a sample size increase of 10 patients became necessary (see above), a number of blocks with randomization ratio of 1:2:1 were inserted 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 randomization ratio of 1:1.09:1).

Randomization was stratified by age group at randomization (1 to <6 years, 6 to <12 years, 12 to <18 years and ≥ 18 years). A minimum number of paediatric patients were randomized in the following age groups: 1 to <6 years [40 patients], 6 to <12 years [40 patients], and 12 to <18 years [40 patients].)

Blinding (masking)

The study was double-blind. Blinding (of the Investigator, patient, and Sponsor) of the Core phase of the study was maintained during the Extension phase until the results for the Core phase became available (no individual patient unblinding was performed at entry into the Extension phase). Unblinding only occurred in the case of patient emergencies.

To maintain the blind throughout the study, placebo tablets for oral suspension (dispersible tablets) were formulated to be indistinguishable from the everolimus (2 mg) dispersible tablets used in the study. Study drug was packaged in blister packs and placed in boxes with colour coded labels including either everolimus or placebo tablets. At each visit a patient was to receive one or multiple boxes of medication of one or both colour labels. Doses were titrated via Interactive Response Technology in a blinded fashion until each patient reached their assigned target trough range. Patients on placebo had random increases and decreases in number of tablets taken to simulate titration and to maintain the blind. Patients in the low trough group had random increases and decreases in placebo tablets to simulate titration for the high trough group.

Statistical methods

Analysis sets:

- The Full Analysis Set (FAS) comprising all patients randomized according to the intent-to-treat principle,
- the Safety Set comprising all patients who received at least one dose of study treatment and had at least one post-Baseline safety assessment in the Core phase,
- the Per-protocol Set (PPS) consisting of a subset of the patients in the FAS who were compliant with the protocol requirements, were evaluable for efficacy, and who completed a minimum exposure requirement,
- the Long-term Evaluation sets (efficacy and safety) comprised all patient data on everolimus in the study during the Core phase and Extension phase.

PK analyses were performed in patients from the Safety Set and Long-term Evaluation Safety Set with valid c_{min} collected prior to dose administration.

The FAS was used for the primary analysis and the analyses of both response rate and percentage reduction in seizure frequency was repeated in the PPS.

The majority of the efficacy assessments were based on seizure counts/information as provided in the patient diaries to be completed by the patient him-/herself or the caregiver. An independent review of the seizure types being recorded by the patient was performed by the Epilepsy Study Consortium in conjunction with the Investigator.

The 50% response rates in the maintenance period of the Core phase were compared between each everolimus arm versus the placebo arm, with a Bonferroni-Holm procedure implemented to control the overall experiment-wise alpha level at 2.5% one-sided. CMH tests stratified by age were used and this stratification was also used for randomization (1 to < 6, 6 to < 12, 12 to < 18, ≥18 years). Confidence intervals (CIs) for response rates were calculated as exact 95% CIs according to Clopper and Pearson. In addition, odds ratios with two-sided 95% Wald confidence limits were calculated as a measure of association between treatment and response from a logistic regression model stratified by age subgroup at randomization.

Percentage reduction in seizure frequency was analysed using rank analysis of covariance (ANCOVA), stratified by age subgroup with Baseline seizure frequency as a covariate. Again, the Bonferroni-Holm procedure was used as a multiplicity correction to control the family-wise type I error rate at 2.5% one-sided. The median percentage reduction from Baseline was presented with 95% bootstrap CIs. There was no adjustment to handle the multiple tests (primary endpoint (response rate) and secondary endpoint (percentage reduction in seizure frequency)). The p-values reported for this secondary endpoint are therefore only supportive in nature.

Sensitivity analyses were pre-specified to assess the robustness of the primary analysis. The sensitivity analyses included an analysis considering patients who discontinued before the end of the Core phase as non-responders and with no change from Baseline in seizure frequency; an analysis considering the calculation of seizure frequency across the entire Core phase (including titration period as well as maintenance period) and an analysis using different imputation methods for missing daily seizure data analysis.

Amongst the secondary endpoints, seizure freedom was presented as rates for each treatment arm in the FAS with exact 95% CIs and the odds ratios versus placebo derived from logistic regression models stratified by age subgroup. The proportion of patients with ≥ 25% reduction from Baseline in TSC seizure frequency, is equivalent to the primary endpoint for response rate except for a lower threshold of ≥ 25%

reduction from Baseline. The proportion of patients were 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. Reduction from Baseline in TSC seizure frequency were presented as distribution of reduction from Baseline in seizure frequency. Frequency of seizure-free days were presented as change from Baseline in frequency of seizure-free days per 28 days by treatment arm. Time from randomization to treatment discontinuation using Kaplan-Meier curves and summary statistics as well as hazard ratio for everolimus arms versus placebo were obtained from a Cox proportional hazards model stratified by age subgroup. Descriptive statistics for the overall quality-of-life score and subscale scores were presented by time point in the FAS for each questionnaire. Change from Baseline to the end of the Core phase in the overall quality-of-life scores were analyzed 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, were presented.

For all exploratory endpoints, response rates are presented with exact 95% CIs, and the median percentage reduction in seizure frequency are presented along with 95% bootstrap CIs.

2.4.2.2. Results

Participant flow

A total of 366 patients were randomized (all of whom received at least one dose of treatment): 117 to the everolimus targeted low-trough arm (LT), 130 to the everolimus targeted high-trough (HT) arm, and 119 to treatment with placebo. Thus, of the 432 patients enrolled, approximately 15% were not subsequently randomized to treatment, mainly because of not meeting the diagnostic/severity criteria (in half of the cases of screen failure), which was due to too low seizure frequency during Baseline in most cases. Other reasons included consent withdrawal (9 patients, 13.6%), use of excluded medications/therapies (9 patients, 13.6%), unacceptable past medical history/concomitant diagnosis (3 patients, 4.5%), unacceptable laboratory values (2 patients, 3.0%) or other (16 patients, 24.2%).

Table 6 – Patient Disposition in Study M2304

Disposition Reason	Everolimus LT target of 3-7 ng/mL N=117 n (%)	Everolimus HT target of 9-15 ng/mL N=130 n (%)	Placebo N=119 n (%)	All patients N=366 n (%)
Patients randomized				
Treated	117 (100.0)	130 (100.0)	119 (100.0)	366 (100.0)
Patients treated: Core phase				
Treatment ongoing [a] in Core phase	0	0	0	0
End of treatment	117 (100.0)	130 (100.0)	119 (100.0)	366 (100.0)
Discontinued in Titration period	3 (2.6)	5 (3.8)	1 (0.8)	9 (2.5)
Discontinued in Maintenance period	4 (3.4)	3 (2.3)	4 (3.4)	11 (3.0)
Completed Core phase	110 (94.0)	122 (93.8)	114 (95.8)	346 (94.5)
Primary reason for end of treatment in Core phase				
Adverse event(s)	5 [b] (4.3)	4 (3.1)	2 (1.7)	11 (3.0)
Lack of efficacy	0	2 (1.5)	2 (1.7)	4 (1.1)
Subject withdrew consent	2 (1.7)	1 (0.8)	1 (0.8)	4 (1.1)
Protocol deviation	0	1 (0.8)	0	1 (0.3)
Patients treated: Extension phase [c]				
Patients entering Extension phase [d]	110 (94.0)	118 (90.8)	114 (95.8)	342 (93.4)
Treatment ongoing [a] in Extension phase	90 (76.9)	102 (78.5)	100 (84.0)	292 (79.8)
End of treatment	20 (17.1)	16 (12.3)	14 (11.8)	50 (13.7)
Discontinued in Extension phase	20 (17.1)	16 (12.3)	14 (11.8)	50 (13.7)
Completed Extension phase	0	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.

[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 one patient who experienced intermittent diarrhea 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.

Major protocol deviations were reported for 6 (5.1%, LT group) and 12 (9.2%, HT group) everolimus subjects and 7 (5.9%) placebo subjects, respectively. They were somewhat more frequent in the HT Everolimus compared to the LT Everolimus and placebo group, respectively, which appeared to be mainly due to protocol violations regarding concomitant AEDs in the HT Everolimus group.

Recruitment

Patients were recruited from 99 enrolling centres across 25 countries participating in the study including

the USA (63 patients [17.2%]), Japan (35 patients [9.6%]), Turkey (30 patients [8.2%]), the Russian Federation (24 patients [6.6%]), Germany and Great Britain (23 patients each [6.3%]), and Taiwan (20 patients [5.5%]).

The study initiation date was 29-Apr-2013 (first patient first visit) and the data cut-off date for the present submission 02-Oct-2015 (when all patients had either completed the Core phase of the study or had discontinued from the study). As of the 02-Oct-2015 data cut-off, 342 patients (93.4%) had entered the Extension phase, 292 of whom (79.8% of all randomized patients) continued to receive study treatment.

Conduct of the study

There were two protocol amendments.

Amendment 1 was dated before the 1st patient was included in the study and the protocol amendments are not considered to have affected the scientific value of the study.

Amendment 2 was dated 14-Mar-2014 and included the following:

- Sample size in the everolimus 9 to 15 ng/mL arm was increased to account for potential loss in power. An error was identified whereby dose titrations in the Interactive Response Technology system for patients randomized to the high trough range may not have achieved the targeted exposure to everolimus.
- The inclusion criteria were updated to expand the definition of TSC seizures and include sensory seizures as the sole seizure type if confirmed to be partial onset by ictal EEG.
- The exclusion definition was modified to exclude patients <2 years of age with untreated infantile spasms, to clarify the eligibility of patients with residual epileptic spasms and to enable such patients to be included in the study.
- A new exclusion criterion was added related to patients on a ketogenic diet (defined as <40 g of carbohydrate/day). Ketogenic diet, a type of antiepilepsy therapy, may mediate its effect through mTOR inhibition. Because the potential interaction of similarly acting therapies may pose risks to patients, it was determined that treatment with a low carbohydrate ketogenic diet should be excluded.
- Investigators expressed a desire to know the everolimus Cmin values of their patients after the Core phase of the study, and to be permitted to make dose adjustments (increases or decreases), during the Extension phase. To accomplish this, patients were first transitioned towards an everolimus trough concentration of 6-10 ng/mL, which preserved the blinding of the original randomization. After this transition, Cmin values were revealed to Investigators who then had the option to modify the dose of study drug. If Investigators chose not to modify dosing, the dose was determined by the Interactive Response Technology to maintain the everolimus trough concentration range between 3 and 15 ng/mL for all patients.

Baseline data

The treatment groups were well balanced with respect to demographic parameters. The majority of study subjects were pediatric/adolescents (>80%). The youngest subject included in the study was 2.2 years old, the oldest 56.3 years. Baseline demographics are summarised in Table 7.

Table 7 – Demographic characteristics at Baseline – Full Analysis Set

	Everolimus		Placebo	All patients
	LT target of 3-7 ng/mL	HT target of 9-15 ng/mL		
Demographic variable	**N=117**	**N=130**	**N=119**	**N=366**
Age (years)				
Mean (standard deviation)	12.57 (10.087)	12.85 (10.010)	12.39 (9.430)	12.61 (9.825)
Median	9.72	10.08	10.34	10.06
Min, Max	2.2, 56.3	2.3, 50.5	2.2, 52.0	2.2, 56.3
Age category (years) – n (%)				
<6 [a]	33 (28.2)	37 (28.5)	34 (28.6)	104 (28.4)
6 to <12	37 (31.6)	39 (30.0)	37 (31.1)	113 (30.9)
12 to <18	26 (22.2)	31 (23.8)	25 (21.0)	82 (22.4)
18 to <65	21 (17.9)	23 (17.7)	23 (19.3)	67 (18.3)
Gender – n (%)				
Male	64 (54.7)	65 (50.0)	61 (51.3)	190 (51.9)
Female	53 (45.3)	65 (50.0)	58 (48.7)	176 (48.1)
Race – n (%)				
Caucasian	76 (65.0)	84 (64.6)	77 (64.7)	237 (64.8)
Asian	29 (24.8)	31 (23.8)	27 (22.7)	87 (23.8)
Black	2 (1.7)	1 (0.8)	1 (0.8)	4 (1.1)
Native American	0	1 (0.8)	0	1 (0.3)
Pacific islander	1 (0.9)	0	0	1 (0.3)
Other	9 (7.7)	13 (10.0)	14 (11.8)	36 (9.8)
Ethnicity – n (%)				
Other	78 (66.7)	88 (67.7)	77 (64.7)	243 (66.4)
Hispanic/Latino	15 (12.8)	17 (13.1)	19 (16.0)	51 (13.9)
Japanese	10 (8.5)	14 (10.8)	11 (9.2)	35 (9.6)
Chinese	9 (7.7)	8 (6.2)	7 (5.9)	24 (6.6)
Mixed ethnicity	4 (3.4)	3 (2.3)	5 (4.2)	12 (3.3)
Indian (Indian subcontinent)	1 (0.9)	0	0	1 (0.3)
Weight (kg)				
Mean (standard deviation)	38.69 (22.802)	40.75 (27.267)	40.50 (24.923)	40.01 (25.093)
Median	31.20	30.70	33.00	31.60
Min, Max	12.0, 126.2	12.2, 147.9	12.5, 104.0	12.0, 147.9
Height (cm)				
Mean (standard deviation)	135.65 (26.171)	136.25 (28.234)	135.67 (27.097)	135.87 (27.145)
Median	138.00	134.50	136.40	136.70
Min, Max	87.8, 190.0	88.0, 205.0	87.0, 188.0	87.0, 205.0
Body surface area (m^2)				
Mean (standard deviation)	1.18 (0.437)	1.20 (0.501)	1.20 (0.476)	1.20 (0.472)
Median	1.09	1.09	1.10	1.10
Min, Max	0.5, 2.4	0.5, 2.6	0.5, 2.2	0.5, 2.6
Body mass index (kg/m^2)				
Mean (standard deviation)	19.29 (5.283)	19.56 (6.233)	19.78 (5.484)	19.55 (5.689)
Median	17.50	17.30	18.00	17.50
Min, Max	13.0, 44.1	10.8, 48.9	10.7, 36.4	10.7, 48.9

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

Baseline disease characteristics

Major features of TSC in the study population are summarized in the following Table 8:

All patients presented with ≥ 2 major clinical features of TSC in line with the modified Gomez criteria. The most frequent TSC manifestation was cortical tubers (in 88.8-96.6% subjects per treatment group). Subependymal nodule(s) were present in 74.4-89.1% of subjects and SEGA in 16.8-17.7%, respectively. Other manifestations were the presence of hypomelanotic macules (83.6%), facial angiofibroma or forehead plaque (68.3%), renal angiomyolipoma (41.5% of patients), and cardiac rhabdomyoma (41.0%).Whereas SEGA was present in a very similar percentage across study groups, cortical tubers as well as SEN were somewhat present at a higher rate in the placebo as compared to the active treatment groups. However, the differences appeared rather small and thus influence on the overall study results appears unlikely.

Epilepsy background and seizure history were generally well balanced across the three treatment arms (Table 8). Study subjects had a history of polymorphic seizures which comprised complex partial and secondarily generalized partial onset seizures, respectively in the majority of subjects. Approximately 12% of study subjects had a history of EEG confirmed generalized onset seizures and nearly 30% had a history of unclassifiable seizures or infantile/epileptic spasms.

Table 8 – Epilepsy Characteristics at Baseline (FAS)

	Everolimus		Placebo	All patients
	LT target of 3-7 ng/mL	HT target of 9-15 ng/mL		
Demographic variable	**N=117**	**N=130**	**N=119**	**N=366**
Time from initial diagnosis of TSC seizures until randomization (years)				
n	117	129	119	365
Mean (SD)	10.6 (9.51)	11.5 (9.65)	11.2 (8.89)	11.1 (9.34)
Median	7.4	8.7	9.0	8.3
Min, Max	0.3, 51.4	0.7, 50.5	1.2, 50.7	0.3, 51.4
Time category (years)				
<2	6 (5.1)	6 (4.6)	5 (4.2)	17 (4.6)
2 to <4	21 (17.9)	22 (16.9)	18 (15.1)	61 (16.7)
4 to <6	16 (13.7)	18 (13.8)	18 (15.1)	52 (14.2)
≥ 6	74 (63.2)	83 (63.8)	78 (65.5)	235 (64.2)
Missing	0	1 (0.8)	0	1 (0.3)
Seizure history				
Complex partial seizure [a]	96 (82.1)	112 (86.2)	93 (78.2)	301 (82.2)
Secondarily generalized seizure [b]	84 (71.8)	90 (69.2)	75 (63.0)	249 (68.0)
Simple partial seizure	44 (37.6)	54 (41.5)	51 (42.9)	149 (40.7)
Status epilepticus	11 (9.4)	26 (20.0)	19 (16.0)	56 (15.3)
Within 52 weeks of screening	0	1 (0.8)	0	1 (0.3)
Generalized onset seizure [c]	14 (12.0)	14 (10.8)	15 (12.6)	43 (11.7)
Other [d]	30 (25.6)	37 (28.5)	35 (29.4)	102 (27.9)

Baseline seizure characteristics are summarized in Table 9. The majority of subjects had complex partial and/or secondarily generalized seizures at Baseline. EEG confirmed generalized onset seizures occurred in less than 2% of subjects during Baseline. Similarly, the proportion of subjects with “other” seizure types (i.e. unclassifiable seizures or infantile/epileptic spasms) was low.

Inclusion criteria required ≥ 16 POS during the Baseline period (8 weeks), and the actual Baseline seizure frequency was indeed high with a median of 34.5 (LT), 37.8 (HT) and 42.0 (placebo group) per 28 days.

Median (but not mean) seizure frequency appeared higher in the placebo group compared to both active treatment groups.

Table 9 – Seizure characteristics during the Baseline phase – Full Analysis Set

	Everolimus		Placebo	All patients
	LT target of 3-7 ng/mL	HT target of 9-15 ng/mL		
Seizure characteristics	**N=117**	**N=130**	**N=119**	**N=366**
Complex partial seizure	79 (67.5)	87 (66.9)	72 (60.5)	238 (65.0)
Predominantly stare and facial automatisms (atypical absence-like)	40 (34.2)	43 (33.1)	40 (33.6)	123 (33.6)
Predominantly stare (typical absence-like)	24 (20.5)	22 (16.9)	9 (7.6)	55 (15.0)
Not otherwise specified	32 (27.4)	32 (24.6)	31 (26.1)	95 (26.0)
Secondarily generalized seizure	60 (51.3)	68 (52.3)	63 (52.9)	191 (52.2)
Tonic	40 (34.2)	43 (33.1)	26 (21.8)	109 (29.8)
Tonic-clonic	20 (17.1)	22 (16.9)	26 (21.8)	68 (18.6)
Atonic	8 (6.8)	9 (6.9)	13 (10.9)	30 (8.2)
Clonic	6 (5.1)	2 (1.5)	8 (6.7)	16 (4.4)
Myoclonic	5 (4.3)	4 (3.1)	5 (4.2)	14 (3.8)
Not otherwise specified	5 (4.3)	2 (1.5)	5 (4.2)	12 (3.3)
Simple partial seizure	19 (16.2)	24 (18.5)	25 (21.0)	68 (18.6)
Generalized onset seizure	2 (1.7)	2 (1.5)	2 (1.7)	6 (1.6)
Tonic	2 (1.7)	0	1 (0.8)	3 (0.8)
Myoclonic	1 (0.9)	0	0	1 (0.3)
Absence	0	1 (0.8)	0	1 (0.3)
Atonic	0	1 (0.8)	0	1 (0.3)
Not otherwise specified	0	0	1 (0.8)	1 (0.3)
Other-	5 (4.3)	2 (1.5)	5 (4.2)	12 (3.3)
Seizure frequency at Baseline (number of seizures per week) [a]				
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	

Note: All seizures types except for Generalized onset" and "Others" qualified to the protocol defined partial-onset seizures considered in the primary endpoints.

[a] Calculated seizure frequency excludes seizure types that do not qualify as partial-onset seizures

Prior and concomitant antiepileptic therapy

Data on antiepileptic therapy prior Baseline showed that patients were heavily pre-treated and highly refractory with 48.6% of patients having failed ≥ 6 AEDs prior to study. The median number of failed AEDs prior to study entry was approximately 5 in both everolimus arms and 6 in the placebo arm.

Use of concomitant antiepileptic therapy during Baseline is given in the following table.

Table 10 – Antiepileptic therapy at Baseline (FAS)

	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
Antiepileptic therapy	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Vagal nerve stimulation	**13 (11.1)**	**11 (8.5)**	**10 (8.4)**	**34 (9.3)**
Ketogenic diet treatment	**1 (0.9)**	**2 (1.5)**	**4 (3.4)**	**7 (1.9)**
Any background AEDs	**117 (100.0)**	**130 (100.0)**	**119 (100.0)**	**366 (100.0)**
Number of AEDs in the regimen				
1	7 (6.0)	18 (13.8)	15 (12.6)	40 (10.9)
2	55 (47.0)	55 (42.3)	41 (34.5)	151 (41.3)
3	55 (47.0)	56 (43.1)	62 (52.1)	173 (47.3)
>3	0	1 (0.8)	1 (0.8)	2 (0.5)
Start date ≥ 4 weeks prior to Screening	**116 (99.1)**	**128 (98.5)**	**118 (99.2)**	**362 (98.9)**
Longest interruption in any AED				
1-3 days	0	0	0	0
4-7 days	0	0	0	0
>7 days	0	0	0	0
Change in dose in any AED or new AED started				
No	116 (99.1)	124 (95.4)	118 (99.2)	358 (97.8)
Yes	1 (0.9)	6 (4.6)	1 (0.8)	8 (2.2)
Compliant patient during Baseline phase [a]	**115 (98.3)**	**122 (93.8)**	**116 (97.5)**	**353 (96.4)**

AED(s) = antiepileptic drug(s)

[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

Nearly half of the study population (47.3%) used 3 concomitant AEDs, and more than 40% received 2 concomitant AEDs. The number of subjects with 3 AEDs was somewhat higher in the placebo group (52.1%) compared to the LT (47%) and HT group (43.1%), respectively. With regard to concomitant AED regimen or -dose a slightly lower proportion of HT subjects (93.8%) was compliant compared to the placebo group (97.5%). Compliance was highest in the LT group (98.3%).

Prior medication for TSC was administered to 23 patients (6.3%) The majority of these patients (15/23) applied topical medication.

Prior rescue medication was taken by 28 patients (7.7%). The majority of these patients (21/28) required rescue medication for 1 to 2 days.

Numbers analysed

All 366 subjects randomised were treated with at least one dose of study treatment. The FAS and the safety set (i.e. patients who received at least one dose of study drug and had at least one valid post-Baseline safety evaluation) were identical. A total of 27 subjects (7.4%) were excluded from the PP set, including 25 subjects for major protocol deviations (please see conduct of the study, above) and 2 further subjects due to insufficient treatment exposure and ineligibility for efficacy, respectively.

Table 11 – Analysis Set including Age Strata

	Everolimus		Placebo	All patients
	LT target of 3-7 ng/mL	HT target of 9-15 ng/mL		
Analysis set	N=117	N=130	N=119	N=366
Randomization stratum	n (%)	n (%)	n (%)	n (%)
Full Analysis Set	**117 (100.0)**	**130 (100.0)**	**119 (100.0)**	**366 (100.0)**
Age <6 years	34 (29.1)	36 (27.7)	34 (28.6)	104 (28.4)
Age 6 to <12 years	36 (30.8)	40 (30.8)	37 (31.1)	113 (30.9)
Age 12 to <18 years	26 (22.2)	31 (23.8)	26 (21.8)	83 (22.7)
Age ≥ 18 years	21 (17.9)	23 (17.7)	22 (18.5)	66 (18.0)
Safety Set	**117 (100.0)**	**130 (100.0)**	**119 (100.0)**	**366 (100.0)**
Age <6 years	34 (29.1)	36 (27.7)	34 (28.6)	104 (28.4)
Age 6 to <12 years	36 (30.8)	40 (30.8)	37 (31.1)	113 (30.9)
Age 12 to <18 years	26 (22.2)	31 (23.8)	26 (21.8)	83 (22.7)
Age ≥ 18 years	21 (17.9)	23 (17.7)	22 (18.5)	66 (18.0)
Per-protocol Set	**110 (94.0)**	**118 (90.8)**	**111 (93.3)**	**339 (92.6)**
Age <6 years	31 (26.5)	33 (25.4)	33 (27.7)	97 (26.5)
Age 6 to <12 years	34 (29.1)	36 (27.7)	35 (29.4)	105 (28.7)
Age 12 to <18 years	24 (20.5)	30 (23.1)	23 (19.3)	77 (21.0)
Age ≥ 18 years	21 (17.9)	19 (14.6)	20 (16.8)	60 (16.4)

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

The Long-term Evaluation Set for Efficacy comprised 117, 130, and 114 patients in the LT, HT and placebo group, respectively.

Outcomes and estimation

Primary efficacy endpoint: 50% response rate

Table 12 summarises the results for the primary efficacy endpoint in the EU, i.e. the percentage of patients with at least 50% reduction of their average weekly TSC seizure frequency during the Maintenance phase compared to Baseline. Response rates were 28.2% (95% CI: 20.3, 37.3) and 40.0% (95% CI: 31.5, 49.0) for the everolimus LT and HT arms compared with 15.1% (95% CI: 9.2, 22.8) for the placebo arm. The difference for both everolimus arms to placebo was statistically significant ($p=0.008$ and $p<0.001$).
The estimated odds of subjects being a responder was 2.21-fold (LT) and 3.93-fold (HT) higher in the everolimus groups relative to placebo.

Table 12 – Primary Efficacy Variable - 50% Response Rate (FAS)

	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 favors 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

Several sensitivity analyses were conducted including analysis on the entire Core phase (including Titration and Maintenance period), analysis by patients discontinuation (patients discontinuing before the end of Core phase are assumed to be non-responders/to have no change from Baseline in seizure frequency), analysis where seizure frequency was calculated assuming that on days with missing information, patients experienced 0 seizures in the maintenance period of the Core phase and the maximum reported daily seizure count in the Baseline phase (best case scenario), and analysis where seizure frequency were calculated assuming that on days with missing information, patients experienced the maximum reported daily seizure count in the Maintenance period of the Core phase and 0 seizures in the Baseline phase (worst case scenario).

All sensitivity analyses as well as PP analysis produced results which were highly consistent with the primary analysis. Odds ratios versus placebo ranged from 2.18 to 2.69 in favour of the everolimus LT arm and from 3.77 to 4.18 in favour of the everolimus HT arm.

Secondary efficacy endpoints

- Percentage reduction from Baseline in average weekly TSC seizure frequency

As shown in Table 13, 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 LT and HT arms, respectively, compared with 14.9% (95% CI: 0.1, 21.7) for the placebo arm. The differences for both everolimus arms to placebo were statistically significant (p=0.003 and p<0.001, respectively).

Table 13 – Percentage Reduction from Baseline in Weekly Seizure Frequency (FAS)

	Everolimus		Placebo
	LT target of 3-7 ng/mL	HT target of 9-15 ng/mL	
Seizure frequency (seizures per week)	**N=117**	**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
[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)

Similar to the primary endpoint, results of predefined sensitivity analyses and PP analysis were consistent with the primary analysis. The differences versus placebo ranged from 18.35% to 30.95% median reductions in seizure frequency in the everolimus LT arm and 34.91% to 40.72% median reductions in the everolimus HT arm, compared with 9.68% to 15.90% median reductions in the placebo arm.

- Seizure free rate

Seizure freedom was reported for 5.1% and 3.8% of subjects from the everolimus LT and HT treatment arms, respectively, compared with 0.8% placebo subjects. The estimated odds for being seizure-free

were 6.55-fold and 4.99-fold higher for the everolimus LT and HT treatment arms compared with placebo although the corresponding confidence intervals were large (i.e. 0.77, 55.73 and 0.57, 44.03, respectively) and overlapping with the placebo arm. Results of predefined sensitivity analysis where patients discontinuing before end of Maintenance phase were assumed not to be seizure free yielded identical results.

- Proportion of patients with at least 25% reduction in seizure frequency

Higher proportions of everolimus-treated patients experienced ≥ 25% reductions in seizure frequency (52.1% and 70.0% of patients from the LT and HT treatment arms, respectively, compared with 37.8% on placebo). The odds ratios versus placebo were 1.77 (95% CI: 1.05, 2.97) for the LT arm and 3.82 (95% CI: 2.25, 6.48) for the HT arm.

- Distribution of change in TSC seizure frequency from Baseline

The results are summarized in Table 14.

Table 14 – Distribution of change from Baseline in seizure frequency (FAS)

		Everolimus						Placebo			
		LT target of 3-7 ng/mL N=117				HT target of 9-15 ng/mL N=130				N=119	
		Category		Cumulative		Category		Cumulative		Category		Cumulative	
Percentage reduction	Label	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
100	Seizure-free	6	(5.1)	6	(5.1)	5	(3.8)	5	(3.8)	1	(0.8)	1	(0.8)
≥ 75 to <100	75% responder	7	(6.0)	13	(11.1)	20	(15.4)	25	(19.2)	6	(5.0)	7	(5.9)
≥ 50 to <75	50% responder	20	(17.1)	33	(28.2)	27	(20.8)	52	(40.0)	11	(9.2)	18	(15.1)
≥ 25 to <50	25% responder	28	(23.9)	61	(52.1)	39	(30.0)	91	(70.0)	27	(22.7)	45	(37.8)
>-25 to <25	No change	41	(35.0)	102	(87.2)	24	(18.5)	115	(88.5)	49	(41.2)	94	(79.0)
≤ -25	Exacerbation	15	(12.8)	117	(100.0)	15	(11.5)	130	(100.0)	24	(20.2)	118	(99.2)
Missing	Missing	0		0		0		0		1	(0.8)	119	(100.0)

In line with the results for the 50% responder rates, higher proportions of responders in both everolimus treatment arms were also seen for the ≥ 25%-, ≥ 75%- and 100% response rates as well as other categories of responder rates. Except for seizure-freedom (which was only reported in 6 (LT) and 5 (HT) subjects of the everolimus arms), higher responder rates were seen with higher everolimus exposure (HT compared to LT everolimus group) with regard to all other response categories. Conversely, the proportions of subjects with no change (i.e., up to 25% increase to < 25% reduction in seizure frequency) as well as exacerbation (≥ 25% increase in seizure frequency) were each highest in the placebo group and lowest in the HT everolimus group.

- Seizure-free days

The median number of seizure free days per 28 day period increased from 8.07 days (LT), 7.22 days (HT) and 6.50 days (placebo), respectively, at Baseline by 2.00 days (LT), 4.01 days (HT) and 0.47 (placebo) days.

- Treatment duration

Time to treatment discontinuation during the Core phase of the study was similar across the three treatment arms. The probability of receiving treatment for 18 weeks during the Core phase was 70.1% and 71.5% in the everolimus LT and HT arms compared to 75.6% in the placebo arm.

- Long-term seizure reduction

The Extension phase was designed to target similar c_{min} ranges (i.e. 6-10 ng/mL) across the 3 study arms during the first 8 weeks. Afterwards c_{min} could be titrated according to clinical response within the range of 3-15 ng/m. The response rates during long-term everolimus treatment, available at the time of data cut-off for this report, are presented in the following table.

Table 15 – 50% Response Rate over Time (Long-term Evaluation Efficacy Set)

Everolimus LT target of 3-7 ng/mL (N=117)									
	Week 18	**Week 30**	**Week 42**	**Week 54**	**Week 66**	**Week 78**	**Week 90**	**Week 102**	**Week 114**
	n=114	**n=106**	**n=83**	**n=68**	**n=56**	**n=37**	**n=22**	**n=10**	**n=3**
Responders - n (%)	32 (28.1)	39 (36.8)	33 (39.8)	32 (47.1)	24 (42.9)	16 (43.2)	11 (50.0)	5 (50.0)	2 (66.7)
Response rate 95% CI	20.1, 37.3	27.6, 46.7	29.2, 51.1	34.8, 59.6	29.7, 56.8	27.1, 60.5	28.2, 71.8	18.7, 81.3	9.4, 99.2
Everolimus HT target of 9-15 ng/mL (N=130)									
	Week 18	**Week 30**	**Week 42**	**Week 54**	**Week 66**	**Week 78**	**Week 90**	**Week 102**	**Week 114**
	n=126	**n=117**	**n=91**	**n=72**	**n=50**	**n=41**	**n=29**	**n=14**	**n=6**
Responders - n (%)	54 (42.9)	53 (45.3)	45 (49.5)	35 (48.6)	28 (56.0)	23 (56.1)	14 (48.3)	8 (57.1)	5 (83.3)
Response rate 95% CI	34.1, 52.0	36.1, 54.8	38.8, 60.1	36.7, 60.7	41.3, 70.0	39.7, 71.5	29.4, 67.5	28.9, 82.3	35.9, 99.6
Everolimus start Ext (N=114)									
	Week 18	**Week 30**	**Week 42**	**Week 54**	**Week 66**	**Week 78**	**Week 90**	**Week 102**	
	n=101	**n=77**	**n=63**	**n=46**	**n=35**	**n=16**	**n=6**	**n=4**	
Responders - n (%)	21 (20.8)	25 (32.5)	23 (36.5)	13 (28.3)	15 (42.9)	5 (31.3)	2 (33.3)	2 (50.0)	
Response rate 95% CI	13.4, 30.0	22.2, 44.1	24.7, 49.6	16.0, 43.5	26.3, 60.6	11.0, 58.7	4.3, 77.7	6.8, 93.2	
Everolimus all patients (N=361)									
	Week 18	**Week 30**	**Week 42**	**Week 54**	**Week 66**	**Week 78**	**Week 90**	**Week 102**	**Week 114**
	n=341	**n=300**	**n=237**	**n=186**	**n=141**	**n=94**	**n=57**	**n=28**	**n=9**
Responders - n (%)	107 (31.4)	117 (39.0)	101 (42.6)	80 (43.0)	67 (47.5)	44 (46.8)	27 (47.4)	15 (53.6)	7 (77.8)
Response rate 95% CI	26.5, 36.6	33.4, 44.8	36.2, 49.2	35.8, 50.5	39.1, 56.1	36.4, 57.4	34.0, 61.0	33.9, 72.5	40.0, 97.2

Only includes patients with a baseline value and a value at the assessment
Exact 95% CI obtained using Clopper-Pearson method

After 18 weeks of treatment with everolimus (combining patients who had been randomized to placebo but had been treated with everolimus for 18 weeks in the Extension phase with patients who had been randomized to everolimus and received 18 weeks of treatment in the Core phase) the median percentage change in seizure frequency had decreased by more than 30% from Baseline. The median seizure frequency remained below 30% from Baseline at the next time windows, for this combined population. However, median seizure frequency after 54 weeks should be interpreted with caution owing to the small sample sizes and the large 95% CI.

- Quality of life

QOLCE (patients aged < 11 years) and QOLIE-AD-48 (patients aged ≥11 to <18 years): There were marginal changes in all 3 treatment arms with no meaningful differences between the 3 treatment arms.

Qolie-31-P (patients aged ≥ 18 years): Numerical differences were observed between the respective everolimus LT and HT treatment arms and placebo in the QOLIE-31-P overall quality-of-life score during the Core phase of the study for patients aged ≥ 18 years. The numerical differences were in favour of placebo. However, with only approx. 50% of adult study subjects completing the questionnaire at Baseline and end of Core phase, there were too many missing values and a high potential for selection regarding questionnaire completion can be assumed. Evaluable data on change in QoL were available for only 10-12 subjects per group and respective results showed high variability.

Ancillary analyses

This section provides a summary of relevant subgroup analyses and other exploratory analyses.

Treatment with everolimus was associated with both improved response rates and increased reductions in seizure frequency relative to placebo for all age categories (<6 years, 6 to <12 years, 12 to <18 years, and ≥ 18 years).

Table 16 – Response Rate and Percentage Reduction from Baseline in Seizure Frequency by Age (FAS)

	Everolimus		Placebo
	LT target of 3-7 ng/mL	HT target of 9-15 ng/mL	
Age category	**N=117**	**N=130**	**N=119**
<6 years	**n=33**	**n=37**	**n=34**
Response rate (95% CI) [a]	30.3 (15.6, 48.7)	59.5 (42.1, 75.2)	17.6 (6.8, 34.5)
Median percentage reduction from Baseline (95% CI) [b]	29.29 (13.43, 46.30)	54.65 (43.53, 73.11)	12.27 (-10.12, 24.77)
6 to <12 years	**n=37**	**n=39**	**n=37**
Response rate (95% CI) [a]	29.7 (15.9, 47.0)	28.2 (15.0, 44.9)	10.8 (3.0, 25.4)
Median percentage reduction from Baseline (95% CI) [b]	32.92 (3.11, 44.14)	34.68 (26.10, 43.74)	6.03 (-8.81, 26.75)
12 to <18 years	**n=26**	**n=31**	**n=25**
Response rate (95% CI) [a]	23.1 (9.0, 43.6)	32.3 (16.7, 51.4)	16.0 (4.5, 36.1)
Median percentage reduction from Baseline (95% CI) [b]	30.75 (15.91, 44.22)	35.17 (14.24, 48.97)	22.46 (-5.50, 38.46)
≥ 18 years	**n=21**	**n=23**	**n=23**
Response rate (95% CI) [a]	28.6 (11.3, 52.2)	39.1 (19.7, 61.5)	17.4 (5.0, 38.8)
Median percentage reduction from Baseline (95% CI) [b]	21.86 (-5.37, 48.48)	35.90 (16.84, 56.61)	17.54 (-6.96, 38.40)

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

By gender, no notable differences were seen in the magnitude of the responder rates or percentage reduction in TSC seizure frequency.

By race (Caucasian, Asian, Other), the resulting response rates and percentage reduction in TSC seizure frequency were better in the everolimus arms compared to placebo. Responder rate and seizure reduction by ethnicity favoured everolimus in Hispanic/Latino, Japanese and Other ethnicities, whereas results for Chinese were inconclusive due to low subject numbers per treatment arm (N=7-9).

Subgroup analyses by Baseline seizure frequency showed that responder rates and percentage reduction from Baseline seizure frequency were higher in the active treatment groups compared to placebo, irrespective of Baseline seizure frequency category (<4.7, 4.7 - <9.4, 9.4 - <20.6, ≥20.6) except for median percentage reduction from Baseline in the LT group in the 9.4 - < 20.6 seizure subgroup, where similar percentage reduction in TSC seizure frequency was observed as for placebo.

Patients continued to exhibit polymorphic seizures during the Core phase of the trial including 58.8% of patients with complex partial seizures, 51.3% with secondarily generalized seizures, 21.8% with simple partial seizures, and 1.7% with (EEG confirmed) generalized onset seizures. Response rates and percentage reductions in seizure frequency from Baseline were generally improved in the everolimus LT and HT treatment arms relative to placebo, irrespective of seizure type (see Table 17). The exception was for generalized tonic-clonic seizures where the median percentage reduction from Baseline was higher in the placebo arm; this result should be interpreted with caution because the sample sizes were small in the three arms (<20 patients each).

Table 17 – Response Rate and Percentage Reduction from Baseline in Seizure Frequency by Seizure Type (FAS)

	Everolimus		Placebo
	LT target of 3-7 ng/mL	HT target of 9-15 ng/mL	
	N=117	N=130	N=119
Seizure type: IA (IA1+IA2A)	**n=15**	**n=20**	**n=21**
Response rate (95% CI) [a]	26.7 (7.8, 55.1)	60.0 (36.1, 80.9)	14.3 (3.0, 36.3)
Median percentage reduction from Baseline (95% CI) [b]	24.40 (-0.34, 51.11)	57.65 (36.82, 90.70)	10.79 (-5.50, 34.03)
Seizure type: IB (IB1+IB2+IB3)	**n=74**	**n=79**	**n=67**
Response rate (95% CI) [a]	33.8 (23.2, 45.7)	49.4 (37.9, 60.9)	23.5 (14.1, 35.4)
Median percentage reduction from Baseline (95% CI) [b]	32.70 (15.56, 44.93)	48.97 (38.81, 61.58)	14.86 (-0.18, 35.62)
Seizure type: IC (IC1+IC2+IC3+IC4+IC5 +IC6)	**n=53**	**n=60**	**n=50**
Response rate (95% CI) [a]	26.4 (15.3, 40.3)	31.7 (20.3, 45.0)	22.0 (11.5, 36.0)
Median percentage reduction from Baseline (95% CI) [b]	32.50 (18.85, 42.86)	34.81 (14.29, 47.88)	22.95 (-2.51, 33.33)
Seizure type: convulsive Grand mal seizures and drop attacks (IC3+IC4 +IC5+IID+IIE+IIF) [c]	**n=49**	**n=55**	**n=44**
Response rate (95% CI) [a]	28.6 (16.6, 43.3)	30.9 (19.1, 44.8)	22.7 (11.5, 37.8)
Median percentage reduction from Baseline (95% CI) [b]	35.68 (22.31, 43.26)	33.56 (12.39, 47.93)	26.10 (0.49, 37.52)
Seizure type: generalized tonic-clonic seizures (IC4)	**n=14**	**n=14**	**n=18**
Response rate (95% CI) [a]	35.7 (12.8, 64.9)	35.7 (12.8, 64.9)	27.8 (9.7, 53.5)
Median percentage reduction from Baseline (95% CI) [b]	22.82 (9.46, 71.35)	24.07 (-30.15, 72.53)	35.98 (12.26, 49.50)

[a] Exact 95% CI obtained using Clopper-Pearson method
[b] 95% CI of the median based on bootstrap percentiles
[c] Includes seizure types that do not qualify as partial-onset seizures
Note:
- Only reductions in seizures of each particular type of interest were calculated
- Only patients with at least 16 seizures of each particular type were considered in this analysis

Results for response rates and percentage reduction in seizure frequency across all seizure types combined (including POS and generalized onset seizures) as well as for seizures lasting > 10 minutes were largely in line with the respective primary analyses (of POS as defined in the study). Although the number of subjects with seizures that lasted > 10 minutes at Baseline was low (N=8-22), the respective results provide some reassurance with respect to long-lasting, i.e. more severe seizures.

Exploratory subgroup analyses have also been performed with an *a posteriori* re-grouping of seizure types into the following groups:

1. Focal with retained awareness (sensory with EEG or motor), i.e. type IA1+IA2a

2. Focal with impaired awareness -predominantly non-motor, i.e. IB1 + IB2

3. Focal motor, i.e. IB3 + IC1-6

4. Generalized onset (EEG confirmed), i.e. Type II.

This corresponds to a recent, new seizure classification by the ILAE which clarifies that any seizure type

can be generalized or focal (ILAE 2016). In this revised classification, the term 'secondary generalized' has been excluded and seizures are classified as focal, or generalized, or unknown.

Respective subgroup analyses have been presented for groups 1-3. These analyses were conducted on patients having at least one of the seizure type of interest at Baseline. The number of patients with generalised seizure onset (6 overall) was too small for a meaningful analysis.

Table 18 – Percentage reduction from Baseline in seizure frequency and response rate (new classification, FAS)

	Everolimus LT target of 3-7 ng/mL N=117	Everolimus HT target of 9-15 ng/mL N=130	Placebo N=119
Focal with retained awareness (sensory with EEG or motor): IA1+IA2a	**n=20**	**n=25**	**n=26**
Responder rate (%)	25.0	60.0	15.4
Response rate 95% CI [1]	8.7, 49.1	38.7, 78.9	4.4, 34.9
Percentage reduction from Baseline to Core phase			
Mean (SD)	0.72 (81.095)	-34.14 (397.462)	-27.71 (165.843)
Median	21.02	59.29	8.38
Min; Max	-194.3; 100.0	-1900.0; 100.0	-800.0; 95.9
95% CI of median [2]	-10.13, 46.98	34.33, 93.01	-14.49, 32.12
Focal with impaired awareness - predominantly non-motor: IB1+IB2	**n=58**	**n=60**	**n=46**
Responder rate (%)	36.2	50.0	27.7
Response rate 95% CI [1]	24.0, 49.9	36.8, 63.2	15.6, 42.6
Percentage reduction from Baseline to Core phase			
Mean (SD)	-16.96 (161.454)	19.46 (191.063)	0.61 (75.974)
Median	33.33	49.52	15.27
Min; Max	-958.2; 100.0	-1383.3; 100.0	-257.6; 100.0
95% CI of median [2]	3.97, 48.15	37.96, 63.89	-7.09, 36.33
Focal motor seizures: IB3 + IC1 to 6	**n=84**	**n=88**	**n=81**
Responder rate (%)	25.0	36.4	16.0
Response rate 95% CI [1]	16.2, 35.6	26.4, 47.3	8.8, 25.9
Percentage reduction from Baseline to Core phase			
Mean (SD)	13.04 (84.513)	23.00 (83.676)	-0.35 (87.053)
Median	29.14	35.03	14.86
Min; Max	-382.2; 100.0	-527.3; 100.0	-623.8; 100.0
95% CI of median [2]	16.13, 40.27	24.10, 47.52	-0.18, 24.77

[1] Exact 95% CI obtained using Clopper-Pearson method
[2] 95% CI of the median based on bootstrap percentiles.

Subgroup analyses by number of concomitant AEDs response rates and percentage reductions in seizure frequency were always higher in both everolimus treatment arms compared to placebo irrespective of the number of concomitant AEDs (1, 2 or 3, respectively).

Responder rates and percentage change in seizure frequency by named AED have been analysed *post-hoc*. Results of a retrospective exploratory analysis generally indicated that everolimus was associated

with an increased reduction in seizure frequency relative to placebo for each of the 6 concomitant AEDs evaluated (vigabatrin, levetiracetam, lamotrigine, topiramate, clobazam, oxcarbazepine), although interpretation of these data should be made with caution due to the limited sample sizes, the unplanned nature of these analyses, and that most patients were receiving multiple AEDs. Placebo response was rather high in subjects with concomitant topiramate (response rate of 33.3%, n=30) or clobazam (response rate of 33.3%, n=21). Both responder rates and percent seizure frequency reduction were similar in the placebo group and the LT group in subjects with concomitant topiramate. However, the magnitude of effect in subjects with concomitant topiramate was still higher in the HT arm compared to the respective placebo subgroup and was generally comparable for both everolimus arms to that of the overall LT and HT groups, respectively.

Rescue medications was administered more frequently to patients in the everolimus HT treatment group (17.7%) during the Core phase of the trial than in either the everolimus LT (10.3%) group or the placebo group (11.8%). Rescue medication consisted almost exclusively of single doses of a benzodiazepine.

Seizure frequency by TSC features were evaluated for presence/absence of SEGA and cortical tubers as well as renal angiomyolipoma (Table 19).

Table 19 – Response Rate and Percentage Reduction in Seizure Frequency from Baseline by TSC features (FAS)

	Everolimus		Placebo
	LT target of 3-7 ng/mL	HT target of 9-15 ng/mL	
	N=117	N=130	N=119
Patients with ≥ 1 SEGA at Baseline	**n=20**	**n=23**	**n=20**
Response rate (95% CI) [a]	25.0 (8.7, 49.1)	52.2 (30.6, 73.2)	10.0 (1.2, 31.7)
Median percentage reduction from Baseline (95% CI) [b]	39.12 (3.68, 44.93)	51.98 (26.10, 63.08)	17.58 (-7.06, 31.31)
Patients without SEGA at Baseline	**n=97**	**n=107**	**n=98**
Response rate (95% CI) [a]	28.9 (20.1, 39.0)	37.4 (28.2, 47.3)	16.3 (9.6, 25.2)
Median percentage reduction from Baseline (95% CI) [b]	26.39 (16.05, 42.73)	38.78 (34.68, 44.75)	10.79 (-0.18, 24.19)
Patients with ≥ 1 renal angiomyolipoma at Baseline	**n=49**	**n=56**	**n=47**
Response rate (95% CI) [a]	26.5 (14.9, 41.1)	33.9 (21.8, 47.8)	17.0 (7.6, 30.8)
Median percentage reduction from Baseline (95% CI) [b]	30.56 (7.05, 44.14)	34.62 (21.34, 46.35)	18.54 (-6.67, 29.99)
Patients without renal angiomyolipoma at Baseline	**n=68**	**n=74**	**n=71**
Response rate (95% CI) [a]	29.4 (19.0, 41.7)	44.6 (33.0, 56.6)	14.1 (7.0, 24.4)
Median percentage reduction from Baseline (95% CI) [b]	29.26 (15.21, 43.49)	44.17 (38.05, 51.98)	12.83 (-4.12, 20.01)
Patients with cortical tubers at Baseline	**n=103**	**n=117**	**n=115**
Response rate (95% CI) [a]	26.2 (18.0, 35.8)	41.0 (32.0, 50.5)	14.8 (8.9, 22.6)
Median percentage reduction from Baseline (95% CI) [b]	24.58 (13.43, 36.77)	41.23 (35.17, 50.52)	12.83 (0.78, 20.43)
Patients without cortical tubers at Baseline	**n=14**	**n=13**	**n=4**
Response rate (95% CI) [a]	42.9 (17.7, 71.1)	30.8 (9.1, 61.4)	25.0 (0.6, 80.6)
Median percentage reduction from Baseline (95% CI) [b]	48.28 (38.23, 58.62)	37.05 (30.29, 50.00)	37.35 (-12.43, 90.73)

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

Finally, response rate and percentage reduction in seizure frequency were compared between each everolimus arm and placebo according to TSC1/TSC2 mutation status (see Table 20). TSC1/2 mutation status was only available for approximately 40% of the trial population at the time of this report. Analyses of TSC1/2 mutations using germline DNA were ongoing from patients for whom prior local data on TSC1/2 mutation status was unavailable.

Table 20 – Response rate and percentage reduction from Baseline in weekly seizure frequency based on TSC1/2 mutation status in patients with prior TSC mutation testing

	Everolimus				Placebo	
	LT target of 3-7 ng/mL		HT target of 9-15 ng/mL			
	N=43		N=52		N=40	
TSC1 mutations only (n=23)	n=7		n=9		n=7	
Response rate (%) (95% CI) [a]	0	(0, 41.0)	44.4	(13.7, 78.8)	28.6	(3.7, 71.0)
Median percentage reduction from Baseline to Core phase (95% CI) [b]	24.4	(13.2, 40.5)	37.1	(-70.4, 85.5)	17.6	(-7.0, 55.6)
TSC2 mutations only (n=101)	n=33		n=38		n=30	
Response rate (%) (95% CI) [a]	21.2	(9.0, 38.9)	39.5	(24.0, 56.6)	10.0	(2.1, 26.5)
Median percentage reduction from Baseline to Core phase (95% CI) [b]	24.8	(-0.3, 44.1)	40.0	(31.4, 56.4)	14.3	(-12.0, 28.5)
Both TSC1 and TSC2 mutations (n=2)	n=1		n=1		n=0	
Response rate (%) (95% CI) [a]	0	(NE, NE)	0	(NE, NE)		
Median percentage reduction from Baseline to Core phase(95% CI) [b]	5.9	(NE, NE)	19.2	(NE, NE)		
No mutation identified (n=9)	n=2		n=4		n=3	
Response rate (%) (95% CI) [a]	0	(0, 84.2)	25.0	(0.6, 80.6)	0	(0, 70.8)
Median percentage reduction from Baseline to Core phase (95% CI) [b]	-19.0	(-45.1, 7.1)	42.2	(-91.6, 58.2)	-37.5	(-57.2, 44.5)

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

Abbreviations: CI – confidence interval; HT – high trough target concentration; LT – low trough target concentration; NE – not evaluable; TSC – tuberous sclerosis complex

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. The summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 21 - Summary of Efficacy for trial CRAD001M2304

Title: A three-arm, randomized, 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		
Study identifier	Company Code: CRAD001M2304 EudraCT Number: 2011-000860-90	
Design	Multicentre, randomised, double-blind, three-arm, placebo-controlled	
	Duration of main phase:	18 weeks : 6 week titration plus 12 week maintenance
	Duration of Run-in phase:	8 week prospective Baseline

	Duration of Extension phase:		Until 48 weeks after last patient completed Core phase
Hypothesis	Superiority		
Treatments groups	Everolimus low-trough (LT)		1-3 concomitant AEDs + Everolimus 2 mg dispersible tablets with titration to trough range of 3-7 ng/mL, 18 weeks Patients randomised: 117
	Everolimus high-trough (HT)		1-3 concomitant AEDs + Everolimus 2 mg dispersible tablets with titration to trough range of 9-15 ng/mL, 18 weeks Patients randomised: 130
	Placebo		1-3 concomitant AEDs + Placebo dispersible tablets, 18 weeks Patients randomised: 119
Endpoints and definitions	Primary endpoint	50% response rate	50% reduction from Baseline in average weekly TSC seizure frequency during the maintenance period.
	Secondary endpoint (FDA Primary endpoint)	% reduction in seizure frequency	Percentage reduction from Baseline in average weekly TSC seizure frequency during the maintenance period
	Secondary endpoint	Seizure-free rate	Remaining seizure free during maintenance period (or during titration period for subjects discontinuing during Titration phase)
Database lock	Cut-off date: 02 October 2015		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full analysis set (FAS), comprising all patients randomized. Maintenance phase: 12 weeks			
Descriptive statistics and estimate variability	**Treatment group**	**Everolimus LT**	**Everolimus HT**	**Placebo**
	Number of subjects	**117**	**130**	**119**
	50% response rate, n (%)	33 (28.2)	52 (40.0)	18 (15.1)
	95% CI	20.3, 37.3	31.5, 49.0	9.2, 22.8
	% reduction on seizure frequency (median)	29.3	39.6	14.9
	95% CI of median	18.82, 41.88	35.03, 48.74	0.11, 21.71
	Seizure freedom rate, n (%)	6 (5.1)	5 (3.8)	1 (0.8)
	95% CI	1.9, 10.8	1.3, 8.7	0.0, 4.6
Effect estimate per comparison	Primary endpoint: 50% response rate	Comparison groups	(1) Everolimus LT vs PBO (2) Everolimus HT vs PBO	
		Odds ratio	(1) 2.21 (2) 3.93	
		95% CI	(1) 1.2, 4.2 (2) 2.1, 7.3	

		P-value	(1) 0.008 (2) <0.001
	Secondary endpoint: % reduction on seizure frequency	Comparison groups	(1) Everolimus LT vs PBO (2) Everolimus HT vs PBO
		Difference in median % reduction - median	(1) 15.96 (2) 27.46
		95% CI of median	(1) 1.98, 31.68 (2) 16.36, 43.36
		P-value	(1) 0.003 (2) <0.001
	Secondary endpoint: Seizure freedom rate	Comparison groups	(1) Everolimus LT vs. PBO (2) Everolimus HT vs PBO
		Odds ratio	(1) 6.55 (2) 4.99
		95% CI	(1) 0.77, 55.73 (2) 0.57, 44.03

2.4.3. Supportive study(ies)

Supportive data were provided from 3 studies, which had already been submitted previously and had been assessed in the context of the review of the applications for the indications of SEGA with TSC (C2485, M2301) and angiomyolipoma with TSC (M2302). In these 3 studies, efficacy of everolimus in TSC-associated seizures was investigated as secondary or exploratory objective. In Studies C2485 and M2301, 24 hours video-EEG recording was used to assess the frequency of the seizures at two time points (Baseline and one post-Baseline), as it enables a rapid measurement of seizure frequency without requiring the extensive data collection of detailed seizure diaries that would have potentially deflected attention from the primary objective of the trials.

Relevant data are briefly summarised in this section.

- Study C2485

Study C2485 was a single-arm, open-label trial designed to evaluate the safety and efficacy of everolimus therapy in patients (≥ 3 years of age) with TSC who have SEGA. Efficacy was a secondary objective of this study. The study included 28 patients, aged ≥ 3 years, with a confirmed diagnosis of TSC and radiological evidence of serial SEGA growth. Of these, 16 patients had seizures at study start (> 1 seizure in the 6 months prior to enrollment). All patients received treatment with everolimus (starting dose: 3.0 mg/m²/day; target trough concentration: 5-15 ng/mL).

After 6 months of treatment, 9/16 (56.3%) patients experienced decreases in seizure frequency, 6/16 (37.5%) patients had no change in seizure frequency (5 of whom were event-free at both time points), and 1 (6.3%) patient experienced an increase in seizures. Median change in overall seizure frequency was -1.0, p=0.022. Further evaluation of the 9 patients for whom a reduction in seizure frequency was reported revealed that increases in AED doses (or additional AED therapy) were apparent for 5 of these patients. The patients all had minimal variations in AED exposure levels pre- and posttreatment despite adjustments in dosage.

Furthermore, based on caregiver observation, the proportion of patients experiencing seizures on a daily basis was reduced from 26.9% (7 of 26 patients) at Baseline to 8.0% (2 out of 25 patients) at Month 6 and subsequently to 11.1% (2 out of 18 patients) at Month 60.

Table 22 – Overview of Seizure Frequencies in Study C2485

	Baseline			Month 6			Change from baseline		
	n	Mean (SD)	Median (range)	n	Mean (SD)	Median (range)	n	Mean (SD)	Median (range)
24-hour EEG performed	18			17					
Total number of seizures (per 24 hours)	17	6.30 (7.880)	1.00 (0.0 to 25.0)	17	2.75 (8.654)	0.00 (0.0 to 35.8)	16	-2.65 (6.089)	-0.99 (-17.0 to 10.8)
p-value [a]									0.022
Clinical seizures (per 24 hours)									
Partial onset	17	0.53 (1.067)	0.00 (0.0 to 3.0)	17	0.11 (0.321)	0.00 (0.0 to 1.0)	16	-0.44 (0.969)	0.00 (-3.0 to 0.0)
Generalized onset	17	1.53 (5.359)	0.00 (0.0 to 22.0)	17	2.10 (8.677)	0.00 (0.0 to 35.8)	16	0.61 (3.653)	0.00 (-4.0 to 13.8)
Subclinical seizures (per 24 hours)									
Partial onset	17	3.48 (5.365)	0.98 (0.0 to 18.0)	17	0.53 (1.580)	0.00 (0.0 to 6.0)	16	-2.01 (2.988)	-0.49 (-10.0 to 0.0)
Generalized onset	17	0.76 (3.149)	0.00 (0.0 to 13.0)	17	0.00 (0.000)	0.00 (0.0 to 0.0)	16	-0.81 (3.245)	0.00 (-13.0 to 0.0)

[a] p-value obtained from a sign test

Seizure event not counted if EEG recording lasted <18 hours

- Study M2301

Study M2301 was a prospective, double-blind, randomized, parallel-group, placebo controlled, multi-centre trial evaluating the treatment with everolimus versus placebo in patients of any age with TSC who have SEGA. A total of 78 subjects were randomised to everolimus (starting dose: 4.5 mg/m²; target trough concentration: 5-15 ng/ml), 39 subjects received placebo.

There was no statistically significant difference in seizure frequency change from Baseline to Week 24 in the total number of seizures per 24 hours, in the everolimus arm relative to placebo (one-sided rank ANCOVA, p=0.20). However, these data should be interpreted with caution as seizures were only observed at Baseline in 27 of 78 patients in the everolimus arm and in 13 of 39 patients in the placebo arm. As a result, the median number of seizures in both treatment arms was 0 (zero) at Baseline and thus, any reduction in seizure frequency was highly unlikely. Among the patients with a known seizure frequency at Baseline and at Week 24 (n=34), the reduction in median seizure frequency from Baseline to week 24 was -3.01 (95% CI: -5.00; -1.36).

- Study M2302

Study M2302 was a prospective double-blind, randomized, parallel-group, placebo-controlled trial to evaluate the efficacy and safety of a once daily oral dose of everolimus 10 mg versus placebo in adult patients with angiomyolipoma associated with clinically definitive diagnosis of either TSC or sporadic lymphangioleiomyomatosis. In Study M2302, the clinical activity of everolimus in TSC-associated seizures was an exploratory objective. Changes from Baseline in the severity of seizures were assessed using the seizure severity questionnaire in those patients who were taking AEDs at Baseline.

Only 10 out of 79 patients in the everolimus arm and 5 out of 39 patients in the placebo arm filled in the seizure severity questionnaire. There was not a meaningful difference in median global change score between everolimus- (3.50, range: 2.00-4.75) and placebo- (3.88, range: 3.50-4.75) treated patients at Week 24.

Study by Krueger et al. (2013, Ann Neurol, 74:679-87): Everolimus treatment of refractory epilepsy in tuberous sclerosis complex

The study was a small, prospective, uncontrolled, open-label, Phase I/II trial in 2 USA centres in patients ≥ 2 years of age with confirmed diagnosis of TSC and refractory epilepsy. Subjects had to have ≥8 seizures during the 4 week prospective Baseline period, which was followed by a 4 week titration and

8 week maintenance period (starting dose: 5 mg/m²/day; target trough concentration: 5-15 ng/mL). Concomitant AED had to remain stable during the study.

In this study, seizure frequency was reduced by ≥ 50% in 12 of 20 patients treated with everolimus, as measured during the last 4 weeks of maintenance compared to 4 week Baseline period (primary endpoint). A total of 3 subjects had 25-50% seizure frequency reduction, 3 subjects had an increase in seizure frequency. The median seizure frequency decreased by 73% (31 versus 8.5 seizures per 28 days, p< 0001). Improvement in seizure frequency/duration was also noted on 23-hour video-EEG before/after treatment with everolimus. According to the authors, the response was 'driven primarily by a reduction in POS (p=0.048), although it is interesting to note that the 2 subjects with the highest number of generalized onset seizure at Baseline (40 and 24, respectively) showed the greatest improvement overall (-33 and -22, respectively)'.

2.4.4. Discussion on clinical efficacy

Design and conduct of clinical studies

The main support of the present application for an extension of the indication of Votubia to adjunctive treatment of patients aged 2 years and older with refractory seizures associated with TSC, consisted of the results of the pivotal phase III study M2304. This study was a three-arm, randomized, double-blind, placebo-controlled superiority study conducted in patients aged 2-65 years with clinically definitive diagnosis of TSC and treatment-resistant epilepsy. Supportive data were also presented from previous studies in SEGA and renal angiomyolipoma patients, which collected information on seizure frequency as secondary or exploratory objectives. However, as these studies were not specifically designed for the purpose of investigating the effect of everolimus on TSC seizures (e.g. no seizures required at Baseline, no stable existing AED regimen) and were not sufficiently powered to allow a meaningful data analyses, the studies were only of limited added value. The CHMP furthermore noted a small, uncontrolled published study (Krueger et al., 2013) with encouraging results suggesting a benefit of everolimus in TSC seizures treatment.

The primary objective of study M2304 was to compare the effect of everolimus in reducing TSC seizure frequency for each of two trough ranges (LT group: 3 to 7 ng/mL and HT group: 9 to 15 ng/mL) versus placebo in patients with TSC who were taking 1-3 concomitant AEDs at stable doses. A total of 366 patients were randomized (stratified by age): 117 to everolimus LT, 130 to everolimus HT and 119 to placebo. After an 8 week Baseline period, patients entered an 18 week blinded Core phase comprising 6 week titration and 12 week maintenance period. Similarly high proportions of subjects across all 3 treatment groups completed the Core phase (94-96%). Discontinuations due to lack of effect were rare and occurred for 2 patients each in the everolimus HT and the placebo group. The optional extension study part during which all subjects received everolimus was scheduled until 48 weeks after the last patient had completed the Maintenance period. At the time of the cut-off for the study report submitted in support of this application (02-Oct-2015), the Extension part of the study was still ongoing. Only approximately 50 % of subjects who initiated the extension study part had already completed 54 weeks of treatment.

Generally, in- and exclusion criteria for this study were considered by the CHMP adequate in order to recruit patients in line with the sought target patient population. Eligible patients had to have partial-onset epilepsy according to the classification of the ILAE definition from 1989 and as revised in 2009 (Berg 2010). This classification was further modified defining POS in patients with 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 generalized seizure on ictal EEG. The CHMP agreed that seizures in TSC subjects derive from multifocal cortical disease and thus can

be expected to be of focal origin. In fact, the majority of subjects had complex partial (65% of subjects) and/or secondarily generalized POS seizures (52% of subjects) at Baseline. EEG confirmed generalized onset seizures occurred in less than 2% of subjects during Baseline, 3.3% of subjects had “other” seizures types (unclassifiable seizures or infantile/epileptic spasms). Patients with infantile spasms were only allowed to be included in the study if the latter seizure types were treated and residual.

The primary and most secondary efficacy endpoints referred to a similar definition of TSC seizures as in the inclusion criteria, i.e. seizures with motor signs or sensory seizures (without motor signs) with EEG evidence of focal onset. The CHMP noted that this definition was not in line with the initially claimed indication, i.e. seizures associated with TSC, without restriction to focal-onset. In fact, there were only few patients with generalized-onset seizures (6 patients in total) or Lennox Gastaut Syndrome (5 patients) and patients with infantile spasms were only allowed to be included, if the latter seizure types were treated and residual. Furthermore, there was no category for epileptic spasms so that such spasms would have been reported based on the clinical presentation, e.g. atonic or tonic seizures. Therefore, the study did not allow to definitely assessing the effect of everolimus in these epilepsy forms and seizure types. Consequently, the indication was limited to patients whose refractory POS with or without secondary generalization are associated with TSC. Notably, such wording does not exclude patients, who besides POS also suffer from other seizure types (e.g. generalised onset seizures or infantile/epileptic spasms).

The CHMP furthermore noted the inclusion criteria requiring ≥ 16 POS during the study Baseline period (8 weeks), and the actual Baseline seizure frequency was indeed high with a median of 34.5 (LT), 37.8 (HT) and 42.0 (placebo group) per 28 days. This was despite the vast majority of patients was taking 2 or 3 concomitant AEDs. This and the fact that nearly half of the study populations failed 6 or more prior AEDs illustrate the extent of refractory epilepsy in the study population.

The CHMP also noted that patients weighing less than 12 kg were excluded from study participation which seemed contradictory to the PIP requirement to include patients down to the age of 12 months. This was because of the volume of blood drawn in the study, and in line with the Ethical considerations for clinical trials on medicinal products conducted with the paediatric population, recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use. This justification was considered acceptable by the CHMP. However, the weight restriction excluded many patients of the lower age range and in fact no patient below the age of 2 years was recruited. This was adequately reflected by the proposed minimum age of 2 years for the TSC seizure indication.

The trial population is otherwise considered appropriate. There were no particularly notable exclusion criteria that might raise issues regarding the external validity of the trial to the proposed indicated patient population. The exclusion of patients with an episode of status epilepticus within the preceding year is considered a reasonable precaution and it is not necessary to restrict the indicated patient population accordingly.

The primary efficacy endpoint for this application was the 50% response rate of TSC seizures during the Maintenance phase compared to Baseline. Secondary efficacy endpoints included percentage reduction from Baseline in TSC seizure frequency, seizure-free rate, categorized reduction or exacerbation (≥ 25 % increase) from Baseline seizure frequency, long-term evaluation of seizure frequency and QoL.

Overall, the study design including the choice of endpoints was in line with the recommendations of the guideline on clinical investigation of medicinal products in the treatment of epileptic disorders (CHMP/EWP/566/98 Rev.2/Corr) regarding confirmatory studies in adjunctive treatment in treatment resistant seizures. The statistical methods were also considered appropriate.

Efficacy data and additional analyses

The 50% response rates, i.e. percentage of patients with a reduction of at least 50% in TSC seizure frequency were 28.2% (95% CI: 20.3, 37.3) and 40.0% (95% CI: 31.5, 49.0) in the everolimus LT and HT arms compared with 15.1% (95% CI: 9.2, 22.8) in the placebo arm. The difference for both everolimus arms to placebo was statistically significant ($p=0.008$ and $p<0.001$). Median percentage reduction in weekly TSC seizure frequency was 29.3% (95% CI: 18.8, 41.9) and 39.6% (95% CI: 35.0, 48.7) for the everolimus LT and HT arms, respectively, compared with 14.9% (95% CI: 0.1, 21.7) for the placebo arm ($p=0.003$ and $p<0.001$, respectively). Sensitivity analyses as well as the PP analyses were highly consistent with the primary analysis of both endpoints.

The magnitude of effect, i.e. 13.1% (LT) and 24.9% (HT) more patients with a ≥50% reduction from Baseline in TSC seizures in the everolimus groups compared to the placebo group, and 16% (HT) and 27.5% (HT) difference between everolimus and placebo in median percentage seizure frequency reduction from Baseline was considered clinically relevant in particular considering that the study population was clearly treatment refractory with a high Baseline seizure frequency.

Seizure freedom rates during study maintenance phase were low (5.1%, 3.8% and 0.8% in the LT, HT and placebo arms, respectively), which, taking into account the high refractoriness and Baseline seizure frequency of study subjects, was not surprising. The rates of patients without seizures were higher in both everolimus arms compared to placebo, although confidence intervals were overlapping.

In line with the results for the 50% responder rates, higher proportions of responders in both everolimus treatment arms were also seen for other response categories (25%-, 75%- and 100% responder rates). Conversely, the proportions of subjects with no change (i.e., up to 25% increase to <25% reduction in seizure frequency) as well as exacerbation (≥25% increase in seizure frequency) were each highest in the placebo group and lowest in the HT everolimus group.

In children and adolescents no remarkable differences were found with respect to quality of life between active and placebo treatment, while the Qolie-31-P questionnaire used in adults did not deliver interpretable data.

Subgroup analyses by age, gender, race, ethnicity, Baseline seizure frequency, number as well as name of concomitant AEDs and TSC features, respectively, were generally in line with the overall study results showing an advantage of everolimus over placebo in reducing TSC seizures across the different subgroup categories.

More than 80% of the study population were aged less than 18 years. Subgroup analyses by age showed higher response rates and increased reductions in seizure frequency for both everolimus treatment groups relative to placebo for all age categories (<6 years, 6 to <12 years, 12 to <18 years, and ≥ 18 years). Seizure frequency appeared markedly reduced within the lowest age category (2-5 years). Further analyses within the 1 to <6 age category showed that 26% of the subjects were actually 2 years and 22% 3 years old. Response rates as well as median % reduction in seizure frequency in these very young (2-3 year old) children were similar to that of the entire age category of 1 to <6 year old children and appeared somewhat higher than the respective efficacy results of the older age categories (6 to < 12, 12 to < 18 and ≥ 18 years, respectively).

Subgroup analyses by seizure type indicated that the effect of everolimus in reducing TSC seizures was not limited to or does not exclude a particular subtype, including simple partial, complex partial or secondary generalized seizures. Due to the concern if some of the seizures classified in study M2304 as POS could actually have had a generalised onset, further analyses were conducted by the MAH based on a more restricted classification of POS, i.e. excluding seizure types which would be regarded as generalised onset seizures in patients without underlying TSC (e.g. absence like seizures) and including only type IA1 and IA2a (as simple partial seizures), type IB3 (as complex partial seizures) and type IC2-4

seizures (as secondarily generalised convulsive seizures with clonic features, tonic features or with tonic-clonic features, respectively). The restricted analyses for all POS showed very similar results compared to the primary analysis with regard to response rate as well as median percentage reduction in seizure frequency from Baseline, which was considered reassuring by the CHMP. Analyses of response rates and percentage reduction from Baseline for all seizures types combined, including generalized onset and other seizures were also largely in line with the respective primary efficacy analyses. Too few subjects had confirmed generalized onset seizures at Baseline (2 in each treatment arm), thus not allowing firm conclusions regarding this seizure type. In fact, albeit not considered a robust finding for methodological reasons and due to the low number of patients with seizures at Baseline, an increase in mean frequency of generalised onset seizures was found in the SEGA study C2485.

More severe TSC has been described in literature in patients with TSC2- compared to TSC1 gene mutations. Subgroup analyses by TSC1/TSC2 mutations status were available for approximately 40% of study subjects for whom information on TSC mutation status was available from local testing. The majority (approx. 75%) of these tested subjects had TSC 2 mutations only, and the presented efficacy analyses regarding responder rate and reduction in seizure frequency from Baseline in subjects with TSC 2 mutation only was generally in line with the primary efficacy analysis of study M2304, which was reassuring. The hitherto identified number of subjects with identified TSC 1 mutation only was low (7-9 per treatment arm) and while the respective results did not raise any concern, no firm conclusions could be drawn.

There were some Baseline imbalances in the study which potentially may have disadvantaged the placebo group compared to the active treatment groups. Median seizure frequency appeared higher in the placebo group compared to both active treatment groups. Baseline seizure frequency was found to be a statistically significant factor in the exposure-efficacy models (see section 2.3.) and could have been a disadvantage for the placebo group. However, the effect appeared to be small and was not considered clinically relevant. This was further supported by relevant subgroup analyses, whereby 50% responder rates and percentage reduction in seizure frequency were higher in the active treatment groups compared to placebo for all Baseline seizure frequency category (<4.7, 4.7 to <9.4, 9.4 to <20.6, and ≥20.6) except for median percentage reduction from Baseline in the LT group in the 9.4 - < 20.6 seizure subgroup, where similar percentage reduction in TSC seizure frequency was observed as for placebo. There was also slightly higher percentages of subjects in the placebo group with 3 concomitant AEDs, with cortical tubers or with SEN compared to the active treatment groups, but subgroup analyses by TSC features or number of concomitant AEDs, respectively, were generally in line with the overall study results. The possible impact of each one of these imbalances on the overall study results was considered small. Given that the effect of everolimus in reducing TSC seizures was large, it was unlikely that the imbalances together could have driven the positive study result, although without the imbalances the overall effect might have been slightly lower.

With regards to TSC features, only few subjects without cortical tubers were enrolled (14, 13, and 4 patients in the HT, LT and placebo arm, respectively), which is not surprising given that cortical tubers have been discussed as epileptogenic foci in subjects with TSC. Consequently, data of everolimus for the treatment of seizures in TSC subjects with or without cortical tubers is limited.

Finally, a higher frequency of use of rescue medication was observed in the HT arm (17.7%) compared to placebo (11.8%) and LT (10.3%). However, rescue medication consisted almost exclusively of a single dose of a benzodiazepine and was therefore not expected to have impacted the overall study results. Additional analysis in which patients who used rescue medication were considered as non-responders, showed results consistent with the primary analysis, although the absolute rates recorded were somewhat lower.

With regards to long-term data, the preliminary data derived from the extension study, in which all

patients received everolimus (trough concentrations: 3 to 15ng/mL), indicated maintenance of the effect, with 50% responder rates increasing over time, responder rates across the three treatment arms approximating over time, an acceptable level of discontinuations (13.7% of all randomized patients) with lack of efficacy being given as primary reason for discontinuation in only 1.6% of subjects. However, only half of the patients who initiated the extension part of the study had already completed 54 weeks of treatment and no subject had completed the extension, and thus the data at later time points should be interpreted with caution. Updated long-term efficacy data should be submitted as soon as possible including the final clinical study report (anticipated by March 2017) in order to allow for a better interpretability of long-term efficacy of everolimus in the treatment of TSC seizures.

Dosing regimen

The applicant proposes a target trough concentration range of everolimus of 5-15 ng/mL which is in line with the target range approved for the TSC SEGA indication. Based on the observed positive exposure response relationship and since model-based analysis predicted a time-normalized c_{min} of 5.3 ng/mL as minimum efficacious dose, as well as an overall considered acceptable safety profile across this trough concentration range (see discussion on safety in 2.5.1.) without a clear worsening of the safety profile towards the higher end of the target range, this proposal was considered acceptable by the CHMP.

The starting dose in study M2304 was determined based on age and concomitant use of CYP3A4/PgP inducers. Based on the study results, new daily starting doses were proposed differing from the doses used in the clinical trial as follows:

Age	Starting dose without co-administration of CYP3A4/PgP inducer	Starting dose with co-administration of CYP3A4/PgP inducer
<6 years	6 mg/m^2	9 mg/m^2
≥6 years	5 mg/m^2	8 mg/m^2

In short, an increase of the starting dose in adults was proposed compared to the doses used in the study (3.0 and 5.0 mg/m^2/day with and without inducer) due to the finding that median c_{min} values after Week 1 of treatment for patients ≥ 18 years of age was below 5 ng/mL and was lower than among patients of other age ranges (see also section 2.3.). Furthermore, a simplification of the age-based starting dose scheme was proposed. The recommended starting doses are defined according to two categories of age (<6 years and ≥ 6 years) instead of three as in Study M2304 (<10 years, 10-18 years, and ≥ 18 years). This also meant a decrease of the starting dose in patients 6 to 10 years of age (from 6.0 and 9.0 mg/m^2/day with and without inducer to 5.0 and 8.0 mg/m^2/day). This new scheme was supported by simulations of c_{min} values in patients of age ranges ≥ 1 to <3, ≥ 3 to <6, ≥ 6 to <12, ≥ 12 to <18, and ≥ 18 years.

To support the use of the adjusted starting doses, the MAH conducted supportive simulations. The results of these simulations showed that in adults, indeed, the increase of the starting dose from 3 to 5.0 mg/m^2/day resulted in a higher c_{min}. However, in some patients, there was a large variability exceeding the higher limit of the target range for some patients. Nevertheless, taking into account that doses are titrated to the individually clinical optimal dose, overall, the proposed dosing investigated in the study was accepted by the CHMP.

As for the titration scheme, more flexibility was introduced compared to the fixed 2 mg titration dose (or 4 mg for patients with concomitant use of CYP3A4/PgP inducer) used in Study M2304 by proposing increments of 1 – 4 mg steps. This was considered acceptable by the CHMP.

Therapeutic drug monitoring to maintain c_{min} within the target concentration range is recommended as for the SEGA indication of Votubia. This was considered adequate given that the data showed that higher trough levels are more efficacious and considering that various factors might affect exposure levels, including the wide range of body sizes in paediatric and adult patients, different CYP3A4 activity in

children of different age groups, and possible co-administration of enzyme inducers. Given the half-life of everolimus, whole blood trough concentrations should be assessed at least 1 week after commencing treatment.

2.4.5. Conclusions on the clinical efficacy

The CHMP concluded that the application for use of Votubia as adjunctive treatment of patients aged 2 years and older whose refractory POS, with or without secondary generalisation, are associated with TSC at a target everolimus trough concentration range of 5-15 ng/mL, has been adequately supported by clinical efficacy data. A clinically relevant effect in patients representative of the proposed target population was shown for both the everolimus LT and the HT and a positive exposure-response relationship was seen. Available long-term data seem to support maintenance of the effect, but additional data should be provided as soon as possible to supplement the limited data available at the time of this report. Finally, the CHMP was of the view that the recommended dosing regimen, though slightly deviating from the starting and titration doses studied in the pivotal trial, has been adequately substantiated.

2.5. Clinical safety

Introduction

Given the experience with a range of medicinal products and indications for which everolimus has been approved for marketing in the EU for several years, the safety profile can be considered well established. However, despite several attempts and various analyses, a clear exposure-adverse events (AEs) relationship had not been established at the time of this report.

Side effects reported with everolimus therapy across different populations include stomatitis/oral mucositis, hyperlipidemia, skin toxicity (rash and related events), hyperglycemia, non-infectious pneumonitis, and infection. Additional known risks with everolimus therapy requiring close monitoring include hypersensitivity (anaphylactic reactions), wound healing complications, increased creatinine/proteinuria/renal failure, dyslipidemia, hypophosphatemia, cardiac failure, cytopenia, haemorrhage, thrombotic and embolic events, female fertility (including secondary amenorrhea), pre-existing infections (reactivation, aggravation, or exacerbation), and safety in patients with hepatic impairment.

The evaluation of safety for the present application was primarily based on study M2304 including data from 366 patients with refractory TSC seizures. In addition, two long-term safety data pools were used as follows:

- 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.

AEs were summarised by presenting the number and percentage of patients having at least one AE, and having at least one AE in each body system/primary system organ class (SOC), and for each preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) coding version 18.1. A subject with multiple occurrences of an AE was counted only once in the AE category. AE summaries included all AEs starting on or after Study Day 1 (i.e. on or after the day of the first intake of study drug) and starting no later than 28 (Studies in the Old Safety Pool) or 30 days (M2304) after the last treatment date.

A revised strategy for adverse drug reaction selection for SmPC section 4.8 compared to previous assessments was applied, based on all AEs (irrespective of reported causality with the study drug) reported from the four TSC studies (M2301, M2302, C2485, and M2304). The final assessment was made using the Bradford Hill criteria.

Patient exposure

Study M2304

For a summary of the study design, methods and Baseline characteristics, see section 2.4.2.

Study M2304 comprised 366 patients (safety set), 357 of whom received everolimus (247 were randomized to everolimus in the Core phase [6-week titration plus 12 weeks maintenance period], and 110 patients from the placebo arm in the Core phase who subsequently switched to receive everolimus during the Extension phase). Of the 247 patients receiving everolimus, 117 were allocated to the low trough (LT) range (target trough 3-7 ng/mL) treatment arm and 130 were assigned to the high trough (HT) range (target trough 9-15 ng/mL).

During the Core phase of study M2304, the total exposure amounted to 39.2 and 43.7 patient-years for patients randomized to the everolimus LT and HT arms, respectively, versus 40.3 patient-years for those randomized to the placebo arm.

As of the 02-Oct-2015 data cut-off date for this report, the Long-term Evaluation Set for Safety comprised 117, 130, and 110 patients in the LT, HT and placebo group, respectively. The maximum duration of exposure to everolimus in the Long-term Evaluation Safety Set was 117 weeks. The median duration of exposure to everolimus increased to 55.4 weeks (range: 2 to 112) and 48.9 weeks (range: 3 to 117), respectively, in the LT and HT treatment groups. Median exposure to treatment with everolimus for patients who were randomized to placebo and subsequently switched to everolimus in the Extension phase was 38.2 weeks (range: 0 to 98). The total patient exposure amounted to 353.46 patient-years (126.03, 136.72, and 90.72 patient-years in the LT, HT and the placebo group, respectively)

- Cumulative everolimus dose and dose intensity

In the Core phase, median dose intensities were 5.18, 7.49, and 6.12 mg/m^2/day for the everolimus LT, HT, and placebo treatment groups, respectively.

For the Core and Extension phase combined, overall, the median dose intensity of everolimus was 6.38 mg/m^2/day (range: 1.1 to 26.1). Median dose intensities were 5.38 and 8.36 mg/m^2/day for the everolimus LT and HT treatment groups, respectively, and 5.87 mg/m^2/day for patients who were randomized to placebo and subsequently switched to everolimus in the Extension phase.

- Everolimus concentration at trough (c_{min})

The majority of patients randomized to the everolimus LT treatment group achieved the target c_{min} range of 3 to 7 ng/mL using the starting dose, based on the PK sampling performed at Week 1. The median c_{min} was maintained within the target range during the entire Core phase for most patients. The HT treatment group demonstrated similar c_{min} values as the LT group at Week 1 because the same starting doses were administered to both treatment arms.

As a result of dose titrations, the mean and median c_{min} values for the HT group gradually increased from Week 1 through the end of the Core phase (Week 18). Different c_{min} ranges were exhibited by the two treatment groups at the start of the maintenance period (Week 10), but considerable overlap was evident. Almost 60% of patients randomized to the HT group were below the lower limit of the target C_{min} range (9 ng/mL) after the 18 weeks of exposure to everolimus during the Core phase.

At Week 18, the everolimus LT group had a median c_{min} of 5.05 ng/mL while the median c_{min} for the HT

group was 8.32 ng/mL. See also Table 3 for an overview of the trough concentration by time window during the Core phase.

For the Core and Extension phase combined, median c_{min} for the LT treatment arm remained within the 3 to 7 ng/mL target range during the Extension phase. For the HT treatment arm, c_{min} values were generally maintained at the level attained by Week 18 (end of the Core phase) for the duration of the Extension phase.

Patient disposition and demographics as well as disease characteristics are summarised in section 2.4.2.1.

Old TSC Safety Pool (excluding Study M2304)

The Old TSC Safety Pool included 251 patients who received everolimus (111 patients from study M2301, 112 patients from study M2302 and 28 patients from study C2485). Median duration of exposure was 47.2 months (range: 0.5 to 83.2), and the cumulative exposure in the TSC setting was 927 patient-years.

The demographic characteristics in the pooled dataset were comparable with those in study M2304 for the majority of the characteristics assessed, with the exception of age and age categories. The median age of patients in the Old TSC Safety Pool was 19.0 years (min-max: 1-61) compared to 10.1 years (min-max: 2.2-56.3 years) in Study M2304. There were a higher proportion of patients in the Old TSC Safety Pool who were aged ≥18 years (54.2% vs. 18.3% in Study M2304). This difference in age could be attributed to the fact that Study M2302 enrolled adult patients only. The proportion of Asian patients was higher in Study M2304 than in the Old TSC Safety Pool (23.8% vs. 4.4%).

New TSC Safety Pool (including Study M2304)

The New TSC Safety Pool comprised in total 608 patients who received everolimus. The median duration of exposure in the New TSC Safety Pool was 18.3 months (range: 0.1 to 83.2), and the cumulative exposure in the TSC setting was 1281 patient-years.

Adverse events

Study M2304

In the Core phase, the majority of patients (>90%) receiving treatment with everolimus experienced at least one AE during the course of the study, compared to 77.3% of patients in the placebo treatment group. The overall incidence of AEs was similar in both LT (92.3%) and HT (94.6%) groups. However, AEs suspected to be drug related, grade 3/4 AEs, AEs requiring dose interruption or reduction, and AEs requiring additional therapy were more frequently reported in the everolimus HT group (with a difference of >5% relative to the LT group) (Table 23).

Table 23 – Summary of Safety (Core Phase) - AEs in Study M2304 (Safety Set)

	Everolimus		Placebo
	LT target of 3-7 ng/mL	HT target of 9-15 ng/mL	
	N=117	N=130	N=119
Category	n (%)	n (%)	n (%)
Adverse events (AEs) [a]	**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)
All deaths [b]	**0**	**0**	**0**
On-treatment deaths [c]	0	0	0
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 [d]	94 (80.3)	112 (86.2)	63 (52.9)

[a] 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
[b] Includes deaths before the start of everolimus in the Extension phase
[c] Includes deaths up to 30 days after the last dose of study treatment and before start of everolimus in the Extension phase
[d] Additional therapy includes all non-drug therapy and concomitant medications

Table 24 provides a summary of AEs, whether related or unrelated to study drug, by SOC during the Core phase. No clear trend to a higher frequency in AEs in the HT arm compared to the LT group was seen. Rather, sometimes the frequencies are actually numerically lower than in the LT arm.

Table 24 – Summary of AEs in Study M2304 (Safety Set)

	Everolimus		Placebo
	LT target of 3-7 ng/mL	HT target of 9-15 ng/mL	
	N=117	N=130	N=119
Primary system organ class	**n (%)**	**n (%)**	**n (%)**
Any primary system organ class	**108 (92.3)**	**123 (94.6)**	**92 (77.3)**
Gastrointestinal disorders	78 (66.7)	97 (74.6)	36 (30.3)
Infections and infestations	64 (54.7)	84 (64.6)	54 (45.4)
Skin and subcutaneous tissue disorders	29 (24.8)	34 (26.2)	18 (15.1)
Respiratory, thoracic and mediastinal disorders	30 (25.6)	33 (25.4)	9 (7.6)
General disorders and administration site conditions	29 (24.8)	26 (20.0)	11 (9.2)
Metabolism and nutrition disorders	24 (20.5)	24 (18.5)	15 (12.6)
Nervous system disorders	20 (17.1)	24 (18.5)	10 (8.4)
Investigations	21 (17.9)	23 (17.7)	14 (11.8)
Injury, poisoning and procedural complications	12 (10.3)	14 (10.8)	12 (10.1)
Psychiatric disorders	15 (12.8)	12 (9.2)	9 (7.6)
Reproductive system and breast disorders	6 (5.1)	11 (8.5)	9 (7.6)
Blood and lymphatic system disorders	7 (6.0)	8 (6.2)	8 (6.7)
Musculoskeletal and connective tissue disorders	7 (6.0)	5 (3.8)	5 (4.2)
Ear and labyrinth disorders	2 (1.7)	3 (2.3)	1 (0.8)
Eye disorders	2 (1.7)	3 (2.3)	0
Renal and urinary disorders	2 (1.7)	3 (2.3)	1 (0.8)
Cardiac disorders	0	2 (1.5)	1 (0.8)
Vascular disorders	6 (5.1)	2 (1.5)	5 (4.2)
Hepatobiliary disorders	2 (1.7)	1 (0.8)	0
Immune system disorders	1 (0.9)	1 (0.8)	0
Endocrine disorders	1 (0.9)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (0.8)

Primary system organ classes are presented in descending frequency, as reported in the Everolimus 9-15 ng/ml column
A patient with multiple adverse events within a primary system organ class is counted only once in the total row
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.

The most commonly reported AEs (≥ 20% of patients) by PT in the Core phase were stomatitis (28.2%) and mouth ulceration (23.9%) in the LT group and stomatitis (30.8%), mouth ulceration (21.5%), and diarrhoea (21.5%) in the HT group. These events were primarily grade 1 (mild) or grade 2 (moderate) events.

An overview of AEs observed more frequently (≥5%) in the everolimus arms than in the placebo arm is provided in Table 25.

Table 25 – AEs reported more frequently (≥5%) in Everolimus Treatment Groups compared to Placebo (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	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Stomatitis	33 (28.2)	2 (1.7)	40 (30.8)	3 (2.3)	4 (3.4)	0
Diarrhoea	20 (17.1)	0	28 (21.5)	0	6 (5.0)	0
Mouth ulceration	28 (23.9)	2 (1.7)	28 (21.5)	0	5 (4.2)	0
Aphthous ulcer	5 (4.3)	0	19 (14.6)	2 (1.5)	2 (1.7)	0
Pyrexia	23 (19.7)	0	18 (13.8)	1 (0.8)	6 (5.0)	0
Cough	13 (11.1)	0	13 (10.0)	0	4 (3.4)	0
Rash	7 (6.0)	0	13 (10.0)	0	3 (2.5)	0
Blood cholesterol increased	6 (5.1)	0	9 (6.9)	1 (0.8)	1 (0.8)	0
Pharyngitis	6 (5.1)	2 (1.7)	8 (6.2)	0	1 (0.8)	0

Preferred terms are sorted in descending frequency of all grades column, 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

Grade 3/4 events represented only a small proportion of the overall incidence of all events (17.9% and 23.8% of patients reported in the everolimus LT and HT treatment groups, respectively, and 10.9% in the placebo treatment group). The most frequent grade 3/4 events in the everolimus LT and HT treatment groups were stomatitis (1.7% and 2.3%, respectively), neutropenia (1.7% and 2.3%), Status epilepticus (1.7% and 1.5%), pneumonia (0.9% and 2.3%), and irregular menstruation (0.0% and 2.3%). The incidence of grade 3/4 neutropenia was similar in the placebo treatment group (2.5%).

Only seven patients experienced grade 4 AEs: two (1.7%) in the everolimus LT treatment group (single cases of ear infection and status epilepticus) and five (3.8%) in the everolimus HT group (two cases of neutropenia and single reports of increased blood triglycerides, infectious croup, and pneumonia). Five of these events were suspected to be drug related (including both events in the everolimus LT group and the cases of increased blood triglycerides, neutropenia, and pneumonia in the everolimus HT group). All seven events subsequently resolved.

- AEs suspected to be related to everolimus

AEs suspected to be related to everolimus were less frequently reported in the everolimus LT compared to the everolimus HT group (66.7% vs. 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%), and aphthous ulcer (+2.6% and +11.4%).

- Long-term data (patients receiving everolimus during the Core or Extension phases combined)

The overall incidence of AEs for the Core and Extension phase combined was comparable with the Core phase (see Table 26). However, AEs suspected to be drug related, grade 3/4 AEs, SAEs, AEs leading to discontinuations, AEs requiring dose interruption or reduction, and AEs requiring additional therapy were

more frequently reported during the combined Core and Extension period.

Table 26 - Summary of Long-Term Safety - AEs in Study M2304 (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 N=357	
Category	n (%)		n (%)		n (%)		n (%)	
Adverse events (AEs) [a]	**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)
All deaths [b]	**0**		**1**	**(0.8)**	**0**		**1**	**(0.3)**
On-treatment deaths [c]	0		1	(0.8)	0		1	(0.3)
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 [d]	109	(93.2)	124	(95.4)	85	(77.3)	318	(89.1)

[a] Includes AEs occurring on or after the start of study treatment and no more than 30 days after the discontinuation of everolimus
[b] Includes deaths on or after the start of everolimus
[c] Includes deaths on or after the start of everolimus and up to 30 days after the last dose of everolimus
[d] Additional therapy includes all non-drug therapy and concomitant medications

Similar to the Core phase, stomatitis (32.8%), pyrexia (25.8%), diarrhoea (24.1%), and mouth ulceration (22.1%) were the most common AEs reported in the Long Term Evaluation Safety Set. Also as observed in the Core phase, stomatitis (31.4%), mouth ulceration (20.7%), and aphthous ulcer (10.1%) were the most common AEs suspected to be related to everolimus.

Overall, minimal differences were observed in the incidence of AEs between the everolimus LT and HT treatment groups.

Furthermore, overall 65 patients (18.2%) experienced AEs belonging to MedDRA SOC Injury, poisoning, and procedural complications. The most commonly reported AEs (with at least ≥ 2% of patients) in this SOC included fall (19 patients, 5.3%), contusion (11 patients, 3.1%), skin abrasion (9 patients, 2.5%), and arthropod bite, laceration (each seven patients, 2.0%). Head injury was reported in six patients (1.7%). Of the 19 patients who experienced fall, four cases were attributed to or were as a consequence of a seizure. Two cases of fall were considered serious. Of the six patients who had head injury, fall due to seizure was reported for one patient. This was not suspected to be drug-related and no action was taken and the event head injury was reported as resolved at the same day. For one patient limb injury and skin abrasion were reported as due to a seizure-related fall. Both the events were grade 1 and were not suspected to be drug-related. The patient was treated with concomitant medications and non-drug therapy.

When evaluating emerging AEs overtime, a trend was observed in the reduction of the incidence of most AEs with continued everolimus therapy. The incidence of emerging AEs decreased from 93.3% in the first 6 months of therapy to 64.4% in the second year of therapy. The incidences of overall and specific AEs were similar in Months >6 to ≤ 12 and Months >12 to ≤24.

Old TSC Safety Pool

The overall incidence of AEs was similar between the Old TSC Safety Pool and Study M2304 (see Table 27). However, there are differences in incidence of certain AEs categories namely, grade 3 or 4 AEs, SAEs, and AEs leading to study drug interruption/reduction or additional therapies, where incidence was higher in the Old TSC Safety Pool compared to the Study M2304 patient population.

Table 27 – Summary of Safety – AEs in the Old TSC Safety Pool

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.

Overall, the pattern of AEs was similar as observed in study M2304 with slight difference in the incidence rates (see Table 28). The most commonly reported AEs (≥ 20% of patients) by PT were: stomatitis (48.6%), nasopharyngitis (39.0%), upper respiratory tract infection (29.1%), mouth ulceration (28.3%), acne and diarrhea (each 26.3%), cough, seizure, vomiting (each 24.3%), headache (23.1%), pyrexia (22.7%), hypercholesterolemia (21.5%), sinusitis (20.7%), and urinary tract infection (20.3%).

Grade 3/4 events were observed in 138 patients (55.0%). With the exception of pneumonia (8.8%), seizure (6.4%), and stomatitis (6.0%), grade 3/4 events were observed in <5% patients.

The overall profile of AEs suspected to be study drug-related was similar to long-term evaluation in study M2304. However, the incidence rate of AEs was higher compared to study M2304 (94.8% vs. 79.0%). Consistent with study M2304, stomatitis and mouth ulceration were the most frequently observed AEs suspected to be related to everolimus in the Old TSC Safety Pool.

Table 28 – Frequently reported AEs (≥10% in all grades) irrespective of causality by PT - TSC pooled studies excluding Study M2304 (Long-term Evaluation Safety Set)

	Everolimus N=251	
	All grades	Grades 3/4
Preferred term	**n (%)**	**n (%)**
Any preferred term	**250 (99.6)**	**138 (55.0)**
Stomatitis	122 (48.6)	15 (6.0)
Nasopharyngitis	98 (39.0)	1 (0.4)
Upper respiratory tract infection	73 (29.1)	2 (0.8)
Mouth ulceration	71 (28.3)	6 (2.4)
Acne	66 (26.3)	1 (0.4)
Diarrhoea	66 (26.3)	0
Cough	61 (24.3)	0
Seizure	61 (24.3)	16 (6.4)
Vomiting	61 (24.3)	2 (0.8)
Headache	58 (23.1)	0
Pyrexia	57 (22.7)	9 (3.6)
Hypercholesterolaemia	54 (21.5)	1 (0.4)
Sinusitis	52 (20.7)	3 (1.2)
Urinary tract infection	51 (20.3)	2 (0.8)
Fatigue	47 (18.7)	1 (0.4)
Hypertension	45 (17.9)	1 (0.4)
Pneumonia	45 (17.9)	22 (8.8)
Otitis media	39 (15.5)	3 (1.2)
Bronchitis	38 (15.1)	6 (2.4)
Gastroenteritis	35 (13.9)	5 (2.0)
Decreased appetite	34 (13.5)	1 (0.4)
Aphthous ulcer	33 (13.1)	1 (0.4)
Nausea	33 (13.1)	0
Pharyngitis	33 (13.1)	0
Blood cholesterol increased	32 (12.7)	1 (0.4)
Constipation	31 (12.4)	1 (0.4)
Abdominal pain	29 (11.6)	0
Oedema peripheral	29 (11.6)	1 (0.4)
Rash	29 (11.6)	0
Proteinuria	28 (11.2)	2 (0.8)
Amenorrhoea	27 (10.8)	7 (2.8)
Back pain	27 (10.8)	0
Ear infection	26 (10.4)	2 (0.8)
Blood triglycerides increased	25 (10.0)	1 (0.4)
Conjunctivitis	25 (10.0)	0
Dizziness	25 (10.0)	1 (0.4)

Preferred terms are sorted in descending frequency
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 28 days after the discontinuation of everolimus
MedDRA version 18.1, CTCAE version 3.0, TSC Case Retrieval Strategy dated 24-Nov-2015
Data from following trials are included in the analysis: C2485, M2301, and M2302

Results of the Old TSC Safety Pool were generally consistent with those from Study M2304 with regards to incidence of emerging AEs over time, with a trend of a reduction in AE emergence with continued everolimus therapy. The incidence of emerging AEs decreased from 98.4% during the first 6 months to 55.6% beyond Month 48.

For the period of ≤ 6 month: the overall incidence of emerging AEs was similar between the Old TSC Safety Pool and Study M2304 (98.4% vs. 93.3%, respectively); however, differences in incidence were noted with respect to some of the AEs reported (≥ 5% difference in event rates for a particular AE reported in ≥ 10% of patients in either dataset). Stomatitis (+10.7%), acne (+10.1%), hypercholesterolemia (+9.3%), fatigue (+7.8%), and headache (+6.2%) were reported at a higher frequency in the Old TSC Safety Pool relative to Study M2304 while diarrhoea (-6.9%) and pyrexia (-6.5%) were observed less frequently.

For Months >6 to ≤ 12, the overall incidence of emerging AEs was higher in the Old TSC Safety Pool than in Study M2304 (82.9% vs. 64.9%). In general, the incidence of specific AEs was similar. With regards to Months >12 to ≤ 24, the overall incidence of emerging AEs was higher in the Old TSC Safety Pool than in Study M2304 (91.4% vs. 64.4%). Differences in incidence (using the same criteria as identified above) were noted for some of the AEs reported, with stomatitis (+7.3%), nasopharyngitis (+6.6%), and upper respiratory tract infection (+5.0%) reported more frequently in the Old TSC Safety Pool.

There was a marked decrease in the incidence of stomatitis emerging over time in both Study M2304 and the Old TSC Safety Pool. The incidence rates of emerging stomatitis decreased by approximately 20% and 25% in Study M2304 and the Old TSC Safety Pool, respectively, over time (for Months >12 to ≤ 24 relative to Months ≤ 6).

In the Old TSC Safety Pool, the incidence of emerging AEs was similar in Years 2, 3, and 4.

New TSC Safety Pool

The overall incidence of AEs was comparable in study M2304 and the Old TSC Safety Pool. The incidences of individual AEs and grade 3/4 AEs was higher in the Old TSC Safety Pool compared to the New TSC Safety Pool and Study M2304.

Table 29 - AEs irrespective of causality by SOC, PT and Maximum Grade - TSC pooled studies including Study M2304 (Long-term Evaluation Safety Set)

System organ class	Preferred term	Everolimus Overall All grades N=608	Everolimus Overall Grade 3/4 N=608
Blood and lymphatic system disorders			
	Anaemia	37 (6.1)	3 (0.5)
	Neutropenia	33 (5.4)	16 (2.6)
	Leukopenia	19 (3.1)	0
	Thrombocytopenia	13 (2.1)	0
	Lymphopenia	11 (1.8)	2 (0.3)
Gastrointestinal disorders			
	Stomatitis	239 (39.3)	24 (3.9)
	Diarrhoea	152 (25.0)	2 (0.3)
	Mouth ulceration	150 (24.7)	9 (1.5)
	Vomiting	126 (20.7)	4 (0.7)
	Constipation	48 (7.9)	2 (0.3)
	Nausea	46 (7.6)	1 (0.2)
	Abdominal pain	41 (6.7)	1 (0.2)
	Flatulence	14 (2.3)	0
	Oral pain	10 (1.6)	0
	Gastritis	8 (1.3)	0

System organ class	Preferred term	Everolimus Overall All grades N=608	Everolimus Overall Grade 3/4 N=608
	Tongue ulceration	8 (1.3)	0
	Lip ulceration	7 (1.2)	0
	Gingival pain	4 (0.7)	0
	Glossitis	3 (0.5)	0
General disorders and administration site conditions			
	Pyrexia	149 (24.5)	13 (2.1)
	Fatigue	65 (10.7)	1 (0.2)
Immune system disorders			
	Hypersensitivity	11 (1.8)	1 (0.2)
Infections and infestations			
	Nasopharyngitis	168 (27.6)	2 (0.3)
	Upper respiratory tract infection	138 (22.7)	3 (0.5)
	Pneumonia	68 (11.2)	35 (5.8)
	Sinusitis	66 (10.9)	5 (0.8)
	Urinary tract infection	66 (10.9)	4 (0.7)
	Pharyngitis	59 (9.7)	3 (0.5)
	Otitis media	47 (7.7)	3 (0.5)
	Cellulitis	32 (5.3)	6 (1.0)
	Pharyngitis streptococcal	28 (4.6)	1 (0.2)
	Gastroenteritis viral	26 (4.3)	4 (0.7)
	Gingivitis	13 (2.1)	0
	Herpes zoster	4 (0.7)	0
	Bronchitis viral	1 (0.2)	1 (0.2)
Investigations			
	Blood lactate dehydrogenase increased	20 (3.3)	0
	Blood luteinising hormone increased	6 (1.0)	0
	Blood follicle stimulating hormone increased	2 (0.3)	0
Metabolism and nutrition disorders			
	Hypercholesterolaemia	65 (10.7)	1 (0.2)
	Decreased appetite	63 (10.4)	3 (0.5)
	Hypertriglyceridaemia	43 (7.1)	2 (0.3)
	Hyperlipidaemia	33 (5.4)	2 (0.3)
	Hypophosphataemia	22 (3.6)	5 (0.8)
	Hyperglycaemia	11 (1.8)	1 (0.2)
Nervous system disorders			
	Headache	92 (15.1)	1 (0.2)
	Dysgeusia	5 (0.8)	0
Psychiatric disorders			
	Insomnia	33 (5.4)	1 (0.2)
	Aggression	25 (4.1)	5 (0.8)
	Irritability	21 (3.5)	2 (0.3)
Renal and urinary disorders			
	Proteinuria	33 (5.4)	2 (0.3)
Reproductive system and breast disorders			
	Amenorrhoea	32 (5.3)	7 (1.2)
	Menstruation irregular	29 (4.8)	3 (0.5)
	Menorrhagia	21 (3.5)	0
	Vaginal haemorrhage	13 (2.1)	0
	Ovarian cyst	12 (2.0)	2 (0.3)
	Menstruation delayed	2 (0.3)	0

System organ class	Preferred term	Everolimus Overall All grades N=608	Everolimus Overall Grade 3/4 N=608
Respiratory, thoracic and mediastinal disorders			
	Cough	111 (18.3)	0
	Epistaxis	37 (6.1)	0
	Pneumonitis	4 (0.7)	0
Skin and subcutaneous tissue disorders			
	Acne	85 (14.0)	1 (0.2)
	Rash	59 (9.7)	0
	Dry skin	31 (5.1)	0
	Dermatitis acneiform	16 (2.6)	0
	Rash erythematous	6 (1.0)	0
	Rash generalised	5 (0.8)	1 (0.2)
	Erythema	4 (0.7)	0
	Rash maculo-papular	4 (0.7)	0
	Angioedema	2 (0.3)	2 (0.3)
	Rash macular	2 (0.3)	0
Vascular disorders			
	Hypertension	54 (8.9)	2 (0.3)
	Lymphedema	6 (1.0)	0

Serious adverse event/deaths/other significant events

- Serious AEs (SAEs)

Study M2304

In the Core phase, SAEs were reported more frequently in the everolimus treatment groups (13.7% vs. 13.8% vs. 2.5% for the LT, HT, and placebo groups, respectively). However, the incidence of specific SAEs was low for all treatment groups. Events within the infections and infestations SOC (+6.0% and +6.9% for the LT and HT groups, respectively relative to placebo) and the nervous system disorders SOC (+4.3% and +3.0% for the LT and HT groups, respectively relative to placebo) were more evident for patients receiving treatment with everolimus LT and HT than with placebo.

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. 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%).

When Core and Extension phase were combined, SAEs were observed with comparable incidence for the everolimus LT (25.6%) and HT (26.2%) treatment groups. Overall, the incidence of specific SAEs was low, with only pneumonia (4.8%) and seizures (3.4%) reported in more than 2% of patients.

Old TSC Safety Pool

SAEs were reported in 100 patients (39.8%). With the exception of pneumonia (21 patients, 8.4%), seizure (9 patients, 3.6%), and epilepsy (8 patients, 3.2%), SAEs were reported in less than 3% of patients. SAEs related to study drug were observed in a small proportion of patients in the Old TSC Safety Pool (43 patients, 17.1%). Except for pneumonia (15 patients, 6.0%), other related AEs by PT were observed in one, two, or three patients each.

- Death

Study M2304

No deaths were reported during the Core phase of the study, although 1 adolescent patient died 2 weeks after Screening during the Baseline phase of the study, prior to randomization. No study medication was administered.

One patient, initially randomized 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 was assessed as the cause of death. This was not suspected by the Investigator to be drug related. A second death was reported in the Extension phase (secondary to pneumonia, suspected to be study drug related) after the data cut-off date of 02-Oct-2015 for the primary analysis.

Old TSC Safety Pool

Three deaths were reported in the Old TSC Safety Pool, none of which was considered to be related to everolimus.

One paediatric patient in study M2301 died three years after start of everolimus due to asphyxia (strangulation). The death was accidental and not considered by the Investigator to be related to study drug. One adolescent patient in Study C2485, died due to epilepsy in the fifth year of the study. The Investigator did not suspect a relationship between the event and the study medication. Finally, one adult patient in Study M2302, died due to seizure disorder (complication of TSC). The Investigator did not suspect a relationship between the event and the study medication.

- Overview of adverse events of special interest (AESIs)

The assessment of the relatively comprehensive analysis of AESIs is limited to the Core phase of trial M2304. Groupings of AESI where higher proportions of everolimus-treated patients reported events (and where there was a ≥ 10% difference relative to placebo) included: stomatitis (+45.5% and +54.6% for the everolimus LT and HT treatment groups, respectively), dyslipidemia in pediatric population (+7.3% and +12.6%), and hyperglycaemia/new-onset diabetes mellitus (+6.9% and +10.1%).

Table 30 – AESIs in the Core Phase of Study M2304 irrespective of Causality (Safety Set)

	Everolimus		Placebo
	LT target of 3-7 ng/mL	HT target of 9-15 ng/mL	
	N=117	N=130	N=119
Grouping	n (%)	n (%)	n (%)
Stomatitis	64 (54.7)	83 (63.8)	11 (9.2)
Dyslipidemia in pediatric population (patients less than 18 years) [a]	12 (12.5)	19 (17.8)	5 (5.2)
Hyperglycemia/new-onset of diabetes mellitus	17 (14.5)	23 (17.7)	9 (7.6)
Hypersensitivity (anaphylactic reactions)	16 (13.7)	20 (15.4)	8 (6.7)
Effects of everolimus on brain growth and development, particularly in patients under 3 years of age [b]	4 (50.0)	1 (14.3)	1 (8.3)

Female fertility (including secondary amenorrhoea) [c]	4 (13.8)	4 (11.8)	4 (10.8)
Haemorrhages	7 (6.0)	15 (11.5)	4 (3.4)
Cytopenia	9 (7.7)	10 (7.7)	9 (7.6)
Increased creatinine/proteinuria/renal failure	1 (0.9)	5 (3.8)	3 (2.5)
Postnatal developmental toxicity[d]	1 (1.0)	2 (1.9)	2 (2.1)
Non infectious pneumonitis	0	1 (0.8)	0
Thrombotic and embolic events	0	1 (0.8)	0
Hypophosphatemia	2 (1.7)	0	0
Male infertility [e]	1 (3.3)	0	0
Pre-existing infection (reactivation, aggravation, or exacerbation)	0	0	1 (0.8)

Groupings 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.
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

[a] Percentages are calculated based on the number of patients aged <18 years (n=96/107/97 for the everolimus LT, HT, and placebo treatment groups, respectively)
[b] Percentages are calculated based on the number of patients aged <3 years (n=8/7/12 for the everolimus LT, HT, and placebo treatment groups, respectively)
[c] Percentages are calculated based on the number of female patients aged 10 to 55 years (n=29/34/37 for the everolimus LT, HT, and placebo treatment groups, respectively)
[d] Percentages are calculated based on the number of patients aged ≤ 18 years (n=98/108/97 for the everolimus LT, HT, and placebo treatment groups, respectively)
[e] Percentages are calculated based on the number of male patients aged ≥ 10 years (n=30/36/26 for the everolimus LT, HT, and placebo treatment groups, respectively).

A more detailed analysis of the effect of everolimus on brain growth and development (in particular in patients under 3 years of age) was provided in Table 31.

Table 31 – Effects of everolimus on brain growth and development 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

Laboratory findings

- Haematology

In the Core phase of study M2304, haematology abnormalities that were more frequently reported in the everolimus treatment groups (with differences of ≥ 10% relative to placebo) included absolute neutrophils (hypo) (+2.1% and +14.2% for the everolimus LT and HT treatment groups, respectively), and absolute lymphocytes (hyper) (+15.6% and +1.7%). Decreases in absolute neutrophils, haemoglobin, and white blood cells, and increases in absolute lymphocytes were the most frequently observed haematological abnormalities in the Long-term Evaluation Safety Set of the study (noted in ≥ 25% of all patients).

In the Old TSC Safety Pool, the pattern of haematological abnormalities was similar to Study M2304, except for abnormalities of coagulation pathways, including partial thromboplastin time and prothrombin time which were not measured in Study M2304.

- Clinical chemistry

In the Core phase of study M2304, the frequency of biochemical abnormalities was similar in the three treatment groups. These abnormalities were predominantly grade 1-2. Abnormalities that were more frequent in the everolimus treatment groups relative to placebo (with ≥ 10% differences) included cholesterol increased (+27.5% and +27.4% for the everolimus LT and HT treatment groups,

respectively), triglycerides increased (+20.9% and +16.7%), SGPT (ALT) increased (+11.2% and +16.4%), SGOT (AST) increased (+8.6% and +14.3%) and phosphate decreased (+6.0% and +12.8%).

In the Core and Extension phase combined, clinical chemistry abnormalities were reported in the majority of patients receiving treatment with everolimus, with increases in cholesterol, calcium, triglycerides, magnesium, creatinine, and sodium, and decreases in calcium observed in ≥ 25% of patients. As observed in Core phase of the study, the grade 3/4 abnormalities were infrequent.

In the Old TSC Safety Pool, the most frequently occurring (≥ 25% of patients) clinical chemistry abnormalities included: increase in cholesterol, triglycerides, AST, ALT, alkaline phosphatase, and decrease in bicarbonate, fibrinogen, and phosphate. The grade 3/4 abnormalities were infrequent.

Safety in special populations

Age

Subgroup analyses by age (≥ 1 to < 3 years; ≥ 3 to < 6 years; ≥ 6 to <12 years; ≥ 12 to <18 years; ≥ 18 years) showed a higher frequency of some events (e.g. bronchitis, nasopharyngitis, upper respiratory tract infection, pyrexia) in younger age (<6 years usually). However, this should be interpreted with caution as these events are also usually more frequent in the general population at this age, and also the sample size in the age group 1-3 years was small.

Gender

No consistent trends were evident that were considered indicative of an increased risk for an event on the basis of gender.

Race and ethnicity

Analyses of AEs by race and ethnicity showed patterns that were generally consistent with those of the overall population.

Discontinuation due to adverse events

In the Core phase of study M2304, six patients (5.1%) and four patients (3.1%) in the everolimus LT and HT treatment groups, respectively, and two patients (1.7%) in the placebo group discontinued treatment with study drug due to AEs. The most common AE leading to study drug discontinuation was stomatitis (three patients, 2 in the LT group and 1 in the HT group). All the other events were reported in one patient each (mouth ulceration, neutropenia, and pneumonia in the HT group; anxiety, diarrhoea, immunodeficiency, and pyrexia in the LT group; respiratory tract infection viral and weight decreased in the placebo group).

The rate of study drug discontinuation due to AEs was higher during the long-term evaluation phase (Core or Extension phases combined) compared to Core phase. AEs leading to study drug discontinuation were more evident in the everolimus LT treatment group than in the HT group. Overall the most common AEs leading to study drug discontinuation were stomatitis (five patients), pneumonia (four patients), and pyrexia (two patients), all the other events were reported in one patient each.

The rate of study drug discontinuation due to AEs was higher in Study M2304 compared to the Old TSC Safety Pool. AEs leading to discontinuation of study drug for patients in the pooled dataset were reported in 8.4% of patients, and these AEs were reported infrequently in one patient each.

Post marketing experience

The total worldwide cumulative market exposure to Afinitor®/Votubia® in the Oncology and TSC settings combined through 31-Mar-2015 was estimated to be 84.021 patient-treatment-years. The total cumulative worldwide patient exposure (until 31-Mar-2015) based on the worldwide sales of tablets sold

per defined daily dose, has been estimated at 79.056 patient-treatment years for the Oncology setting and 4.965 patient-treatment years for the TSC setting.

2.5.1. Discussion on clinical safety

The safety evaluation of the present application for an indication of adjunctive treatment of patients aged 2 years and older whose refractory partial-onset seizures, with or without secondary generalisation, are associated with TSC, was mainly based on the pivotal study M2304. M2304 is the largest trial performed in TSC, and provides the largest randomized controlled safety data source submitted until the time of this report. However, the data remain limited, but for a rare disease, the data base would not be expected to be much larger.

Votubia is already approved for use in patients with renal angiomyolipoma and SEGA associated with TSC and the safety profile in TSC is considered well established. Seizures and SEGA occur in a widely overlapping (mainly but not exclusively paediatric) population. Thus, to support the safety evaluation of this application, the MAH provided safety pools of the data from previous studies in TSC patients (studies C2485, M2301, and M2302). Two safety pools were considered, one with and the other without the data of study M2304. Data from previous TSC studies covered data in patients treated with everolimus for a substantially longer period in time (median duration of exposure: 47.2 months) than in study M2304 combining core and extension phases (median duration of exposure: 55.4 and 48.9 weeks in the LT and HT treatment groups respectively).

During the review of the data, it was questioned if data from trial M2302 should have been included for means of (safety) pooling since the population in this trial in renal angiomyolipoma is different from the populations studied in C2485, M2301, and M2304. The major difference (besides the hamartoma primarily intended to be treated) in the populations is that M2302 is a trial exclusively in adults. However, since by the time of this report no major safety difference between adults and paediatric patients have been detected (with the exceptions of a higher frequency of infections in the very young paediatric population plus a trend to lower c_{min} levels in older children and adults explained by a higher clearance in older patients), inclusion of data from study M2302 was not objected.

The majority of patients (>90%) in study M2304 receiving treatment with everolimus experienced at least one AE during the course of the study. In several MedDRA SOCs (gastrointestinal disorders [primarily stomatitis, mouth ulceration, and diarrhoea], infections and infestations, respiratory, thoracic and mediastinal disorders, skin and subcutaneous tissue disorders, general disorders and administration site conditions, nervous system disorders) frequency of AEs were considerably higher in the active treatment arms compared to placebo. However, the findings were broadly in line with the known safety profile of Votubia.

Most of the AEs were no more than modest in severity (typically grade 1 or 2). However, in the Extension phase of study M2304, death on treatment occurred in 2 patients. The causes of the 2 deaths were seizure (sudden unexpected death in epilepsy) and pneumonia (infection), respectively. The first case, while not suspected by the Investigator to be study drug related, could be remotely related to study drug in the sense of lack of efficacy. As for the latter case, the potential causal relationship to everolimus was difficult to assess, but indeed, direct adverse effects of everolimus (neutropenia, general immunosuppression, and stomatitis reducing the epithelial barrier against bacterial infection) can cause lethal side effects. Notably, no patient on placebo died. However, due to the 2 active groups and 1:1:1 randomisation, the *a priori* likelihood to die on treatment was twice as high in the LT and HT arms compared to placebo, and during the Extension phase all patients were on treatment.

The review of AEs of special interest effect showed a very high reporting rate of 50% for effects of everolimus on brain growth and development (in particular in patients under 3 years of age) in the LT

arm. However, the size of the subgroups (8, 7, and 12 patients aged less than 3 years for the LT, HT and placebo group, respectively) and possibly lower efficacy in the LT compared to the HT arm (2 of the 4 cases in the LT group were seizure related) likely explain this finding.

As found in previous studies, no clear correlation between plasma levels and AE frequency was seen in study M2304, although there was a small trend towards a higher frequency of AEs suspected to be related to everolimus in the HT group compared to the LT group.

Evaluation of emerging AE incidence rates over time indicated that these were considerably higher during the first 6 months of treatment with everolimus, and that the incidence tapered off thereafter. The incidence of emerging AEs was observed to be the lowest for exposure beyond Month 48 of treatment.

Analyses by age revealed a higher frequency of some events (e.g. bronchitis, nasopharyngitis, upper respiratory tract infection, pyrexia) in younger patients (<6 years). However, this should be interpreted with caution as these events are also usually more frequent in the general population at this age, and also the sample size in the age group 1-3 years is small and does not allow for a meaningful interpretation. SmPC section 4.8, already states that cases of infections were reported at a higher frequency, especially in children below the age of 3 years.

No patient in trial M2304 was older than 65 years of age, which was considered in line with the target population of this study. However, the current safety information referring to oncological settings was considered sufficient by the CHMP.

When comparing the data from study M2304 with the Old TSC safety pool (including all previous TSC studies but not study M2304), a trend was observed, whereby AEs were reported less frequently for trial M2304, and also with a lower severity than in the preceding trials. This was mainly attributed by the MAH to the longer exposure duration in the previous TSC trials. While indeed an increase in AE frequencies with longer treatment duration could be expected, the CHMP considered that other factors most likely were more relevant, in particular the already established risk profile of Votubia in TSC in general leading not only to a lower sensitivity reporting AEs, but eventually also to a better treatment of AEs, better dose titrating etc. compared to the preceding trials. Two AEs occurred, at least initially, more frequently in trial M2304 compared to the Old TSC safety pool, namely diarrhoea and pyrexia. An explanation by patient factors suggested that this finding is likely to be attributable to the younger patient population evaluated in the safety pool. The majority (81.7%) of patients in Study M2304 were children, including 28.4% who were <6 years of age; the corresponding figures for the Old TSC pool were 45.8% and 15.1%, respectively. This explanation was accepted as younger children are more prone to develop infection.

Overall, the data (discontinuation rate in the long term Extension phase of study M2304 of less than 20%) suggest that long term treatment of TSC patients (with epilepsy) is feasible and risks are manageable.

Given the similarities in the study populations of previous TSC trials (in particular SEGA) and study M2304, it was not surprising that, albeit being the largest study conducted in TSC up until this report, safety data of trial M2304 in essence confirmed the already established safety profile of everolimus in TSC. However, as a result of the enlargement of the TSC safety database (New TSC Safety Pool) as well as a revised assessment strategy compared to previous applications, the frequency of several adverse reactions as reported in Section 4.8 of the SmPC changed as follows:

- The frequency of Diarrhoea, Vomiting, Pyrexia, Fatigue, Urinary Tract Infection, Decreased Appetite, Headache, Cough and Rash changed from common to very common
- The frequency of Tongue ulceration, Lip ulceration, Hypersensitivity and Insomnia changed from uncommon to common.
- The frequency of Otitis media changed from very common to common.

- The frequency of Herpes zoster, Dysgeusia, Menstruation delayed, Pneumonitis and Erythema changed from common to uncommon.

The revised assessment strategy counting AEs irrespective of reported causality with the study drug was considered acceptable and the reason for several of the increases in frequency.

2.5.2. Conclusions on clinical safety

The CHMP concluded that the additional data provided in this application were consistent with the already known safety profile of everolimus. As in previous studies, no clear exposure-adverse event relationship was found in study M2304. Everolimus was well tolerated, and AEs were generally manageable. Overall, the safety data were considered adequate to support the use of Votubia as adjunctive treatment of patients aged 2 years and older whose refractory partial-onset seizures, with or without secondary generalisation, are associated with TSC. The safety information in the SmPC has been updated in line with the new data and analyses.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan (RMP):

The PRAC considered that the RMP version 12.0 (dated 16 May 2016) could be acceptable if the MAH implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report (AR) dated 2 September 2016.

The CHMP endorsed this advice.

The MAH implemented the changes in the RMP as requested by the PRAC and the CHMP.

The CHMP endorsed the Risk Management Plan version 12.1 (dated 7 October 2016) with the following content:

Safety concerns

Important identified risks	• Non-infectious pneumonitis • Severe infections • Hypersensitivity (anaphylactic reactions) • Stomatitis • Wound healing complications • Increased creatinine / proteinuria / renal failure • Hyperglycemia / new onset diabetes mellitus • Dyslipidemia • Hypophosphatemia • Cardiac failure • Cytopenia • Hemorrhages • Thrombotic and embolic events • Female fertility (including secondary amenorrhea) • Pre-existing infection (reactivation, aggravation, or exacerbation) • Safety in patients with hepatic impairment
Important identified	• Strong CYP3A4 inhibitors and PgP inhibitors

interactions	• Moderate CYP3A4 inhibitors and PgP inhibitor • Strong CYP3A4 inducers and PgP inducers • CYP3A4 substrates and PgP substrates • Increased risk for angioedema when combining mTOR inhibitors and ACE inhibitors
Important potential risks	• Postnatal developmental toxicity • Pregnant or breast-feeding women • Male infertility • Muscle-wasting / muscle-loss
Important potential interaction	**Oncology setting only** • Everolimus with concomitant exemestane use
Missing information	• Off-label use in pediatric and adolescent patients • Long-term safety • Onset of benign or malignant tumors **Oncology setting only** • Patients with uncontrolled cardiac disease • Comparative safety of everolimus and exemestane therapy vs. everolimus monotherapy • Safety in breast cancer patients pre-treated with cytotoxic therapies **TSC setting only** • Effects of everolimus on brain growth and development, particularly in patients under 3 years of age • Neurocognitive and sexual development in pediatric patients

Pharmacovigilance plan

Table 32 - Ongoing and planned additional PhV studies / activities in the PV Plan

Study / activity Type, title, and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
TSC setting				
Clinical study **CRAD001M2304** Three-armed, randomized, double-blind, placebo-controlled study of efficacy and safety of two trough-ranges of everolimus as adjunctive therapy in patients with TSC (**category 3)**	The primary objective is compare the reduction in frequency of partial-onset seizures on each of two trough ranges of everolimus (3 to 7 ng/mL and 9 to 15 ng/mL) vs. placebo in patients with TSC who are taking one to three AEDs.	Long-term safety Neurocognitive and sexual development (TSC setting only)	Ongoing	Final CSR: 2Q2018
Clinical study **CRAD001M2305** Long-term follow-up study to monitor for	The primary objective is to monitor the growth and development of pediatric patients with TSC-associated	Postnatal developmental toxicity Long-term safety	Ongoing	Final CSR for PASS: 2026

growth and development of pediatric patients previously treated with everolimus in study CRAD001M2301 (**category 3)**	SEGA previously enrolled in CRAD001M2301, who had received everolimus as part of study CRAD001M2301 and may or may not be continuing treatment with everolimus.	(TSC-SEGA setting only)		
Disease registry **CRAD001MIC03** An international disease registry collecting data on manifestations, interventions, and outcomes in patients with tuberous sclerosis complex – TOSCA (**category 3)**	To map the course of TSC manifestations and their prognostic role; to identify patients with rare symptoms and co-morbidities; to record interventions and their outcomes; to contribute to create an evidence base for disease assessment and therapy and to inform further promote research in TSC; to measure quality of life in TSC patients; to collect information on sexual maturation/endocrine assessments in patients with TSC, if available.	Male infertility Long-term safety (TSC setting only) Neurocognitive and sexual development (TSC setting only)	Ongoing	Submissions of annual interim analyses are planned yearly until study end. Final CSR for disease registry: Dec-2017 Final CSR for PASS: Dec-2027
Oncology setting				
Clinical study **CRAD001J2301** A randomized, phase III, double-blind, placebo-controlled multicenter trial of everolimus **in combination with trastuzumab and paclitaxel** as first-line therapy in women with HER2 positive locally advanced or metastatic breast cancer (**category 3)**	The primary objective of the study is to compare progression free survival (PFS) between combination treatment of everolimus/ trastuzumab/ paclitaxel and the combination treatment trastuzumab /paclitaxel in patients with HER2 overexpressing, unresectable locally advanced or metastatic breast cancer.	Long-term safety (Oncology setting only)	Ongoing	Final close out CSR planned submission: 4Q2016. Additionally, this planned submission package will include a comprehensive repot providing exposure response relationship data / info for PFS and OS.
Clinical study **CRAD001W2301** A randomized, phase III, double-blind, placebo-controlled multicenter trial of daily everolimus **in combination with trastuzumab and vinorelbine**, in pre-treated women with HER2/neu over-expressing locally advanced or metastatic breast cancer (**category 3)**	The primary objective is to compare the combination of everolimus, vinorelbine and trastuzumab to vinorelbine and trastuzumab alone with respect to progression-free survival in women with HER2/neu overexpressing locally advanced or metastatic breast cancer who are resistant to trastuzumab and have been pre-treated with a taxane.	Long-term safety (Oncology setting only)	Ongoing	Final close-out CSR planned submission: 4Q2016. Additionally, this planned submission package will include a comprehensive repot providing exposure response relationship data / info for PFS and OS.

Clinical study **CRAD001Y2201** A three-arm randomized phase II study investigating the combination of everolimus with exemestane vs. everolimus alone vs. capecitabine in patients with estrogen-receptor positive metastatic breast cancer after recurrence or progression on letrozole or anastrozole **(category 1)**	The primary objective is to estimate the hazard ratio of PFS for everolimus plus exemestane versus everolimus alone in post-menopausal women with ER positive, HER2 negative, advanced breast cancer after recurrence or progression on letrozole or anastrozole.	Comparative safety of everolimus and exemestane therapy vs. everolimus monotherapy Long-term safety (Oncology setting only)	Ongoing	Final CSR planned submission: 3Q2017

*Category 1 studies are imposed activities considered key to the benefit risk of the product.

Category 2 studies are specific obligations

Category 3 studies are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

Risk minimisation measures

Table 33 - Summary table of the Risk Minimisation Measures

Safety concern	**Routine risk minimization measures**	**Additional risk minimization measures**
Important identified risks		
Non-infectious pneumonitis	Wording in SmPC Section 4.2, 4.4.4.8.	None
Severe infections	Wording in SmPC Section 4.4, 4.8.	
Hypersensitivity (anaphylactic reactions)	Wording in SmPC Section 4.3, 4.4, 4.5, 4.8.	
Stomatitis	Wording in SmPC Section 4.2, 4.4, 4.8.	
Wound healing complications	Wording in SmPC Section 4.4, 4.8.	
Increased creatinine/proteinuria/renal failure	Wording in SmPC Section 4.4, 4.8.	
Hyperglycemia/new onset diabetes mellitus	Wording in SmPC Section 4.2, 4.4, 4.8.	
Dyslipidemia	Wording in SmPC Section 4.2, 4.4, 4.8.	
Hypophosphatemia	Wording in SmPC Section 4.8.	

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Cardiac failure	Wording in SmPC Section 4.8.	
Cytopenia	Wording in SmPC Section 4.2, 4.4, 4.8.	
Hemorrhages	Wording in SmPC Section 4.4, 4.8.	
Thrombotic and embolic events	Wording in SmPC Section 4.8.	
Female fertility (including secondary amenorrhea)	Wording in SmPC Section 4.6, 4.8.	None
Pre-existing infection (reactivation, aggravation, or exacerbation)	Wording in SmPC Section 4.4, 4.8.	
Safety in patients with hepatic impairment	Wording in SmPC Section 4.2, 4.4, 5.2.	
Important Identified interactions		
Strong CYP3A4 inhibitors and PgP inhibitors Moderate CYP3A4 inhibitors and PgP inhibitor Strong CYP3A4 inducers and PgP inducers CYP3A4 substrates and PgP substrates Increased risk for angioedema when combining mTOR inhibitors and ACE inhibitors	Wording in SmPC Section 4.4, 4.5, 4.8.	None
Important potential risks		
Postnatal developmental toxicity	Wording in PIL	None
Pregnant or breast-feeding women	Wording in SmPC section 4.6.	None
Male infertility	Wording in SmPC section 4.6, 5.3.	None
Muscle-wasting/muscle-loss	This potential risk is currently considered adequately addressed based on the current PV monitoring plan; risk minimization measures are evaluated on an ongoing basis.	

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Important potential interactions		
Everolimus with concomitant exemestane use	Wording in SmPC section 4.5.	None
Missing information		
Off-label use in pediatric and adolescent patients Long-term safety Onset of benign or malignant tumors **Oncology setting only** Patients with uncontrolled cardiac disease Comparative safety of everolimus and exemestane therapy vs. everolimus monotherapy Safety in breast cancer patients pre-treated with cytotoxic therapies **TSC setting only** Effects of everolimus on brain growth and development, particularly in patients under 3 years of age Neurocognitive and sexual development in pediatric patients	The Safety concerns due to limitations of the current CDP are considered adequately addressed based on the current PV monitoring plan; risk minimization measures are evaluated on an ongoing basis. Prescription only medicinal product with no known non-prescription availability, to be used by experienced physicians (e.g. specialist) in currently approved indications only.	None

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

2.7. Update of the Product information

As a consequence of the extension of the indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC for Votubia 2 mg, 3 mg and 5 mg dispersible tablets have been updated. The main changes to section 4.1 and 4.2 are summarised below (additions **in bold and underlined**, deletions as ~~strike-through~~):

- Section 4.1 Therapeutic indications

Refractory seizures associated with tuberous sclerosis complex (TSC)

Votubia is indicated as adjunctive treatment of patients aged 2 years and older whose refractory partial-onset seizures, with or without secondary generalisation, are associated with tuberous sclerosis complex (TSC).

Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC)

Votubia is indicated for the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not amenable to surgery.

(...)

- Section 4.2 Posology and method of administration

Posology

(...)

Starting dose and target trough concentrations in SEGA associated with TSC

The recommended starting dose for Votubia **for the treatment of patients with SEGA** is 4.5 mg/m2. A higher starting dose of 7 mg/m2 is recommended for patients 1 to less than 3 years of age based on pharmacokinetic simulations (see section 5.2). Different strengths of Votubia dispersible tablets can be combined to attain the desired dose.

~~Everolimus whole blood trough concentrations should be assessed at least 1 week after commencing treatment for patients <3 years of age and approximately 2 weeks after commencing treatment for patients ≥3 years of age. Dosing should be titrated to attain trough concentrations of 5 to 15 ng/ml. The dose may be increased to attain a higher trough concentration within the target range to obtain optimal efficacy, subject to tolerability.~~

Dosing recommendations for paediatric patients with SEGA are consistent with those for the adult SEGA population, except for patients in the range from 1 year to less than 3 years of age, and those with hepatic impairment (see “Hepatic impairment” below and section 5.2).

Starting dose and target trough concentrations in TSC with refractory seizures

The recommended starting dose for Votubia for the treatment of patients with seizures is shown in Table 1. Different strengths of Votubia dispersible tablets can be combined to attain the desired dose.

Table 1 Votubia starting dose for patients with TSC and refractory seizures

Age	Starting dose without co-administration of CYP3A4/PgP inducer	Starting dose with co-administration of CYP3A4/PgP inducer
<6 years	**6 mg/m2**	**9 mg/m2**
≥6 years	**5 mg/m2**	**8 mg/m2**

Dosing recommendations for paediatric patients with seizures are consistent with those for the adult population, except for patients in the range from 2 years to less than 6 years of age, and those with hepatic impairment (see “Hepatic impairment” below and section 5.2).

Dose monitoring

Everolimus whole blood trough concentrations should be assessed at least 1 week after commencing treatment. Dosing should be titrated to attain trough concentrations of 5 to 15 ng/ml. The dose may be increased to attain a higher trough concentration within the target range to obtain optimal efficacy, subject to tolerability.

Titration

Individualised dosing should be titrated by increasing the dose by increments of 1 to 4 mg to attain the target trough concentration for optimal clinical response. Efficacy, safety, concomitant therapy, and the current trough concentration should be considered when planning for dose titration. Individualised dose titration can be based on simple proportion:

New everolimus dose = current dose x (target concentration / current concentration)

For example, a patient's current dose based on BSA is 4 mg with a steady state concentration of 4 ng/ml. In order to achieve a target concentration above the lower Cmin limit of 5 ng/ml, e.g. 8 ng/ml, the new everolimus dose would be 8 mg (an increase of 4 mg from the current daily dose).

Long-term monitoring

For patients with TSC who have SEGA, SEGA volume should be evaluated approximately 3 months after commencing Votubia therapy, with subsequent dose adjustments taking changes in SEGA volume, corresponding trough concentration, and tolerability into consideration.

For patients with TSC who have SEGA and patients with TSC and refractory seizures, o~~O~~nce a stable dose is attained, trough concentrations should be monitored every 3 to 6 months in patients with changing body surface area, or every 6 to 12 months in patients with stable body surface area, for the duration of treatment.

(…)

Therapeutic drug monitoring

Therapeutic drug monitoring of everolimus blood concentrations, using a validated assay, is **required**. Trough concentrations should be assessed ~~approximately~~ **at least 1**~~2~~ week~~s~~ after the initial dose, after any change in dose or pharmaceutical form, after initiation of or change in co-administration of CYP3A4 ~~inducers or~~ inhibitors (see sections 4.4 and 4.5) or after any change in hepatic status (Child-Pugh) (see "Hepatic impairment" below and section 5.2). **Trough concentrations should be assessed 2 to 4 weeks after initiation of or change in co-administration of CYP3A4 inducers (see sections 4.4 and 4.5) since the natural degradation time of the induced enzymes has to be taken into account.**~~For patients <3 years of age, trough concentrations should be monitored at least 1 week after start of treatment or after any change in dose or pharmaceutical form (see section 5.2).~~ When possible, the same assay and laboratory for therapeutic drug monitoring should be used throughout the treatment.

(…)

Hepatic impairment

Patients <18 years of age:

Votubia is not recommended for patients <18 years of age with SEGA **or refractory seizures** and hepatic impairment.

(…)

Paediatric population

The safety, efficacy and pharmacokinetic profile of Votubia in children below the age of 1 year with TSC who have SEGA have not been established. No data are available (see sections 5.1 and 5.2).

The safety, efficacy and pharmacokinetic profile of Votubia in children below the age of 2 years with TSC and refractory seizures have not been established. No data are available (see sections 5.1 and 5.2).

(...)

Method of administration

(...)

Switching pharmaceutical forms

Votubia is available in two pharmaceutical forms: tablets and dispersible tablets. Votubia tablets and Votubia dispersible tablets are **not** to be used interchangeably. The two pharmaceutical forms must not be combined to achieve the desired dose. **The same** ~~One~~ pharmaceutical form ~~or the other~~ must be used **consistently, as appropriate for the indication being treated**.

In addition, SmPC sections 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 are also updated for the 2.5 mg, 5 mg and 10 mg tablets to reflect on data relevant to this pharmaceutical form.

The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template and the SmPC guideline, which were accepted by the CHMP.

The final product information with all changes highlighted is provided as Attachment 1.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable as the changes were not considered to affect readability, thus not requiring new user testing.

3. Benefit-Risk Balance

Benefits

Beneficial effects

With the present application, the MAH sought approval for an extension of the indication of Votubia for the adjunctive treatment of patients aged 2 years and older with refractory seizures associated with tuberous sclerosis complex (TSC). Seizures associated with TSC derive from multifocal cortical disease and thus mainly have a partial onset. The most common seizure type is complex partial seizures including those with secondary generalisation, but TSC patient usually suffer from other seizure types as well, including infantile spasms as well as absence, tonic, atonic, clonic, myoclonic and tonic-clonic generalised seizures.

Seizures associated with TSC can be treated with AEDs and reports in the scientific literature suggest that, at least in some cases, seizure control can be achieved with AEDs approved for the treatment of POS. However, many patients (approximately 60%) continue to experience seizures despite having been treated with adequate anti-seizure regimens and there is a clear need for new effective therapeutic options. mTOR inhibitors such as everolimus provide a promising alternative to existing anti-seizure treatments in this setting, given the association of TSC seizures with tuber burden and abnormal increased mTOR activity.

To support the extension of the indication, the MAH conducted one pivotal phase 3 study M2304. Supportive data were also presented from previous SEGA studies (C2485 and M2301) and study M2302 in patients with angiomyolipoma associated with TSC, as well as from the scientific literature.

Study M2304 was a three-arm, randomised, double-blind, placebo-controlled superiority trial in patients aged 2-65 years with a diagnosis of TSC and treatment-resistant epilepsy. The design, including the choice of endpoints, was generally in line with the recommendations of the CHMP guideline on clinical investigation of medicinal products in the treatment of epileptic disorders (CHMP/EWP/566/98Rev.2/Corr) on confirmatory studies in adjunctive treatment of refractory seizures, and the CHMP protocol assistance issued in 2011. Efficacy and safety of everolimus was investigated at 2 trough ranges (LT group: 3 to 7 ng/mL and HT group: 9 to 15 ng/mL). The study was the largest study (366 patients randomized) conducted with everolimus in TSC. At the time of the cut-off for the study report submitted in support of this application (02-Oct-2015), the extension part of the study was still ongoing.

Patients recruited into the study had a high Baseline seizure frequency [median of 34.5 (LT), 37.8 (HT) and 42.0 (placebo) per 28 days] despite taking 1 to 3 concomitant AEDs and nearly half of them had failed 6 or more prior AEDs, illustrating the extent of refractory epilepsy in the study population. More than 80% of the study population were aged less than 18 years and there was a reasonable number of patients aged less than 6 years (N=104) with the youngest patients being 2 years old.

The primary endpoint of the study was the rate of patients achieving a reduction in their TSC seizure frequency by 50% or more during the 12 weeks maintenance period of the study compared to Baseline (on the FAS). The 50% response rates were 33/117 (28.2%, 95% CI: 20.3, 37.3) and 52/130 (40.0%, 95% CI: 31.5, 49.0) in the everolimus LT and HT arms compared with 18/119 (15.1%, 95% CI: 9.2, 22.8) in the placebo arm. The differences for both everolimus arms to placebo were statistically significant ($p=0.008$ and $p<0.001$). Furthermore, 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 LT and HT arms, respectively, compared with 14.9% (95% CI: 0.1, 21.7) for the placebo arm. The differences for both everolimus arms to placebo were statistically significant ($p=0.003$ and $p<0.001$, respectively).

Similarly, seizure freedom rates were higher in the active treatment arms (5.1% and 3.8%, respectively) compared to placebo (0.8%), although the rates were overall low and confidence intervals were overlapping.

Consistent results were shown throughout all diary derived secondary efficacy endpoints as well as the sensitivity analyses and PP analyses for the 50% response rate and change in seizure frequency. Analyses of response rates and percentage reduction from Baseline for all seizure type combined, including generalized onset and other seizures, were also in line with the respective primary analyses.

Furthermore, subgroup analyses by age, gender, race, ethnicity, Baseline seizure frequency, concomitant AEDs and TSC features including TSC1/2 mutation status, generally favoured everolimus, thus supporting robustness of the study findings. As regards the subgroup analyses by age, these indicated efficacy of everolimus in reducing seizure frequency irrespective of age. Interestingly, 50% response rates as well as median reduction in TSC seizure frequency appeared to be higher in the age category of 1 to <6 year olds than in the older age categories (6 to < 12, 12 to < 18 and ≥ 18 years, respectively).

Throughout the efficacy analyses the effect size in the HT group was generally larger compared to the LT group, thus showing a positive exposure response relationship. Based on these results as supplemented by model-based analysis for the minimum efficacious dose, the recommended target trough concentration was agreed at 5 to 15 ng/mL, which is in line with the target range approved for the TSC SEGA indication and in fact, the populations would be expected to be largely overlapping with most of TSC patients with SEGA also having refractory epilepsy.

Uncertainty in the knowledge about the beneficial effects

During the course of the procedure, the indication was amended to specify the seizure type as POS with or without secondary generalisation, which was in line with the TSC seizure definition applied in the trial, i.e. EEG confirmed partial onset sensory seizures or motor seizures in which a generalized onset had not been demonstrated on EEG. The effect of everolimus on generalised onset seizures could not be established based on the available data as too few subjects had confirmed generalized onset seizures at Baseline (2 in each treatment arm) and, although not considered a robust finding, an increase in mean frequency of generalised onset seizures has previously been observed in a small, uncontrolled, supportive SEGA study. Furthermore, study M2304 was not suitable to allow for evaluating any influence of everolimus on infantile/epileptic spasms or seizures associated with LGS as, again, too few subjects with such seizure types had been enrolled or could not be identified from the reported cases and since infantile spasms were only allowed, if treated and residual. The CHMP furthermore noted that only few subjects without cortical tubers were enrolled. All these limitations of the data set have been reflected in section 5.1 of the SmPC.

No efficacy information of everolimus on elderly subjects is available, which was considered acceptable given that the target population would be mainly paediatric patients and in light of the previous experience with everolimus in the elderly in the oncology setting. As for age, the CHMP also noted that no patients aged less than 2 years was enrolled. While adhering to a lower age limit of 12 months as required by the PIP, at the same time patients weighing less than 12 kg were excluded because of the volume of blood drawn in the study, and this effectively also excluded patients aged less than 2 years. While data in younger children would have been preferred, the lower age limit in the study was adequately reflected by restricting the proposed indication to a minimum age of 2 years.

Some Baseline imbalances were noted, including a higher median seizure frequency, as well as slightly higher percentages of subjects with 3 concomitant AEDs, with cortical tubers or with subependymal nodules in the placebo group. However, the potential impact of these imbalances was judged by the CHMP to be small and in light of the large effect size of everolimus in reducing TSC seizures observed, considered unlikely to be of clinical relevance.

An analysis of patients using rescue treatment yielded a higher proportion of patients in the HT arm (17.7%) compared to placebo (11.8%) and the LT arm (10.3%), respectively. This finding was however not considered to have a relevant impact on the overall study results, as rescue medication consisted largely of a single dose of a benzodiazepines and additional analyses of response rate and median reduction in seizure frequency in which subjects who used rescue medication were considered as non-responders showed results generally consistent with the primary analysis.

Preliminary data derived from the extension part of study M2304 are indicative of maintenance of the treatment effect observed for everolimus during the Core maintenance phase of the study. An additional conservative analysis of available long-term data in which all withdrawals were considered treatment failures was consistent with the primary analysis. However, at the cut-off date of the study report only about half of the subjects had completed 54 weeks of treatment and thus, data at later time points were limited and should be interpreted with caution. Updated long-term efficacy data are expected to be provided as soon as possible including the final clinical study report (anticipated by March 2017) in order to allow for a better interpretability of long-term efficacy of everolimus in the treatment of TSC seizures.

Risks

Unfavourable effects

The safety data from study M2304 were generally consistent with the already established safety profile of Votubia in TSC patients. Notably, M2304 was the largest trial performed with everolimus in TSC, and thus enriched the safety data base substantially. Overall, however, the size of the database remains limited due to the rarity of the disease.

The most commonly reported AEs in the Core phase of study M2304 were stomatitis (28.2%) and mouth ulceration (23.9%) in the LT group and stomatitis (30.8%), mouth ulceration (21.5%), and diarrhoea (21.5%) in the HT group. The most common AEs suspected to be related to everolimus included stomatitis, mouth ulceration and aphthous ulcer. These events were primarily of mild or moderate intensity. The most frequent grade 3/4 events in the everolimus LT and HT treatment groups were stomatitis (1.7% and 2.3%, respectively), neutropenia (1.7% and 2.3%), status epilepticus (1.7% and 1.5%), pneumonia (0.9% and 2.3%), and irregular menstruation (0.0% and 2.3%).

Long-term data from the Core and Extension phases of study M2304 combined were in line with the data from the study Core phase with stomatitis (32.8%), pyrexia (25.8%), diarrhoea (24.1%), and mouth ulceration (22.1%) being the most common AEs reported. Two cases of death (due to seizure/ sudden unexpected death in epilepsy and pneumonia, respectively) were reported in patients receiving everolimus during the Extension phase.

Overall, discontinuation rates were low (less than 20% of patients in the long term extension phase) suggesting an acceptable and manageable safety profile.

Based on the new pooled safety data set, the most frequent adverse reactions with everolimus include stomatitis, nasopharyngitis, diarrhoea, pyrexia, upper respiratory tract infection, vomiting, cough, headache, amenorrhoea, acne, rash, menstruation irregular, pneumonia, sinusitis, urinary tract infection, fatigue, hypercholesterolaemia, and decreased appetite.

The unfavourable effects of concern remain unchanged and mainly include non-infectious pneumonitis (a single grade 2 case reported in trial M2304 itself), pneumonia, and (severe) infections/pyrexia in general. Other identified risks in the RMP also remain unchanged including hypersensitivity (anaphylactic reactions), stomatitis and cytopenia.

Uncertainty in the knowledge about the unfavourable effects

Long-term data were available in the new TSC safety pool including data from study M2304 as well as from studies in TSC patients with SEGA and angiomyolipoma, in which patients had received everolimus for up to 83 months with a median exposure of 18.3 months. However, these data were uncontrolled and the largest uncertainty about unfavourable effects of everolimus in the treatment of TSC remains the fact that it is nearly impossible to investigate long-term safety with a placebo control. Lifelong treatment is needed in TSC patients and it is difficult to fully comprehend the risk of immunosuppression and infections caused by everolimus, some of which may be life threatening. At the same time, both (refractory) seizures and SEGA associated with TSC are potentially life threatening diseases with the main causes of death being status epilepticus and acute hydrocephalus, respectively. In this context, the CHMP noted that the 2 cases of death (sudden unexpected death in epilepsy and pneumonia) on treatment in study M2304 occurred during the Extension phase and were therefore difficult to interpret. Additional long-term safety data from study M2304 (although not placebo controlled) may help to further corroborate the long-term safety of everolimus in the new indication.

From the exposure response analyses conducted, it could be seen that an apparent higher treatment effect in the everolimus HT arm in the youngest age category might be attributable to higher everolimus exposure. This in turn raises the question of whether this might also be reflected in an increased risk of dose related AEs. However, as found in previous studies, no clear correlation between plasma levels and AE frequency was seen in study M2304, although there was a small trend towards a higher frequency of AEs suspected to be related to everolimus in the HT group compared to the LT group.

Effects Table

Table 34 – Effects Table for Votubia for the adjunctive treatment of patients aged 2 years and older whose refractory POS, with or without secondary generalisation, are associated with TSC (data cut-off of study M2304: 02-Oct-2015)

Effect	Short Description	Unit	Treatment Everolimus LT arm	Treatment Everolimus HT arm	Control Placebo	Uncertainties / Strength of evidence	References
Favourable Effects							
50% response rate	Proportion of patients with a reduction in TSC seizure* frequency of 50% or more from Baseline (FAS)	%	28.2 (95% CI: 20.3; 37.3)	40 (95% CI: 31.5; 49.0)	15.1 (95% CI: 9.2; 22.8)	Differences of both active treatment arms to placebo statistically significant. Consistent results in PP analysis, sensitivity analyses, and subgroups analyses. Long-term data indicative of maintenance of effect, but limited data at later time points.	M2304
% reduction in seizures	Median percent reduction in weekly TSC seizure* frequency from Baseline (FAS)	%	29.3 (95% CI: 18.8; 41.9)	39.6 (95% CI: 35.0; 48.7)	14.9 (95% CI: 0.1; 21.7)	Differences of both active treatment arms to placebo statistically significant. Consistent results in PP analysis and sensitivity	M2304

Effect	Short Description	Unit	Treatment Everolimus LT arm	Treatment Everolimus HT arm	Control Placebo	Uncertainties/ Strength of evidence	References
						analyses.	
Unfavourable Effects**							
Non-infectious pneumonia	All incidence rate	%	0	0.8	0	1 case (Grade 2) reported.	M2304*** New Safety Data Pool: C2485, M2301, M2302, M2304
Infections	Pneumonia - All - Grade 3/4		 1.7 0.9	 3.8 2.3	 0 0	New Safety Data Pool All: 11.2% Grade 3/4: 5.8%	
	Upper respiratory tract infection - All - Grade 3/4		 12.8 0	 15.4 0	 12.6 0.8	New Safety Data Pool All: 22.7% Grade 3/4: 0.5%	
	Urinary tract infection - All - Grade 3/4		 2.6 1.7	 2.3 0	 0.8 0	New Safety Data Pool All: 10.9% Grade 3/4: 0.7%	
Neutro-penia	- All - Grade 3/4		2.6 1.7	3.8 2.3	2.5 2.5	New Safety Data Pool All: 5.4% Grade 3/4: 2.6%	
Stomatitis	- All - Grade 3/4		28.2 1.7	30.8 2.3	3.4 0	New Safety Data Pool All: 39.3% Grade 3/4: 3.9%	
Hyper-sensitivity	All incidence rate		0	0	0	New Safety Data Pool All: 1.8% Grade 3/4: 0.2%	

FAS = Full Analysis Set, HT = High trough (everolimus 9 to 15 ng/mL) LT = Low trough (everolimus 3 to 7 ng/mL), TSC = Tuberous sclerosis complex.

* TSC seizures were defined as all EEG confirmed sensory seizures and all motor seizures without demonstration of generalised onset in EEG

** Incidence rates by MedDRA PT.

*** Core Phase of the trial only

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Seizures associated with TSC are a potentially life threatening condition with the main causes of death being status epilepticus and thus, the objective of treatment would be seizure control. Study M2304 demonstrated superiority of everolimus at two target trough ranges (LT: 3 to 7 ng/mL and HT: 9 to 15 ng/mL) over placebo in reducing the frequency of TSC seizures in both paediatric and adult patients with refractory epilepsy. Statistically significantly higher 50% responder rates (difference to placebo: 13.1% and 24.9% for LT and HT, respectively) as well as percent reduction in weekly TSC seizure frequency from Baseline (difference to placebo: 16% and 27.5% for LT and HT, respectively) were found for both tested everolimus groups compared to placebo. The magnitude of effect as measured by both endpoints was considered clinically relevant, in particular taking into consideration that the study population was highly refractory with a high Baseline seizure frequency and several previous failed AED regimens.

Additional analyses (other seizure related endpoints as well as sensitivity, PP and subgroup analyses on the above-mentioned two endpoints) yielded generally consistent results with the primary analysis, supporting the robustness of the findings.

TSC seizures were defined as partial onset in the study and thus the study results support an indication in POS, which is indeed the main seizure type in TSC patients with epilepsy. However, whereas 12% of study subjects had also a history of EEG confirmed generalized onset seizures (besides partial onset seizures), too few study subjects had confirmed generalized onset seizures during Baseline in order to draw firm conclusions on the effect of everolimus on these seizure types. Furthermore, the pivotal study was not adequately designed in order to evaluate the effect of everolimus on infantile/epileptic spasms, a seizure type also commonly associated with TSC, which however usually occurs before the age of 2 years but may continue past infancy. For these reasons, the new indication was limited to the adjunctive treatment of patients with refractory POS, with or without secondary generalisation, associated with TSC. Notably, the revised indication would not exclude patients, who besides POS also suffer from other seizure types.

Unfavourable effects observed in study M2304 were consistent with the known safety profile of everolimus in TSC patients and considered generally manageable. However, everolimus can cause life threatening adverse reactions including immunosuppression and infections, stomatitis and neutropenia.

Benefit-risk balance

The available data demonstrated a clinically relevant effect of Votubia in the reduction of POS associated with TSC in both paediatric (down to 2 years of age) and adult patients with highly refractory epilepsy. The safety profile remained unchanged including potentially serious adverse reactions such as non-infectious pneumonitis, infections, stomatitis and neutropenia. Taken together, the CHMP considered that the benefits of Votubia in the adjunctive treatment of patients aged 2 years and older whose refractory POS, with or without secondary generalization, are associated with TSC at a target trough concentration of 5 to 15 ng/mL outweigh its risks. The benefit-risk balance was thus considered favourable.

Discussion on the Benefit-Risk Balance

N/A

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of Indication to include adjunctive treatment of patients aged 2 years and older with refractory seizures associated with tuberous sclerosis complex (TSC) for Votubia 2 mg, 3 mg and 5 mg dispersible tablets. Sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC were updated in parallel based on the results from the pivotal study. In addition, sections 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 were also updated for the 2.5 mg, 5 mg and 10 mg tablets to reflect on data relevant to these formulations.

The Package Leaflet was updated in accordance.
Furthermore, the PI was brought in line with the latest QRD template version 10.

The variation leads to amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0124/2016 and the results of these studies are reflected in the SmPC and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include adjunctive treatment of patients aged 2 years and older with refractory seizures associated with tuberous sclerosis complex (TSC) for Votubia 2 mg, 3 mg and 5 mg dispersible tablets. Sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC were updated in parallel based on the results from the pivotal study. In addition, sections 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 were also updated for the 2.5 mg, 5 mg and 10 mg tablets to reflect on data relevant to these formulations.

Summary

Please refer to the Scientific Discussion Votubia EMEA/H/C/002311/II/0041.