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EMA/686119/2012
Committee for Medicinal Products for Human Use (CHMP)

CHMP Type II variation assessment report

Votubia

Procedure No. EMEA/H/C/002311/II/0004

Note

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

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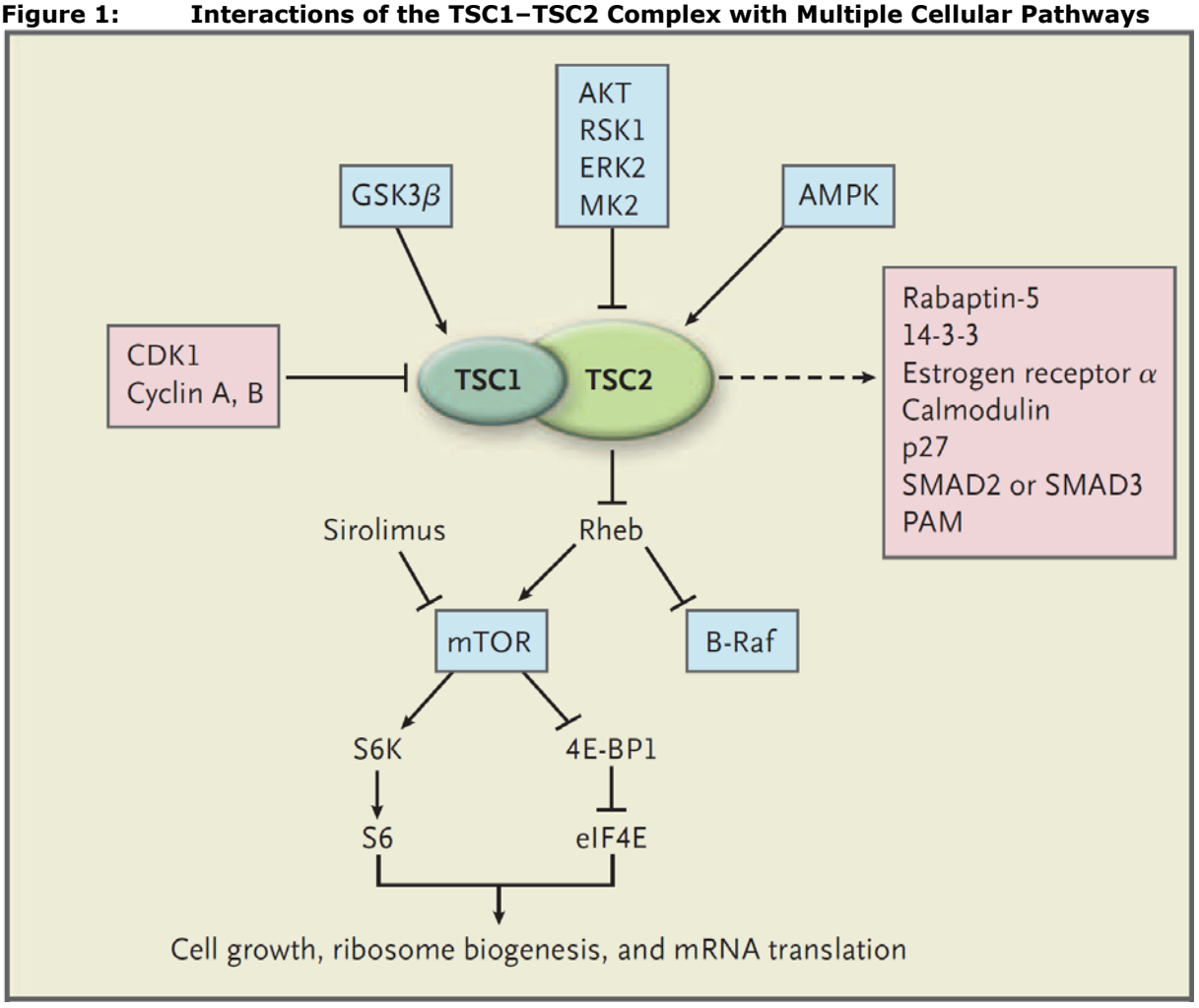
1. Scientific discussion

1.1. Introduction

Tuberous sclerosis complex (TSC) is a congenital disorder that results from mutations in one of two genes, TSC1 gene (encoding hamartin/TSC1) or TSC2 gene (encoding tuberin/TSC2). Estimates for prevalence are in the range of 1 in 6000 live births[1] and of 1.04 cases per 10,000 persons for the EU. Approximately 51,972 persons are affected in the EU.

TSC1 and TSC2 are proteins that act upstream of the mammalian target of rapamycin (mTOR) signalling pathway. Hamartin/TSC1 (a 140-kD protein) interacts with tuberin/TSC2 (200-kD protein) with high affinity to form heterodimers, which then block the mTOR signalling pathway leading to cell growth (see Figure 1).

Figure 1: Interactions of the TSC1–TSC2 Complex with Multiple Cellular Pathways



Mutation in the *TSC1* or *TSC2* gene and the loss of TSC1 or TSC2 activity results in the expression of deficient proteins which constitutively up-regulate mTORC1 (mTOR complex 1) and gives rise to the condition of Tuberous Sclerosis Complex (TSC). The tuberin-hamartin complex regulates mTOR

[1] Paediatr Drugs 10: 299-313, 2008

activation through inhibition of Rheb (Ras homologue enriched in brain), a member of the small GTPase superfamily, which is highly expressed in the brain.

TSC is characterised by often disabling neurologic disorders in TSC patients, including subendymal giant cell astrocytoma (SEGA), epilepsy, mental retardation, and autism. Additional major features of the disease comprise facial angiofibromas, renal angiomyolipomas (AML), and pulmonary lymphangiomyomatosis (LAM). Angiomyolipomas among patients diagnosed with sporadic LAM are usually unilateral, small, and solitary, while those among patients diagnosed with TSC are typically bilateral, larger, and multiple, and more prone to hemorrhage[2].

The clinical diagnosis of TSC is made when a patient has at least 2 major, or 1 major and 2 minor features (Gomez criteria) from the following table:

Table 1: Gomez criteria

Major criteria	Minor criteria
Facial angiofibroma	Multiple pits in dental enamel
Ungual fibroma	Hamartomatous rectal polyps
Shagreen patch	Bone cysts
Hypomelanotic macule	Cerebral white-matter radial migration lines
Cortical tuber	Gingival fibromas
Subependymal nodule	Retinal achromic patch
Subependymal giant-cell tumour	"Confetti" skin lesions (groups of small, lightly pigmented spots)
Retinal hamartoma	Multiple renal cysts
Cardiac rhabdomyoma	
Renal angiomyolipoma	
Lymphangiomyomatosis	

Angiomyolipomas (AMLs) are the most common renal manifestation of TSC, occurring in approximately 60% to 80% of patients with TSC, and typically develop in later childhood and adolescence[3, 4, 5] . In general, renal involvement in TSC is common and potentially serious, only second to CNS complications as a cause of mortality in these patients[6]. AMLs are hamartomas comprised of abnormal blood vessels, immature smooth muscle cells, and adipose tissue. Two major complications are associated with renal AML. The first and more dramatic is Wunderlich syndrome, a retro-peritoneal hemorrhage originating in the angiomyolipoma that may be life-threatening and often requires urgent surgical intervention. The second major morbidity is the insidious encroachment of the angiomyolipoma on normal renal tissue, which may lead to renal failure and the need for dialysis. Patients with LAM (associated with TSC or occurring sporadically) also experience multiple pulmonary function abnormalities, the most common of which are reductions in airflow (FEV1), forced vital capacity (FVC), and carbon monoxide diffusion capacity (DLCO). Cystic destruction of lung tissue, impaired gaseous exchange, respiratory failure, and ultimately death occur in most of these patients. While the rate of progression is variable, most patients survive between 10 and 20 years following

[2] Avila NA, Dwyer AJ, Rabel A, et al (2007). Sporadic lymphangioleiomyomatosis and tuberous sclerosis complex with lymphangioleiomyomatosis: comparison of CT features. Radiology; 242: 277-85.
[3] Ewalt DH, Sheffield E, Sparagana SP, et al (1998). Renal lesion growth in children with tuberous sclerosis complex. J Urol; 160: 141-5.
[4] Casper KA, Donnelly LF, Chen B, et al (2002). Tuberous sclerosis complex: renal imaging findings. Radiology; 225: 451-6.
[5] O'Callaghan FJ, Noakes MJ, Martyn CN, et al (2004). An epidemiological study of renal pathology in tuberous sclerosis complex. BJU Int; 94: 853-7.
[6] Mayo Clin Proc 66:792-96, 1991; Abstract

diagnosis. Two natural history studies found that loss of FEV1 averages 80 to 100 mL per year. Lung transplantation remains the only viable option for end-stage disease[7,8] .

The primary reason for intervention in patients with renal angiomyolipoma is to alleviate symptoms such as pain or hemorrhage. Angiomyolipomas appear to grow over time, and there is evidence of an association between lesion size and hemorrhage[9, 10,11,12]. When patients experience sudden and potentially life-threatening hemorrhages, they are likely to result in total nephrectomy[13]. Partial or nephron-sparing nephrectomies run the risk of significant haemorrhage.

An alternative to the invasive treatment of surgery is embolization of angiomyolipomas. Embolization is currently regarded the best treatment for large (> 4 cm) angiomyolipomas. This procedure obliterates the blood supply to the angiomyolipoma and reduces the risk of hemorrhage. However, embolization is also associated with significant side effects; an estimated 85% of patients develop post-embolization syndrome, including fever and pain. Repeat embolization procedures are required in 0% to 40% of patients due to recurrence of lesions[14, 15]. Embolization and surgical therapies can successfully treat solitary lesions. However, there is no current treatment for the clinical problem of coalescent renal angiomyolipomas that replace renal parenchyma. When bleeding occurs under these circumstances, it can be impossible to identify which lesion is the source and therefore embolization cannot be performed. There is a need for a renal-sparing approach and preservation of renal function for treatment of patients with angiomyolipomas[16].

Everolimus (Afinitor/Certican/Votubia/Zortress) is a selective inhibitor of mTOR. Everolimus was initially developed to prevent allograft rejection following solid organ transplantation. The development program was expanded in 2002 to treat patients with advanced renal cell cancer (RCC), advanced neuroendocrine tumors (NET) and metastatic breast cancer (Afinitor) and for patients with SEGA associated TSC.

The MAH has applied for the following indication:

"Tuberous sclerosis complex (TSC) with renal angiomyolipoma

Votubia is indicated for the treatment of patients with tuberous sclerosis complex (TSC) who have renal angiomyolipoma not requiring immediate surgery."

1.2. Quality aspects

No new data related to the pharmaceutical quality were submitted with this variation application, which is considered acceptable. An updated list of batches of the proposed Votubia tablets involved in clinical trials has been provided including trial M2302. The batches used in trial M2302 were all 5mg tablets and obtained from the current approved manufacturing site for Votubia tablets. All of the clinical

[7] Johnson SR, Whale CI, Hubbard RB, et al (2004). Survival and disease progression in UK patients with lymphangioleiomyomatosis. Thorax; 59: 800-3.
[8] Taveira-DaSilva AM, Stylianou MP, Hedin CJ, et al (2004). Decline in lung function in patients with lymphangioleiomyomatosis treated with or without progesterone. Chest; 126: 1867-74.
[9] Oesterling JE, Fishman EK, Goldman SM, et al (1986). The management of renal angiomyolipoma. J Urol; 135: 1121-4.
[10] Steiner MS, Goldman SM, Fishman EK, et al (1993). The natural history of renal angiomyolipoma. J Urol; 150: 1782-6.
[11] van Baal JG, Smits NJ, Keeman JN, et al (1994). The evolution of renal angiomyolipomas in patients with tuberous sclerosis. J Urol; 152: 35-8.
[12] Dickinson M, Ruckle H, Beaghler M, et al (1998). Renal angiomyolipoma: optimal treatment based on size and symptoms. Clin Nephrol; 49: 281-6.
[13] Bissler JJ, Kingswood JC (2004). Renal angiomyolipomata. Kidney Int; 66: 924-34.
[14] Ewalt DH, Diamond N, Rees C, et al (2005). Long-term outcome of transcatheter embolization of renal angiomyolipomas due to tuberous sclerosis complex. J Urol; 174: 1764-6.
[15] Kothary N, Soulen MC, Clark TW, et al (2005). Renal angiomyolipoma: long-term results after arterial embolization. J Vasc Interv Radiol; 16: 45-50.
[16] Nelson CP, Sanda MG (2002). Contemporary diagnosis and management of renal angiomyolipoma. J Urol; 168: 1315-25.

batches have identical composition. An updated satisfactory validation report for the LC-MS/MS analytical method used in the analysis of everolimus for study M2302 has been provided.

1.3. Non-clinical aspects

1.3.1. Introduction

The MAH submitted a summary of literature data on the role of the mTOR pathway in the development of angiomyolipoma (AML), SEGA and other TSC-related manifestations. An updated pharmacokinetic written summary and tabulated summary were submitted with new data on the potential of everolimus to inhibit hepatic organic anion transporting polypeptides (OATP) mediated uptake.

1.3.2. Pharmacology

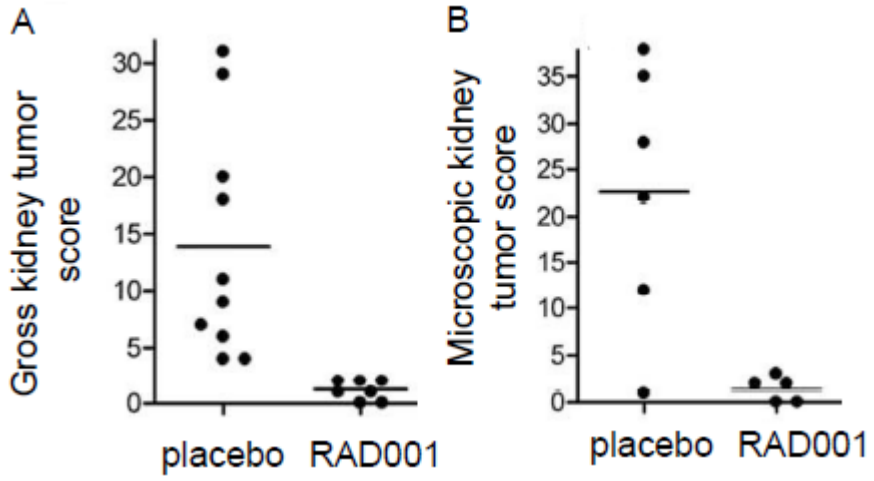
Primary pharmacodynamic studies

Angiomyolipoma and other perivascular epithelioid cell tumors linked with *Tsc 1 / 2* mutations, such as SEGA, exhibit sustained activation of the mTOR pathway[17,18].

There is *in vivo* evidence that inhibiting mTORC1 in preclinical rodent models of TSC or mouse angiomyolipoma-derived human tumor xenograft models reduces tumor formation and growth [19, 20, 21, 22, 21]. In a mouse model for renal tumour development[23] where ENU (Nethyl-N-nitrosourea, an alkylating agent) was used to enhance *Tsc2*$^{+-}$ kidney tumor development, everolimus was able to suppress tumor development during a 4 week treatment period, with a 99% reduction in tumor cell mass (see Figure 2).

[17] Kenerson H, Folpe AL, Takayama TK, et al (2007) Activation of the mTOR pathway in sporadic angiomyolipomas and other perivascular epithelioid cell neoplasms. Hum Pathol.; 38:1361-71.
[18] El-Hashemite N, Zhang H, Henske EP, et al (2003). Mutation in TSC2 and activation of mammalian target of rapamycin signalling pathway in renal angiomyolipoma. Lancet; 361: 1348–9.
[19] Ehninger D, Han S, Shilyansky C, et al (2008). Reversal of learning deficits in a Tsc2+/2 mouse model of tuberous sclerosis. Nat Med; 14: 843–8.
[20] Woodrum C, Nobil A, Dabora SL (2010) Comparison of three rapamycin dosing schedules in A/J Tsc2+/2 mice and improved survival with angiogenesis inhibitor or asparaginase treatment in mice with subcutaneous tuberous sclerosis related tumors. Journal of Translational Medicine; 8:14.
[21] Lee L, Sudentas P, Donohue B, et al (2005). Efficacy of a rapamycin analog (CCI-779) and IFN-gamma in tuberous sclerosis mouse models. Genes Chromosomes Cancer ; 42: 213-27.
[22] Zeng LH, Xu L, Gutmann DH, et al. (2008). Rapamycin prevents epilepsy in a mouse model of tuberous sclerosis complex. Ann Neurol; 63: 444–53.
[23] Pollizzi K, Malinowska-Kolodziej I, Stumm M, et al (2009). Equivalent benefit of mTORC1 blockade and combined PI3K-mTOR blockade in a mouse model of tuberous sclerosis. Mol Cancer.; 8-38.

Figure 2: Renal tumour development blocked by administration of everolimus in the ENU-treatedTsc2+- model in mice



Dot blot analysis of gross kidney tumor score (A) and microscopic kidney tumor score (B) in ENU treated *Tsc2*$^{+-}$ treated mice at age 24 weeks that received either placebo or everolimus (10 mg/kg p.o 5 d/week).

Pharmacodynamic drug interactions

The potential inhibitory effect of everolimus (up to 25 µM) on the transporters OATP1B1 and OATP1B3 was examined using HEK293 cells stably overexpressing human OATP1B1 or OATP1B3. Transport activity was evaluated by comparing the extent of probe substrates accumulation in cells that express OATP1B1 or OATP1B3 compared to control cells. Everolimus reduced [3H]estradiol-17β-glucuronide accumulation into OATP1B1-expressing cells in a dose dependent manner. Additionally, everolimus reduced [3H]estradiol-17βglucuronide and [3H]cholecystokinin-8 accumulation into OATP1B3-expressing cells in a dose dependent manner. The inhibition of OATP1B1and OATP1B3 transport activity in the presence of the highest concentration of everolimus tested (25 µM) was essentially complete. The estimated IC50 value for inhibition of OATP1B1-mediated [3H]estradiol-17β-glucuronide uptake was 96 ng/mL (0.10 µM). The estimated IC50 values for inhibition of OATP1B3mediated [3H]estradiol-17β-glucuronide uptake and [3H]cholecystokinin-8 uptake by everolimus were 604 ng/mL (0.63 µM) and 546 ng/mL (0.57 µM), respectively.

1.3.3. Ecotoxicity/environmental risk assessment

The summary of the main study results are shown in Table 2.

Table 2: Summary of ERA main study results

Substance Everolimus			
CAS-number (if available):918639-08-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD117	log Kow:4.0	no potential PBT
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	PEC $_{surfacewater}$ 0.05 PEC$_{surfacewater\ refined.}$ 0.000341	µg/L	≥ 0.01 threshold Y
Other concerns (e.g. chemical			N

class)					
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	Koc sludge: 1654-3294 L/kg Koc soil: 50197->2348392 L/kg			List all values
Ready Biodegradability Test	OECD 301	2% degradation in 28d			not ready biodegradable, OECD 308 ongoing
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308				Study ongoing
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Daphnia sp. Reproduction Test	OECD 211	NOEC	0.014	µg/L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	2.1	µg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC50 (3 h)	$>10^6$	µg/L	

The ERA included a Phase I and Phase II assessment according to the Guideline EMEA/CHMP/SWP/4447/00. The updated environmental risk assessment indicated that everolimus does not constitute a significant risk to surface waters, sewage treatment plants and groundwater. As a precautionary measure, patients should be advised not to dispose of unused everolimus via domestic sewage but in according to local requirements, as stated in the SmPC section 6.6. The study on Algae Growth Inhibition (OECD 201, NOTOX Study No. 246757) did not fulfill the criteria of validity according to the given guideline. Thus, to further characterise the environmental risk assessment, the data from the following studies need to be provided: Bioconcentration factor in fish (OECD 305), the study on Algae Growth Inhibition (OECD 201,) and the sediment-dwelling larvae of the midge species *Chironomus riparius* (OECD 218).

1.3.4. Discussion on non-clinical aspects

No new information on the pharmacology, pharmacokinetic and toxicology of everolimus was submitted. The MAH has submitted a summary of literature data on the role of the mTOR pathway in the development of angiomyolipoma (AML), SEGA and other TSC-related manifestations to support the new indication. The summary of literature data in this application is acceptable given that the mechanism of action of everolimus has been widely studied and the body of non-clinical data submitted previously.

For the evaluation of the environmental risk assessment, since the value log Kow 4.0 of the n-octanol/water partition coefficient exceeded the trigger for an assessment of the bioaccumulation potential, the MAH was asked to provide a study on the determination of the Bioconcentration factor in fish (OECD 305). The study on Algae Growth Inhibition (OECD 201, NOTOX Study No. 246757) did not fulfill the criteria of validity according to the given guideline and as a consequence a new study on Algae Growth Inhibition (OECD 201) should be performed. In summary, in order to further consider the effect of everolimus on the environment, the MAH was asked to provide the study with the sediment-dwelling larvae of the midge species Chironomus riparius (OECD 218), the additional algae study (OECD 201) and the planned fish bioconcentration study (OECD 305) by 31-May-2013.

1.3.5. Conclusion on the non-clinical aspects

The non-clinical literature submitted was considered adequate and acceptable for the assessment of non-clinical aspects for the product everolimus in the new clinical indication. The submitted data suggest that everolimus may have activity in TSC-associated angiomyolipoma non-clinical models.

The CHMP considers the following measures necessary to address the non-clinical issues:

- The MAH is recommended to provide a fully updated environmental risk assessment addressing all outstanding concerns and including all three remaining studies, i.e. the study with the sediment-dwelling larvae of the midge species Chironomus riparius (OECD 218), the additional algae study (OECD 201) and the planned fish bioconcentration study (OECD 305) by 31-May-2013.

1.4. Clinical aspects

1.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant 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.

- Tabular overview of clinical studies

This application is supported by a single pivotal trial (M2302). A tabulated summary of M2302 is displayed below:

Trial design, objectives and population	No of patients	Dosage and treatment duration	Key efficacy endpoints
Double-blind Randomised Parallel-group Placebo controlled Multi-centre Efficacy/safety tested in patients with TSC or sporadic LAM who have angiomyolipoma	Total: 118 Everolimus arm: 79 Placebo arm: 39	Dose: 10 mg/day with dose adjustments as needed (reduction, interruption or possible dose re-escalation to starting dose) Treatment phases: Core phase: timeframe fixed duration at trial level, from the start of the trial up to the time when the last randomised patient has been treated for 6 months All patients were treated until disease progression, unacceptable toxicity or discontinuation for any other reason	Primary: Angiomyolipoma response rate Key secondary endpoints: time to angiomyolipoma progression skin lesion response rate

1.4.2. Pharmacokinetics

Absorption

No data were submitted for absorption studies.

Distribution

No data were submitted for distribution studies.

Elimination

No data was submitted for elimination studies.

Dose proportionality and time dependencies

A secondary efficacy objective from the pivotal study M2302 was to characterize the PK of everolimus in terms of pre-dose (C_{min}) and two hours post-dose (C_{2h}) exposure in the double-blind treatment period. The C_{2h} samples were collected to allow for determination of concentrations near the true peak concentration (C_{max}) for everolimus.
During the blinded treatment phase of the trial, pre-dose trough blood samples for the determination of everolimus C_{min} were collected immediately prior to dosing at Weeks 2, 4, 12, 24 and 48. Pre-dose blood samples were to be collected prior to dosing on the same day of the trial and approximately 24 ± 4 hours after the patient's last dose of study drug, following 5 days of consistent dosing of the same dose and dose schedule (steady-state conditions).
A PK blood sample (2 ml) was taken 2 hours (± 30 minutes, C_{2h}) after dose administration at Weeks 2, 4, 12, 24 and 48.
Everolimus blood concentrations in whole blood were determined by a liquid chromatography-mass spectroscopy method. The method has a lower limit of quantification (LLOQ) of 0.3 ng/ml.

PK profile of everolimus over time

C_{min} and C_{2h} summary statistics by the planned dose and time window in patients treated with everolimus during the double-blind period are presented in Table 3. Median C_{min} and C_{2h} appeared to be stable over time. Inter-subject variability in C_{min} ranged from 56.4% to 104.5% and inter-subject variability in C2h ranged from 43.8% to 56.7%.

Table 3: Everolimus concentrations (ng/ml) by planned dose and time window (Confirmed PK Sample Set) – Study M2302

		Time window				
Statistic	Scheduled sampling time point	Week 2	Week 4	Week 12	Week 24	Week 48
	C_{min}					
n		43	44	49	46	15
Mean (SD)		7.63 (4.32)	7.72 (4.35)	8.79 (6.75)	9.37 (8.83)	11.49 (12.01)
CV% mean		56.7	56.4	76.8	94.2	104.5
Geo-mean		6.51	6.61	6.79	7.13	8.35
CV% geo-mean		67.3	64.0	85.6	88.5	88.7
Median		6.6	7.0	7.5	6.7	6.9
Range		0.6-19.6	1.4-22.2	1.0-32.6	0.0-52.8	2.5-50.0
	C_{2h}					
n		55	49	56	50	14
Mean (SD)		33.38 (15.66)	30.89 (14.96)	34.48 (15.10)	39.27 (22.25)	33.20 (18.45)
CV% mean		46.9	48.4	43.8	56.7	55.6
Geo-mean		29.17	27.36	31.03	33.27	28.52
CV% geo-mean		63.3	56.7	51.3	67.1	64.9
Median		31.5	28.2	34.4	38.9	29.0
Range		4.9-75.8	4.3-75.9	10.5-77.9	5.4-98.6	10.0-71.2

Dose reduction to 5 mg/day was required for a low number of patients (Table 4). In general, the mean C_{min} and C_{2h} observed with the 5 mg daily dose was within the range observed in previous everolimus

studies with the same dose. Inter-subject variability in C_{min} and C_{2h} ranged from 3.6% to 57.6% and 14.6% to 33.6%, respectively.

Table 4: Everolimus Cmin and C2h (ng/ml) by actual leading dose and time window after 5 mg and 10 mg daily dosing (Confirmed PK Sample Set) – Study M2302

	Week 2	Week 4	Week 12	Week 24	Week 48
C_{min} after 10 mg daily dose					
n	43	41	42	39	11
Mean ± SD (CV%)	7.63 ± 4.32 (56.7%)	7.85 ± 4.49 (57.2%)	9.40 ± 7.03 (74.8%)	10.13 ± 9.34 (92.2%)	13.10 ± 13.69 (105%)
Median (range)	6.6 (0.6 - 19.6)	7.2 (1.4 - 22.2)	7.6 (1.0 - 32.6)	6.9 (0.0 - 52.8)	7.8 (2.5 - 50.0)
C_{min} after 5 mg daily dose					
n		3	5	5	3
Mean ± SD (CV%)		6.04 ± 0.22 (3.6%)	4.89 ± 2.82 (57.6%)	4.57 ± 1.92 (41.9%)	5.30 ± 0.93 (17.6%)
Median (range)		6.0 (5.8 - 6.3)	3.9 (2.1 - 8.0)	5.0 (2.5 - 6.8)	5.7 (4.2 - 6.0)
C_{2h} after 10 mg daily dose					
n	55	46	45	39	10
Mean ± SD (CV%)	33.38 ± 15.66 (46.9%)	31.44 ± 15.28 (48.6%)	37.39 ±14.76 (39.5%)	44.18 ± 22.55 (51.0%)	36.54 ± 21.03 (57.6%)
Median (range)	31.5 (4.9 - 75.8)	29.1 (4.3 - 75.9)	36.2 (10.5 - 77.9)	41.5 (5.4 - 98.6)	35.0 (10.0 - 71.2)
C_{2h} after 5 mg daily dose					
n		3	9	9	4
Mean ± SD (CV%)		22.47 ± 3.29 (14.6%)	19.40 ± 6.26 (32.3%)	19.93 ± 6.69 (33.6%)	24.88 ± 4.34 (17.5%)
Median (range)		21.6 (19.7 - 26.1)	19.7 (11.4 - 30.9)	19.6 (12.6 - 35.7)	24.0 (20.8 - 30.7)

Special populations

No data was submitted in special populations.

Pharmacokinetic interaction studies

Everolimus C_{min} and C_{2h} in patients using and not using EIAED at randomization

Everolimus Cmin and C2h was analysed in patients using and not using enzyme inducing anti-epileptic drugs (EIAED). The mean **C_{min}** values at Weeks 2, 4, 12, 24, and 48 were:

- Using EIAED at randomization: 4.36 ± 1.70 ng/ml (n=8), 4.77 ± 2.78 ng/ml (n=8), 4.30 ± 1.96 ng/ml (n=10), 5.10 ± 3.02 ng/ml (n=9), and 8.26 ± 3.94 ng/ml (n=3), respectively
- Not using EIAED at randomization: 8.38 ± 4.41 ng/ml (n=35), 8.38 ± 4.39 ng/ml (n=36), 9.94 ± 7.07ng/ml (n=39), 10.41 ± 9.47 ng/ml (n=37), and 12.30 ± 13.31 ng/ml (n=12), respectively

Mean **C_{2h}** values at Weeks 2, 4, 12, 24, and 48 were:

- Using EIAED at randomization: 21.38 ± 11.03 ng/ml (n=10), 18.98 ± 8.82 ng/ml (n=9), 26.92 ± 11.97 ng/ml (n=10), 25.94 ± 14.37 ng/ml (n=10), and 18.78 ± 12.47 ng/ml (n=2), respectively
- Not using EIAED at randomization: 36.04 ± 15.37 ng/ml (n=45), 33.57 ± 14.82 ng/ml (n=40), 36.13 ± 15.32 ng/ml (n=46), 42.60 ± 22.75 ng/ml (n=40), and 35.61 ± 18.55 ng/ml (n=12), respectively

Mean C_{min} and C_{2h} values were lower in patients using EIAED at randomization compared to the respective PK parameters in patients who were not using EIAED at randomization.

1.4.3. Pharmacodynamics

Mechanism of action

No data were submitted on the mechanism of action.

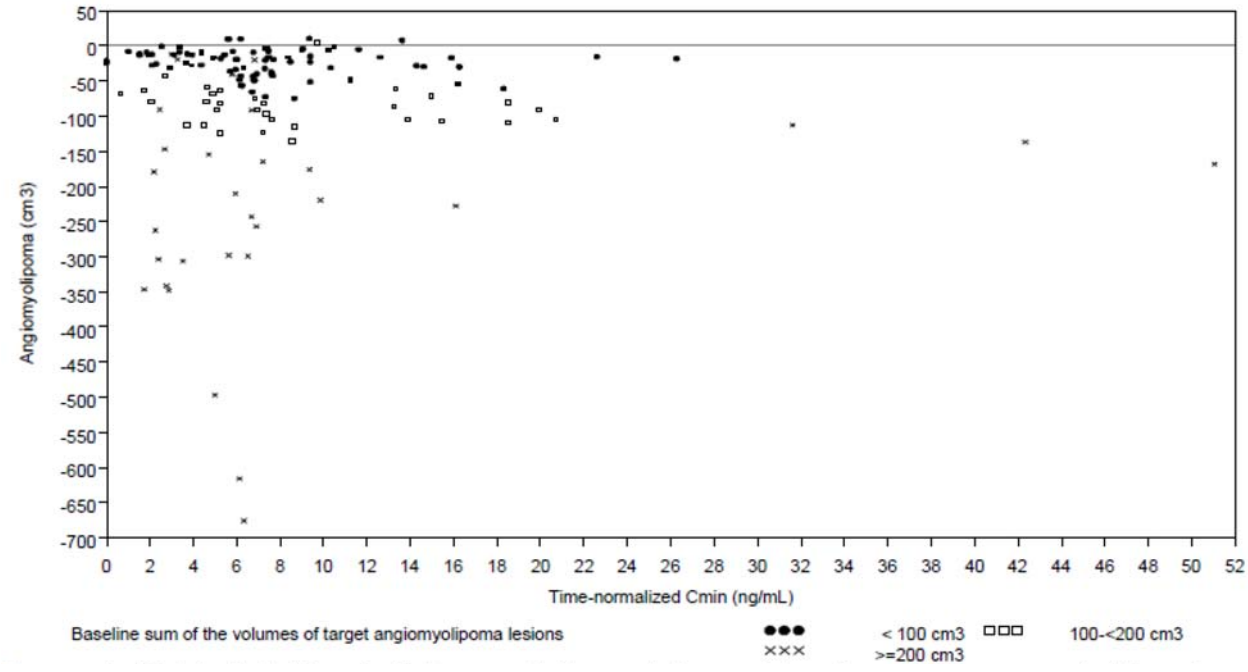
Primary and Secondary pharmacology

Exposure-efficacy relationship

Target angiomyolipoma lesions

The relationship between the absolute change from baseline in angiomyolipoma lesion volume and time-normalized Cmin is illustrated in Figure 3. While there was no apparent relationship between the absolute change from baseline in angiomyolipoma volume and Cmin in any subgroup of patients with different categories of angiomyolipoma volume at baseline (< 100 cm3, 100-200 cm3, and > 200 cm3), it appeared that subgroups of patients with a larger angiomyolipoma volume at baseline had a larger extent of reduction in angiomyolipoma volume from baseline. The analysis using a linear mixed model for the absolute change from baseline in angiomyolipoma lesion volume resulted in a slope of 8.124 (cm3) (95% CI: -18.8, 2.55) per 1-unit log-Cmin increase, which was not statistically significant.

Figure 3: Change from baseline in sum of volumes of target angiomyolipoma lesions versus time-normalized everolimus Cmin between last and current tumor assessment (by sum of volumes of target angiomyolipoma lesions at baseline) (double-blind period) (Confirmed PK Sample Set) – Study M2302



No apparent difference in response-exposure relationship was observed among subgroups of patients of differing categories of angiomyolipoma volume at baseline (< 100 cm^3, 100-200 cm^3, and > 200 cm^3). Results of a linear mixed model indicated a 10.37% (95% CI=-15.96%, -4.40%) tumor size reduction from baseline for a 2-fold C_{min} increase; this was statistically significant at the 5% level.

An analysis was performed to compare the angiomyolipoma response rate between the groups of patients with time-averaged C_{min} ≤ 5 ng/mL and >5 ng/mL.

The C_{min} at Week 2 was considered unlikely to reflect an accurate representation of the exposure related to best overall response. As a result, time-averaged C_{min} was estimated from Study Day 1 to the day of:

- Response for responders
- Progression for patients with PD
- Last tumor assessment for patients with SD or NE (not evaluable)

Response rates were higher for patients with a time-averaged C_{min} >5 ng/mL than for those with C_{min} ≤ 5 ng/mL (Table 5). Of note, when running an alternate analysis excluding patients with a best overall response of NE from the denominator, the difference in response rate between patients with a time averaged C_{min} ≤ 5 ng/mL vs. those >5 ng/mL was more pronounced. This may in part be explained by uncertainty related to patients with NE disease who may have responded.

Table 5 Angiomyolipoma response rates and differences by time-averaged C_{min} category – Study M2302

Population	Time-averaged C_{min} category	Number of patients	Response rate	95% confidence interval
All patients	≤ 5 ng/mL	20	0.300	0.099, 0.501
	>5 ng/mL	42	0.524	0.373, 0.675
	Difference		-0.224	-0.475, 0.027
All patients with the exception of those with a response of NE	≤ 5 ng/mL	18	0.333	0.116, 0.551
	>5 ng/mL	34	0.647	0.486, 0.808
	Difference		-0.314	-0.584, -0.043

NE=not evaluable

Target SEGA lesions

There was no apparent relationship between the absolute or percent change from baseline in SEGA volume and C_{min} for patients with a SEGA volume at baseline < 1 cm^3 and between 1-3 cm^3. The relationship for patients with a SEGA volume at baseline between 3-5 cm^3 and > 5 cm^3 was not interpretable due to small sample sizes (n ≤ 3).

Skin lesions

The median time-normalized C_{min} was higher in patients with partial response (PR) than in patients with stable disease (SD) response at Week 12, while the C_{min} was comparable in patients with PR and SD by Week 24.

1.4.4. Discussion on clinical pharmacology

In the pivotal trial for this application, M2302, exposure-efficacy relationship was investigated for overall 3 endpoints of efficacy i.e. target angiomyolipoma lesions, target SEGA lesions and skin lesions.

No exposure-response relationship in AML (and SEGA) lesions has been established in spite of the high objective response rate (ORR). This is in some contrast to the granted SEGA indication where at least a weak relationship could be found. For SEGA there seems to be weak correlation in-between exposure (c_{min}) and SEGA volume reduction resulting in therapeutic target C_{min} ranges to be monitored after a recommended starting dose. Analysis of the interaction between angiomyolipoma lesion volume at baseline and absolute volume reduction suggests that the exposure-response relationship may have varied in patients with differing angiomyolipoma lesion volumes at baseline.

The data on the relationship between angiomyolipoma response rates and time averaged Cmin category shows that there is a reduction in the response rate when Cmin is below 5 ng/mL. The difference was considered clinically meaningful. Taken into account the limitations of the post-hoc analysis, the CHMP considered that there may be a risk of underdosing below a threshold of 5 ng/mL with the risk of a lower effect on reduction of tumour volume. As a precaution, the option of therapeutic monitoring should be considered in patients treated for AML in order to avoid underexposure after treatment changes or with hepatic impairment. Statements informing the prescriber of the risk of lower treatment effect with lower Cmin have been introduced in section 4.2 and 5.1 of the SmPC. Whereas for SEGA therapeutic drug monitoring (TDM) is required, for AML, in section 4.2, the recommendation for TDM is as follows "Therapeutic drug monitoring of everolimus blood concentrations, using a validated assay, is an **option** to be considered for patients treated for renal angiomyolipoma associated with TSC (see section 5.1) 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)." and in Section 5.1, the statement includes "Post-hoc sub-group analysis of EXIST-2 (study CRAD001M2302) demonstrated that angiomyolipoma response rate is reduced below the threshold of 5 ng/ml (Table 6).". Further recommendation on the dosing in hepatic impaired patients is also stated in section 4.2 and 4.4 of the SmPC.

EIAEDs are strong CYP3A4 inducers and are known to decrease the exposure to everolimus. Patients with baseline use of EIAED had a lower exposure (C_{min}) to everolimus than EIAED non-use but the difference of the effect compared to placebo in both strata was nearly the same. However, considering the risk of underexposure to everolimus, it was necessary to update the recommendations concerning co-administration of everolimus with potents CYP3A4 inducers and moderate CYP3A4 inhibitors in section 4.5 of the SmPC for patients with renal AML associated with TSC.

1.4.5. Conclusions on clinical pharmacology

The analysis of exposure-response relationship in terms both of AML and SEGA response, are supporting the dosing concept as proposed for the SmPC of a fixed dose of 10 mg with the possibility of dose-modifications triggered by tolerability of AEs (and co-administration of EIAEDs) without therapeutic drug monitoring for a C_{min} target range. However, the option of therapeutic dose monitoring should be considered after treatment changes or with hepatic impairment.

1.5. Clinical efficacy

1.5.1. Dose response study

No formal dose-finding trial was performed for the new indication. The investigated (and recommended) dose of 10 mg everolimus daily was based partially on preclinical investigations on the basis of the relationship between systemic drug exposure and pharmacodynamic markers within the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mTOR pathway[24] and clinical experience in the broader everolimus phase-I/II program. Daily administration of everolimus 5 mg or 10 mg completely inhibited the phosphorylation of S6 kinase in tumor and skin samples of patients, whereas

[24] Tanaka C, O'Reilly T, Kovarik JM, et al (2008). Identifying optimal biologic doses of everolimus (RAD001) in patients with cancer based on the modeling of preclinical and clinical pharmacokinetic and pharmacodynamic data. J Clin Oncol; 26:1596-602.

inhibition of 4E-BP1 and eIF-4G was partial with the 5- mg dose and 10-mg daily dosing was required to achieve complete inhibition[25].

The goal for a target posology for renal AML associated with TSC was to achieve an everolimus C_{min} similar to that observed in earlier oncology trials and in SEGA studies that had an acceptable safety and tolerability of everolimus observed in phase II trials[26, 27, 28]. The dose 10 mg everolimus per day is the dose recommended in RCC and is approximately the same as investigated in study M2301. However the current recommended dose in the Votubia SmPC for SEGA is lower than the recommended dose for the new indication. The recommended posology for renal AML associated with TSC in the SmPC is 10 mg once daily.

1.5.2. Main study

Study CRAD001M2302 (Study M2302): A randomized, double-blind, placebo-controlled study of RAD001 in the treatment of angiomyolipoma in patients with either Tuberous Sclerosis Complex (TSC) or Sporadic Lymphangioleiomyomatosis (LAM).

Methods

Study M2302 is a double-blind, 2:1 randomized, parallel-group, placebo-controlled, international, multi-center Phase-III trial of a once daily oral dose of everolimus 10 mg vs. matching placebo in adult (≥18 years) patients with angiomyolipoma associated with clinically definitive diagnosis of either TSC or sporadic LAM. The null-hyphotesis (Ho $RR_{EVEROLIMUS} \leq RR_{PLACEBO}$) characterize the trial as a trial testing one-sided for superiority of everolimus.

Study M2302 was a stratified trial. The original protocol comprised

- TSC and use of EIAED vs.
- TSC and non-use of EIAED vs.
- sporadic LAM

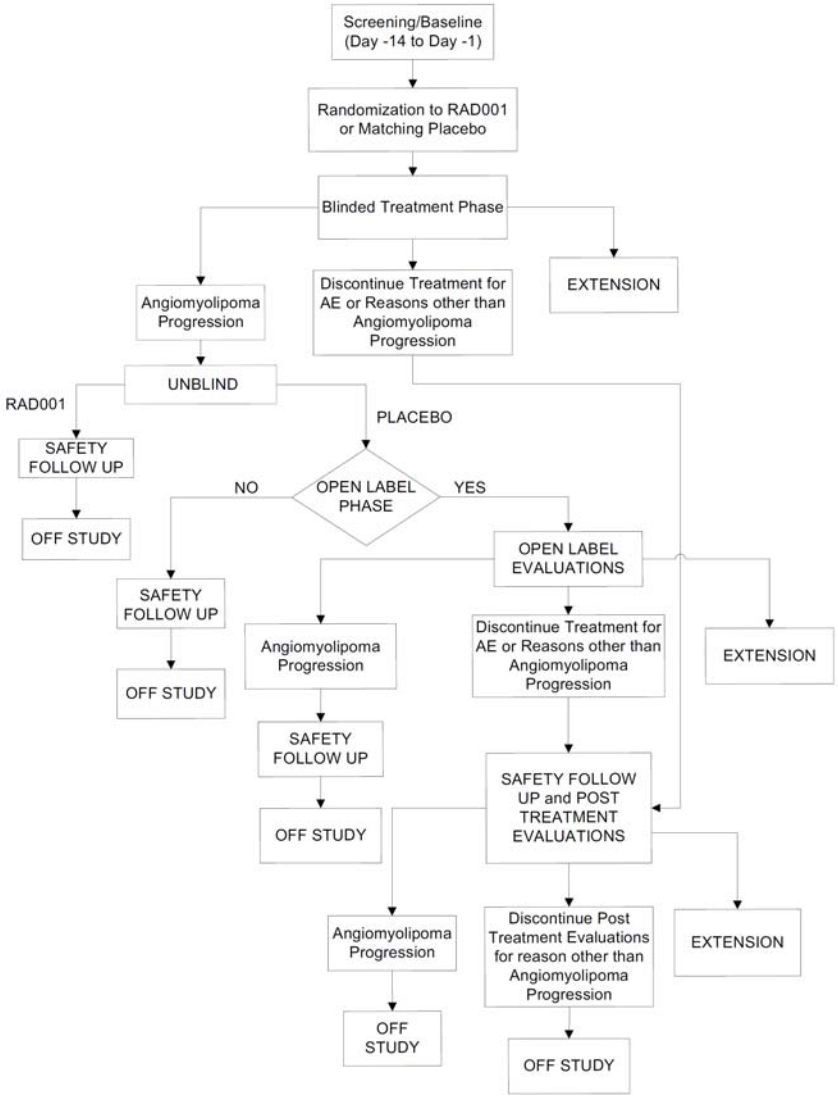
based on the assumption that use of EIADS may affect (by interactions, primarily on the CYP3A4 level) the effect of everolimus, and patients with sporadic LAM requiring only exceptionally EIADS.

The study had overall 4 treatment phases as per the flow chart below (Figure 4).

- screening
- (blinded) core phase (The primary analysis of the core phase was to be performed using all data up to the data cut-off date (30-Jun-2011), which was defined as 6 months after the last patient was randomized.)
- open label phase (offered to patients progressing in the blinded phase on placebo)
- extension (offered to all patients finishing core treatment)

[25] Tabernero J, Rojo F, Calvo E, et al (2008). Dose- and schedule-dependent inhibition of the mammalian target of rapamycin pathway with everolimus: a phase I tumor pharmacodynamics study in patients with advanced solid tumors. J Clin Oncol; 26: 1603-10.
[26] Yao JC, Phan AT, Chang DZ, et al (2008). Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low- to intermediate-grade neuroendocrine tumors: results of a phase II study. J Clin Oncol; 26: 4311-8.
[27] Amato RJ, Jac J, Giessinger S, et al (2009). A phase 2 study with a daily regimen of the oral mTOR inhibitor RAD001 (everolimus) in patients with metastatic clear cell renal cell cancer. Cancer; 115: 2438-46.
[28] Ellard SL, Clemons M, Gelmon KA, et al (2009). Randomized phase II study comparing two schedules of everolimus in patients with recurrent/metastatic breast cancer: NCIC Clinical Trials Group IND.163. J Clin Oncol; 27: 4536-41.

Figure 4: Flowchart Protocol CRAD001M2302



- Full Analysis Set (FAS): The full analysis set consisted of all randomized patients. The FAS was the primary population in all analysis of efficacy. Further pre-specified analysis population were
- Safety Set (SS): The Safety Set consists of all patients who received at least one dose of the double-blind study drug with a valid post-baseline assessment. The Safety Set was the population used in the assessments of safety for the double-blind period.
- Per Protocol Set (PPS):The Per Protocol Set (PPS) consists of all patients from the FAS without any major protocol deviations, who were evaluable for efficacy and who had completed a minimum exposure requirement. However, if a patient had angiomyolipoma progression, discontinued for an AE, or died before the minimum exposure requirement could be met or before he/she could become evaluable for efficacy, that patient was still to be included in the PPS. If a patient had a non-evaluable best overall response but discontinued due to an AE in the first 84 days, then the patient should be included in the PPS; otherwise if the discontinuation due to an AE occurs after 84 days then the patient should be excluded from the PPS. The PPS was used for a supportive analysis of the primary endpoint.

- Open-label everolimus population was defined as patients who received at least one dose of open-label everolimus and had at least one safety or efficacy assessment during the open-label period.

Study Participants

Key inclusion criteria were:

- Male or female ≥ 18 years of age
- Clinically definite diagnosis of TSC according to the modified (see Table 6) Gomez criteria or sporadic LAM.
- Clinically definite diagnosis of renal angiomyolipoma
- Presence of at least one angiomyolipoma ≥ 3 cm in its longest diameter using CT/MRI
- If female and of child-bearing potential, documentation of negative pregnancy test prior to enrollment. Sexually active pre-menopausal female patients (and female partners of male patients) must use adequate contraceptive measures, while on study and for 8 weeks after ending treatment.
- Written informed consent according to local guidelines

Table 6: Diagnostic Criteria for Tuberous Sclerosis Complex (modified Gomez criteria)

Major Features
1. Facial angiofibromas or forehead plaque 2. Nontraumatic ungual or periungual fibroma 3. Hypomelanotic macules (three or more) 4. Shagreen patch (connective tissue nevus) 5. Multiple retinal nodular hamartomas 6. Cortical tuber[a] 7. Subependymal nodule 8. Subependymal giant cell astrocytoma 9. Cardiac rhabdomyoma, single or multiple 10. Lymphangioleiomyomatosis[b] 11. Renal angiomyolipoma[b]
Minor Features
1. Multiple, randomly distributed pits in dental enamel 2. Hamartomatous rectal polyps[c] 3. Bone cysts[d] 4. Cerebral white matter radial migration lines[a,d] 5. Gingival fibromas 6. Nonrenal hamartoma[c] 7. Retinal achromic patch 8. 'Confetti' skin lesions 9. Multiple renal cysts[c]
Definite Tuberous Sclerosis Complex: **Either two Major Features or one Major Feature plus two Minor Features.**
a. The co-occurrence of cerebral cortical dysplasia and cerebral white matter radial migration lines should be considered as one major feature of TSC. b. In patients with both lymphangioleiomyomatosis and renal angiomyolipoma, another feature of TSC must be identified before a definite diagnosis is assigned. c. Histologic confirmation of these features is suggested. d. Radiographic confirmation of these features is sufficient.

Key exclusion criteria were:

- Patients with angiomyolipoma which, in the opinion of the investigator, required surgery at the time of randomization
- Angiomyolipoma-related bleeding or embolization during the 6 months prior to randomization
- History of myocardial infarction, angina or stroke related to atherosclerosis
- Impaired lung function
- Significant hematological or hepatic abnormality (i.e. transaminase levels > 2.5 × upper limit of normal (ULN), serum bilirubin > 1.5 × ULN, hemoglobin < 9g/dL, platelets < 80,000/mm^3, or absolute neutrophil count < 1,000/mm^3)
- Pregnancy or breast feeding
- Prior therapy with mTOR inhibitors (e.g. sirolimus, temsirolimus, everolimus)

Treatments

Everolimus arm: Administered by continuous oral daily dosing of two 5 mg tablets. No fixed treatment duration was specified. Treatment continued until angiomyolipoma progression, unacceptable toxicity, or until discontinuation for any other reason.

Placebo arm: Administered by continuous oral daily dosing of two 5 mg matching placebo tablets. At end of core phase (defined as start of the trial up to the time when the results of the final primary analysis were known), all patients who had not progressed and were still receiving study treatment were be given the option of starting open-label everolimus.

Objectives

The primary objective was to compare the angiomyolipoma response rate on everolimus versus placebo in patients with angiomyolipomata associated with either TSC or sporadic LAM.

Secondary objectives were:

- To compare everolimus versus placebo with respect to:

1. Time to angiomyolipoma progression

2. Skin lesion response rate

3. Change from baseline in plasma angiogenic molecules, e.g., VEGF, basic FGF, PLGF, soluble VEGF receptor1, and soluble VEGF receptor2

4. Renal function assessed using calculated creatinine clearance

5. Safety as assessed by the National Cancer Institute's (NCI) Common Toxicity Criteria for Adverse Events (CTCAE), version 3.0

- Secondary objectives only in the everolimus treatment arm:

1. Characterize the pharmacokinetics of RAD001 in this patient population, specifically in terms of exposure

2. Describe the duration of angiomyolipoma response, the time to angiomyolipoma response and the duration of skin lesion response

Further exploratory objectives were:

1. Changes in additional TSC-associated lesions that are documented at baseline, namely subependymal giant cell astrocytomas (SEGAs), tubers and subependymal nodules (SENs) will be

described in each treatment group. SEGA response will be evaluated in the subgroup of patients who have at least one SEGA lesion with longest diameter ≥ 1.0 cm at baseline

2. To assess change from baseline in pulmonary function (FEV1, FVC, DLCO), stratified by presence or absence of LAM

3. To assess changes from baseline in neuropsychological assessments and cognitive function using an age-appropriate and mental status appropriate battery of neuropsychological tests

4. For angiomyolipomata, assessment of the correlation between volume and longest diameter

5. To assess changes from baseline in the severity of seizures using the Seizure Severity Questionnaire (SSQ)

6. Mutational analysis of TSC1 and TSC2 genes correlated with angiomyolipoma response rate and time to progression

7. To assess the relationship between everolimus concentration and safety/efficacy endpoints

8. To assess the incidence and reasons for angiomyolipoma-related surgery in each treatment arm

Outcomes/endpoints

Primary endpoint

The primary endpoint of study M2302, angiomyolipoma response rate, in terms of a prospectively planned variable, was defined as (wording as of the original protocol):

- the proportion of patients with an angiomyolipoma response, and using data from the Independent Central Radiological Review of MRIs and the AE CRF page (to identify angiomyolipoma-related bleeding of grade 2 or worse as defined by NCI CTCAE version 3.0)

Angiomyolipoma response was defined as:

- a reduction in angiomyolipoma volume of at least 50% relative to baseline, where angiomyolipoma volume is the sum of the volumes of all target angiomyolipomata identified at baseline, and confirmed with a second scan performed at least 4 weeks later

In addition, angiomyolipoma response required satisfying all of the following criteria:

- no new angiomyolipomata ≥ 1.0 cm in longest diameter identified
- neither kidney increases in volume by more than 20% from nadir (where nadir is the lowest kidney volume obtained for the patient, separately for each kidney, previously in the trial including baseline)
- the patient did not have any angiomyolipoma-related bleeding of grade 2 or worse (as defined by NCI CTCAE, version 3.0)

Key secondary endpoints

The secondary efficacy endpoints were to compare everolimus against placebo with respect to time to angiomyolipoma progression and skin lesion response rate.

Time to angiomyolipoma progression

Time to angiomyolipoma progression (TTAP) is defined as the time from the date of randomization to the date of first documented angiomyolipoma progression.

Angiomyolipoma progression was defined as one or more of the following:

- An increase from nadir of ≥ 25% in angiomyolipoma volume to a value greater than baseline (where angiomyolipoma volume was the sum of the volumes of all target lesions identified at baseline and where nadir was the lowest angiomyolipoma volume achieved by the patient previously in the trial, including baseline)
- The appearance of a new angiomyolipoma ≥ 1.0 cm in longest diameter
- An increase from nadir of ≥ 20% in the volume of either kidney to a value greater than baseline, where nadir was the lowest kidney volume obtained for the patient, separately for each kidney, previously measured in the trial (including baseline)
- Angiomyolipoma-related bleeding ≥ grade 2 (CTCAE Version 3.0)

Skin lesion response

Skin lesions were assessed by the investigators; response was evaluated using the Physician's Global Assessment of Clinical Condition (PGA). Digital photographs of all skin lesions were taken at baseline, every 12 weeks thereafter, and at End of Treatment and were archived at the central review facility.

Skin lesions resulting from TSC include hypomelanotic macules, the shagreen patch, periungual or subungual fibromas, facial angiofibromas and/or forehead plaques.

Sample size

Sample size was determined using simulation to guarantee a study power of at least 90%. As a starting value, NQuery (Version 4.0) indicated that for an analysis using Fisher's exact test, a total of 99 patients would provide 93% power at a 2:1 randomization.

For the one-sided null-hypothesis p was set to 0.025. The angiomyolipoma response rate in the placebo arm was expected to be close to 0%. The angiomyolipoma response rate on everolimus was expected to be at least 20%. The relative prevalence of the categories of the stratification factors was expected to be 3:3:2 (assumption 25% with sporadic LAM, the remainder 75% of patients with TSC distributed nearly 1:1 for use/non-use of EIAED).

Table 7: Sensitivity of study power to treatment by stratum interaction assuming 3:3:2 ratio of patients across strata 1-3 – Study M2302

Ratio of patients across strata 1-3	Angiomyolipoma response rate in RAD001 arm				Power*
	Stratum 1 (TSC with EIAED)	Stratum 2 (TSC without EIAED)	Stratum 3 (sporadic LAM)	Overall	
3:3:2	26.67%	26.67%	0%	20%	93.20%
	20%	33.33%	0%	20%	93.53%
	23.33%	23.33%	10%	20%	93.56%
	16.67%	30%	10%	20%	93.48%
	20%	**20%**	**20%**	**20%**	**93.30%**
	10%	30%	20%	20%	93.37%
	13.33%	13.33%	40%	20%	94.09%
	6.67%	20%	40%	20%	93.68%
	0%	0%	80%	20%	98.50%

*Based on 10000 runs, and assumes 66/33 patients on RAD001/Placebo, Placebo response=0%, one-sided exact stratified CMH test at 2.5% level.

Randomisation

The patients were randomized using an Interactive Web Response System (IWRS). The patients were randomized 2:1 for 3 strata.

Blinding (masking)

The study was a double blinded study. Central laboratory and central radiology were to remain blinded to treatment allocation from the time of randomization until final database lock. Treating physician could be unblinded in case of progression.

Statistical methods

The primary analysis was a comparison of the angiomyolipoma response rates in the everolimus and placebo arms using an exact Cochran-Mantel-Haenszel (CMH) test at the onesided 2.5% level, analyzed in the FAS. The test was stratified by the modified stratification factor (use of EIAED versus non-use of EIAED).

The statistical hypotheses were:

H0: $RR_{EVEROLIMUS} \leq RR_{PLACEBO}$ versus H1: $RR_{EVEROLIMUS} > RR_{PLACEBO}$ where RR is the probability of angiomyolipoma response on everolimus or on placebo.

Angiomyolipoma response rates were summarized by treatment group in terms of percentage rates and exact 95% confidence intervals (CIs). The difference in response rates between treatment groups and the exact 95% CI were presented.

The data cut-off date for the final analysis was 6 months after the last patient had been randomized. All data up to the data cut-off date (30-Jun-2011) were included in the analysis, whether they arose from patients on double-blind treatment or on open-label everolimus. However, the focus of the statistical analyses was on data from the double-blind phase of the trial, with data collected during the open-label phase being reported in separate data presentations.

Key secondary endpoints

In order to be able to make a claim with respect to time to angiomyolipoma progression and skin lesion response rate, a multiplicity adjustment was implemented. Multiplicity was controlled via a hierarchical closed testing procedure to ensure that the overall Type I error rate of the trial was maintained at 2.5% (one-sided). Interpretation of the p-values was dependent on the hierarchy used in the closed testing strategy.

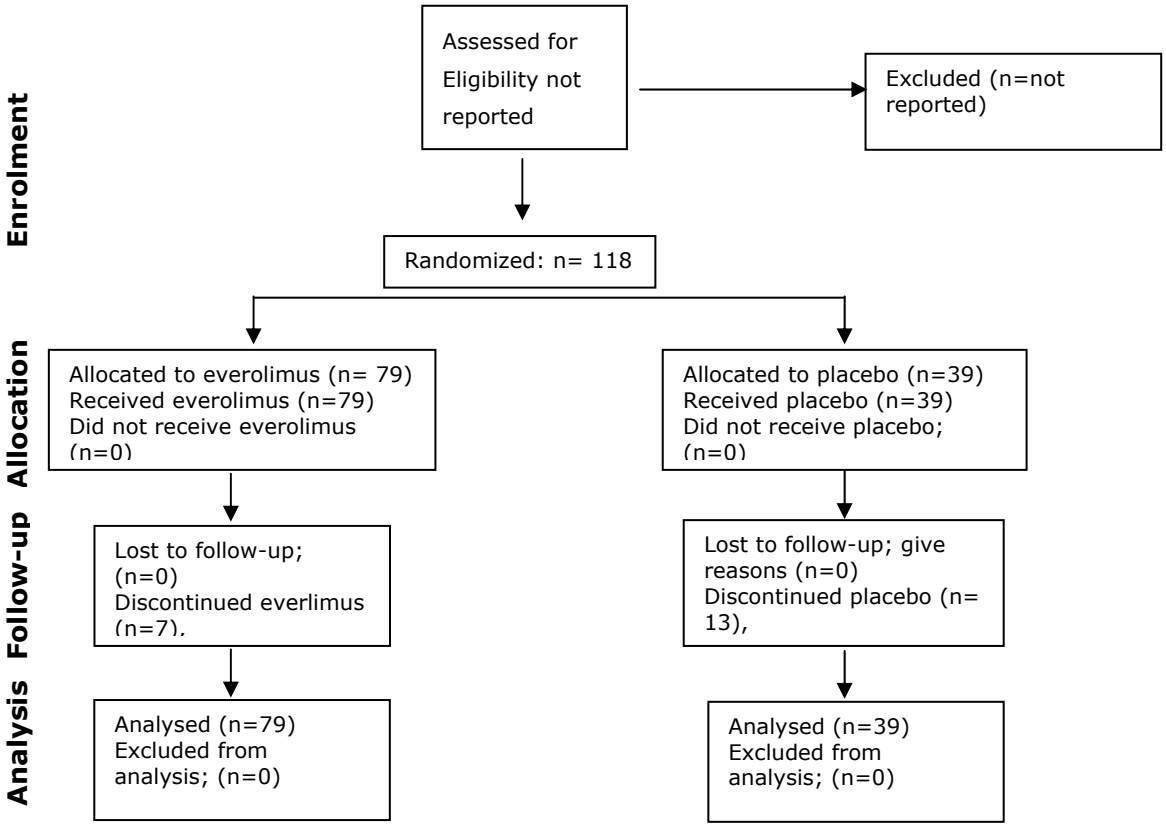
Based on clinical judgment, the key secondary efficacy endpoints were ranked and the closed testing procedure was as follows:

- test primary endpoint of angiomyolipoma response rate
- test time to angiomyolipoma progression
- test skin lesion response rate

The Full Analysis Set (FAS), the primary population for the assessment of efficacy was defined according to the Intention-to-Treat principle and consisted of all randomized patients. Patients were to be analyzed according to the treatment that they were assigned to at randomization.

Results

Participant flow



Recruitment

A total of 118 patients were enrolled and randomized into this trial from 24 sites in 11 countries. The highest enrolling countries were the United States (32 patients), Germany (27), The Netherlands (13), and Japan (10).

Conduct of the study

Patient disposition is shown in Table 8.

Table 8: Patient disposition in the double-blind period (Full Analysis Set) – M2302

Disposition Reason	Everolimus N=79 n (%)	Placebo N=39 n (%)
Ongoing	72 (91.1)	26 (66.7)
Discontinued	7 (8.9)	13 (33.3)
Reason for discontinuation[1]		
Disease progression	0	9 (23.1)
Adverse event(s)	2 (2.5)	4 (10.3)
Abnormal laboratory value(s)	1 (1.3)	0
Subject withdrew consent	1 (1.3)	0
Administrative problems	1 (1.3)	0
Death	1 (1.3)	0
Protocol deviation	1 (1.3)	0

Of note, although none of the patients in the everolimus arm had disease progression as the reason for discontinuation, there were 3 patients (3.8%) from the everolimus arm that actually met the criteria for angiomyolipoma progression according to central radiology review but had not discontinued from the trial because discontinuation for disease progression was at investigator discretion and not mandatory.

Following blinded data review during data validation prior to database lock, it was observed that only 8 patients were stratified as having sporadic LAM at randomization. Upon further review of the baseline data collected on the CRF, only 5 of these 8 patients were correctly stratified as having sporadic LAM. As patients with sporadic LAM were not expected to be using EIAED, as confirmed by the CRF data, it was considered appropriate to combine patients in the stratum "TSC and EIAED non-use" with patients in the stratum "sporadic LAM". Therefore, the newly modified stratification factor to be used in all stratified statistical analyses would contain only two categories: EIAED use versus EIAED non-use at randomization. This change to the statistical analysis plan was made prior to the database lock and unblinding of the data.

The protocol was amended twice. The protocol was amended two times. The key features of each amendment are given below:

Amendment 1 (dated 29-Mar-2010) was issued after the inclusion of 21% of patients and, among other changes, introduced the following changes:

• Allowed assessment of angiomyolipomata to be carried out by CT scan as well as by MRI with the condition that the same imaging modality for assessment of the kidneys must be used throughout the trial for each individual patient

• Patients who met pre-specified criteria at baseline would now be screened for hepatitis B

(HBV) and hepatitis C (HCV) at baseline, using the following tests: HBV DNA, HBV surface antigen (HBsAg), HBV surface antibody (HBsAb), HBV core antibody (HBcAb), HCV RNA-PCR. Hepatitis B and C management guidelines were added for patients who are active prior to the implementation of Amendment 1

• Harmonized the visit window for all visits

• Added revised table of PgP substrates, inhibitors, and inducers

• Added provision for an End of Treatment scan if the patient discontinued for reasons other than progression and enough time had passed since their most recent scan

• Added instructions for the permitted local laboratory collections for the 6 week visit for patients in the United States for whom travel to the clinic was difficult

• Changed the requirement of a confirmatory scan from "at least 4 weeks" after the first assessment of response to "approximately 12" (and no sooner than 8 weeks) after the first assessment of response

• Changed the confirmation of skin lesion response from "at least 4 weeks" after the first response assessment to "approximately 12 weeks" (and no sooner than 8 weeks) after the first response assessment

Amendment 2 (dated 13-May-2010) contained administrative changes to the Visit Evaluation Schedules as well as editorial changes and clarifications.

Major protocol deviations (those leading to exclusion from the PPS) were observed in 2 patients, one randomized to the everolimus arm and one to the placebo arm (both failed to meet the predefined entry criteria for angiomyolipoma). In the everolimus arm, one patient did not have a clinically definite

diagnosis of renal angiomyolipoma and had no angiomyolipoma ≥ 2 cm in longest diameter at baseline per local or central radiology review. In the placebo arm, one patient had no angiomyolipoma ≥ 2 cm in longest diameter at baseline per central radiology review. Minor deviations that were not considered clinically meaningful were reported in 67.1% of patients in the everolimus arm and 64.1% of patients in the placebo arm.

Baseline data

The two treatment groups had a median age of 32 years and 29 years in the everolimus and placebo arms, respectively (Table 9):

Table 9: Demographic characteristics (Full Analysis Set) – Study M2302

Demographic characteristic	Everolimus N=79 n (%)	Placebo N=39 n (%)
Age (years)		
n	79	39
Mean (SD)	32.5 (10.37)	31.0 (9.64)
Median	32.0	29.0
Range	18.0 - 61.0	18.0 - 58.0
Age (years)		
< 30	35 (44.3%)	20 (51.3%)
≥ 30	44 (55.7%)	19 (48.7%)
Gender		
Female	52 (65.8%)	26 (66.7%)
Male	27 (34.2%)	13 (33.3%)
Race		
Caucasian	71 (89.9%)	34 (87.2%)
Asian	7 (8.9%)	4 (10.3%)
Other	1 (1.3%)	1 (2.6%)
Ethnicity		
Hispanic/Latino	0	1 (2.6%)
Chinese	0	1 (2.6%)
Japanese	7 (8.9%)	3 (7.7%)
Mixed ethnicity	1 (1.3%)	0
Other[1]	71 (89.9%)	34 (87.2%)

[1] Other signifies that the patient was neither Hispanic/Latino, Chinese, Japanese nor of mixed ethnicity.

Patients in trial M2302 can be considered as representative of the target patient population. All patients had a clinical diagnosis of TSC or of sporadic LAM (Table 10). In the everolimus arm, a single patient did not have a confirmed angiomyolipoma. In Table 11, this patient is counted (but as having zero target lesions and a "not applicable" longest diameter of angiomyolipoma).

Table 10: Patient and disease characteristics at baseline (Full Analysis Set) – Study M2302

Disease characteristic at baseline	Everolimus N=79 n (%)	Placebo N=39 n (%)
Diagnosis of TSC[1]	77 (97.5)	36 (92.3)
At least 2 major features	77 (97.5)	36 (92.3)
Only one major feature and at least 2 minor features	0	0
Diagnosis of sporadic LAM	2 (2.5)	3 (7.7)
Diagnosis of LAM	22 (27.8)	7 (17.9)
TSC diagnosis criteria (modified Gomez):		

Major features		
1. Renal angiomyolipoma	78 (98.7)	39 (100.0)
2. Facial angiofibromas or forehead plaque	75 (94.9)	35 (89.7)
3. Subependymal nodule	61 (77.2)	31 (79.5)
4. Cortical tuber	56 (70.9)	30 (76.9)
5. Hypomelanotic macules (three or more)	54 (68.4)	17 (43.6)
6. Nontraumatic ungueal or periungueal fibroma	49 (62.0)	22 (56.4)
7. Subependymal giant cell astrocytoma	43 (54.4)	14 (35.9)
8. Shagreen patch (connective tissue nevus)	39 (49.4)	18 (46.2)
9. Multiple retinal nodular hamartomas	30 (38.0)	8 (20.5)
10. Lymphangioleiomyomatosis	24 (30.4)	10 (25.6)
11. Cardiac rhabdomyoma, single or multiple	17 (21.5)	6 (15.4)
Minor features		
1. Multiple, randomly distributed pits in dental enamel	31 (39.2)	9 (23.1)
2. 'Confetti' skin lesions	28 (35.4)	2 (5.1)
3. Multiple renal cysts	18 (22.8)	3 (7.7)
4. Gingival fibromas	18 (22.8)	3 (7.7)
5. Nonrenal hamartoma	12 (15.2)	6 (15.4)
6. Cerebral white matter radial migration lines	11 (13.9)	1 (2.6)
7. Retinal achromic patch	4 (5.1)	1 (2.6)
8. Hamartomatous rectal polyps	3 (3.8)	0
9. Bone cysts	0	1 (2.6)

[1] The co-occurrence of cortical tuber and cerebral white matter radial migration lines is considered as one major feature. In patients with both 2 major features of lymphangioleiomyomatosis and renal angiomyolipoma, another feature must be identified to assign TSC diagnosis.

The distribution of baseline tumour burden per central radiology review with respect to the number of target angiomyolipoma lesions is presented in Table 11.

Table 11: Baseline kidney CT/MRI assessments per central radiology review (Full Analysis Set) – Study M2302

Baseline kidney CT/MRI result	Everolimus N=79	Placebo N=39
Longest diameter of the largest angiomyolipoma lesion		
≥ 8 cm	22 (27.8%)	12 (30.8%)
≥ 4 cm and < 8 cm	45 (57.0%)	19 (48.7%)
≥ 3 cm and < 4 cm	6 (7.6%)	4 (10.3%)
< 3 cm	5 (6.3%)	2 (5.1%)
Unknown	0	1 (2.6)
Not applicable	1 (1.3)	1 (2.6)
Number of target angiomyolipoma lesions ≥ 1 cm in longest diameter		
0	1 (1.3%)	1 (2.6%)
1 - 5	32 (40.5%)	15 (38.5%)
6 - 10	46 (58.2%)	23 (59.0%)
> 10	0	0
Sum of volumes of target angiomyolipoma lesions (cm^3)		
Number of patients with at least one target angiomyolipoma	78	37
Mean (SD)	180.60 (274.001)	277.19 (736.205)
Median	85.40	119.83
Range	8.57 - 1611.54	3.03 - 4520.07
Volume of right kidney (cm^3)		
Number of patients with right kidney volume	72	33
Mean (SD)	447.34 (437.742)	424.93 (318.425)
Median	289.23	296.95
Range	113.03 - 2405.01	143.10 - 1283.30
Volume of left kidney (cm^3)		
Number of patients with left kidney volume	66	32
Mean (SD)	572.14 (632.568)	696.24 (847.517)
Median	335.79	355.23
Range	159.53 - 3750.19	131.13 - 4469.50

Longest diameter of the largest angiomyolipoma lesion is "unknown" when at least one target lesion >1cm is confirmed but no precise diameter could be measured. It is "Not applicable" if there is not at least one target lesion.

A summary of prior anti-angiomyolipoma therapy in each treatment arm is presented in Table 12.

Table 12: Prior anti-angiomyolipoma therapy (Full Analysis Set) – Study M2302

	Everolimus N=79 n (%)	Placebo N=39 n (%)
Any prior anti-angiomyolipoma medication/surgery	31 (39.2%)	15 (38.5%)
Surgery/invasive procedure	31 (39.2%)	15 (38.5%)
Renal embolization	19 (24.1%)	9 (23.1%)
Nephrectomy	14 (17.7%)	8 (20.5%)
Medication	0	0

Numbers analysed

The distribution of patients in the different analysis populations is presented in Table 13.
Sixteen patients (20.3%) in the everolimus arm were excluded from the PPS one patient (1.3%) had a major protocol deviation (did not meet protocol inclusion criteria for a clinically definite diagnosis of renal angiomyolipoma and angiomyolipoma ≥ 2 cm in longest diameter at baseline), 12 patients (15.2%) were not evaluable for efficacy, and 5 patients (6.3%) had insufficient exposure to everolimus. Five patients (12.8%) in the placebo arm were excluded from the PPS: one (2.6%) had a major protocol deviation (did not meet protocol inclusion criterion for angiomyolipoma ≥ 2 cm in longest diameter at baseline), and 5 (12.8%) were non-evaluable for efficacy.

Table 13: Analysis populations by stratum (Full Analysis Set) – Study M2302

Analysis population	Everolimus N=79 n (%)	Placebo N=39 n (%)
Full Analysis Set	79 (100.0)	39 (100.0)
EIAED use	13 (16.5)	7 (17.9)
EIAED non-use	66 (83.5)	32 (82.1)
Per Protocol Set	63 (79.7)	34 (87.2)
EIAED use	13 (16.5)	7 (17.9)
EIAED non-use	50 (63.3)	27 (69.2)
Safety Set	79 (100.0)	39 (100.0)
EIAED use	13 16.5)	7 (17.9)
EIAED non-use	66 (83.5)	32 (82.1)
Open-label Everolimus Population	0	7 (17.9)
EIAED use	0	0
EIAED non-use	0	7 (17.9)

Outcomes and estimation

Primary efficacy endpoint

Angiomyolipoma response rate

The angiomyolipoma response rate is presented in Table 14. The overall best response rate was 41.8% (95% CI: 30.8, 53.4) for the everolimus arm and 0% (95% CI: 0.0, 9.0) for the placebo arm.

Table 14: Best overall angiomyolipoma response as per central radiology review (double-blind period) (Full Analysis Set) – Study M2302

	Everolimus N=79	Placebo N=39	p-value[1]	Difference in response rates[2] [95% CI]
Best overall angiomyolipoma response				
Response	33 (41.8)	0		
Stable disease	32 (40.5)	31 (79.5)		
Progression	1 (1.3)	2 (5.1)		
Not evaluable	13 (16.5)	6 (15.4)		
Primary analysis				
Angiomyolipoma response rate	33 (41.8)	0	<0.0001	41.8
95% CI for angiomyolipoma response rate[3]	[30.8, 53.4]	[0.0; 9.0]		[23.5, 58.4]

Secondary efficacy endpoint

Time to angiomyolypoma progression

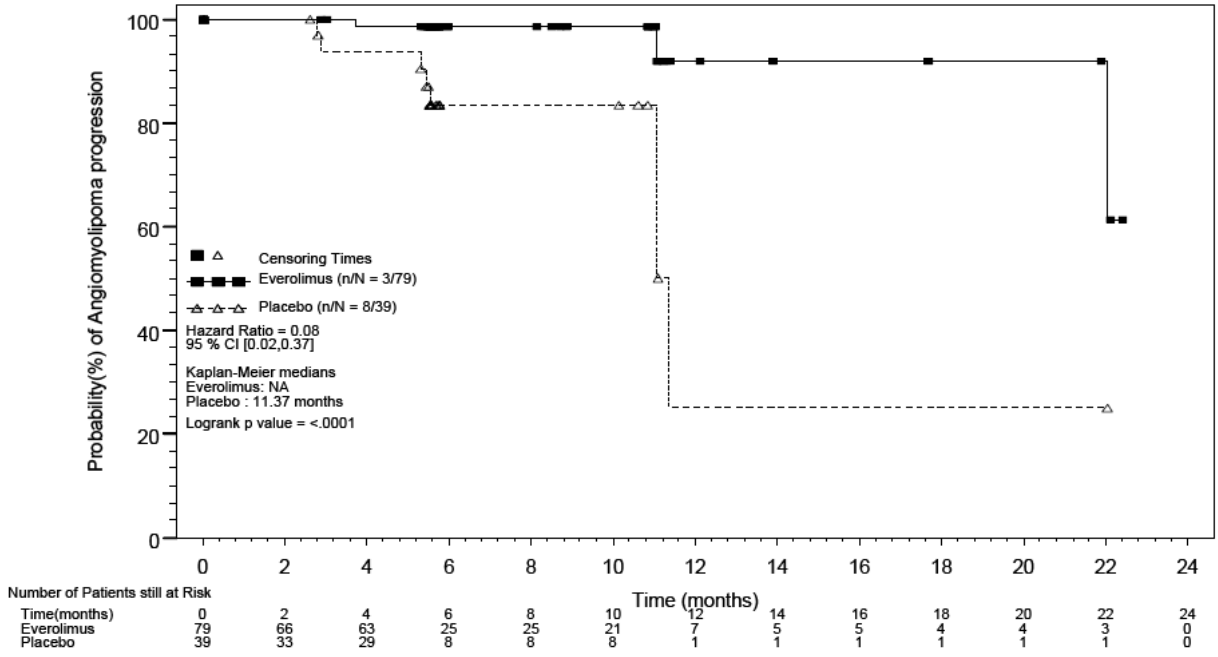
A summary of the time to angiomyolipoma progression is shown in Table 15 and Figure 5. There were 3 (3.8%) patients in the everolimus arm and 8 (20.5%) patients in the placebo arm that had angiomyolipoma progression. There was prolongation of time to angiomyolipoma progression in the everolimus arm compared to the placebo arm (HR 0.08; 95% CI: 0.02, 0.37; p<0.0001). Median time to angiomyolipoma progression was 11.37 months in the placebo arm and was not reached in the everolimus arm. The 3 cases of angiomyolipoma progression in the everolimus arm were assessed on trial days 114, 337, and 671.

Table 15: Time to angiomyolipoma progression as per central radiology review (double-blind period) (Full Analysis Set) – Study M2302

	Everolimus N=79	Placebo N=39	p-value[1]	Hazard ratio[2] [95% CI]
Number of patients with angiomyolipoma progression	3 (3.8)	8 (20.5)	<0.0001	0.08 [0.02, 0.37]
Number censored	76 (96.2)	31 (79.5)		
Kaplan-Meier estimates [95% CI] at:				
6 months	98.4 [89.4,99.8]	83.4 [64.6,92.8]		
12 months	91.9 [64.7,98.4]	25.0 [1.4,64.0]		
25th percentile [95% CI]	22.05 [11.07,NA]	11.07 [5.32,11.37]		
Median time to angiomyolipoma progression (months) [95% CI]	NA [NA, NA]	11.37 [11.07,NA]		
75th percentile [95% CI]	NA [NA,NA]	NA [NA,NA]		

[1] The p-value is obtained from the one-sided log-rank test, stratified by the modified stratification factor (EIAED use versus EIAED non-use).
[2] The HR and 95% CI are obtained from the Cox model, stratified by the modified stratification factor. A HR less than 1 favors the everolimus group.
NA, not applicable

Figure 5: Kaplan-Meier plot of time to angiomyolipoma progression as per central radiology review (double-blind period) (Full Analysis Set) – Study M2302



[1] p-value is obtained from the one-sided stratified log-rank test.
[2] Hazard ratio <1 implies reduced risk of angiomyolipoma progression in the Everolimus group.

Skin lesion response rate

The skin lesion response was determined for the 114 patients with ≥ 1 skin lesion at baseline (Table 16). There was a partial response 9PR) observed with everolimus compared to no response observe in the placebo arm.

Table 16: Best overall skin lesion response as per investigator (only patients with at least one skin lesion at baseline) (Full Analysis Set) – Study M2302

Best overall skin lesion response	Everolimus N=77	Placebo N=37	p-value[1]
Complete Clinical Response (CCR)	0	0	
Partial Response (PR)	20 (26.0)	0	
Stable Disease	55 (71.4)	36 (97.3)	
Progressive Disease	0	0	
Not Evaluable	2 (2.6)	1 (2.7)	
Skin Lesion Response (CCR or PR) Rate	20 (26.0)	0	0.0002
95% CI for Skin lesion Response Rate	[16.6, 37.2]	[0.0, 9.5]	

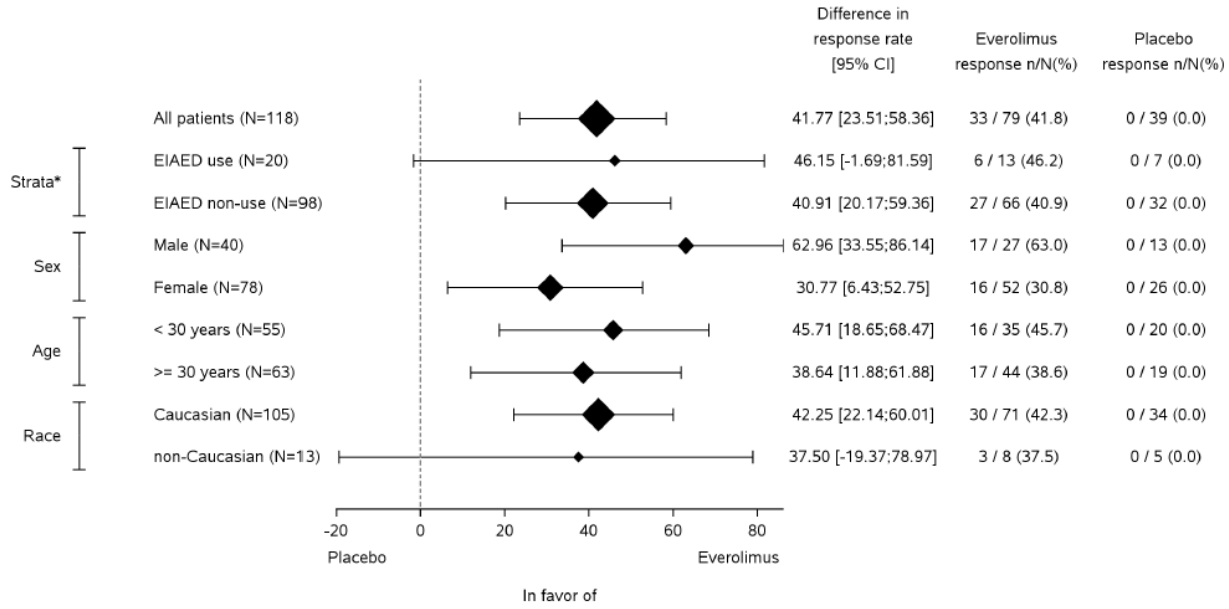
[1] One-sided p-value is obtained from exact Cochran-Mantel-Haenszel test stratified by the modified stratification factor (EIAED use versus EIAED non-use).
[2] Exact 95% confidence interval obtained from the Clopper-Pearson method.

Ancillary analyses

Subgroup analyses

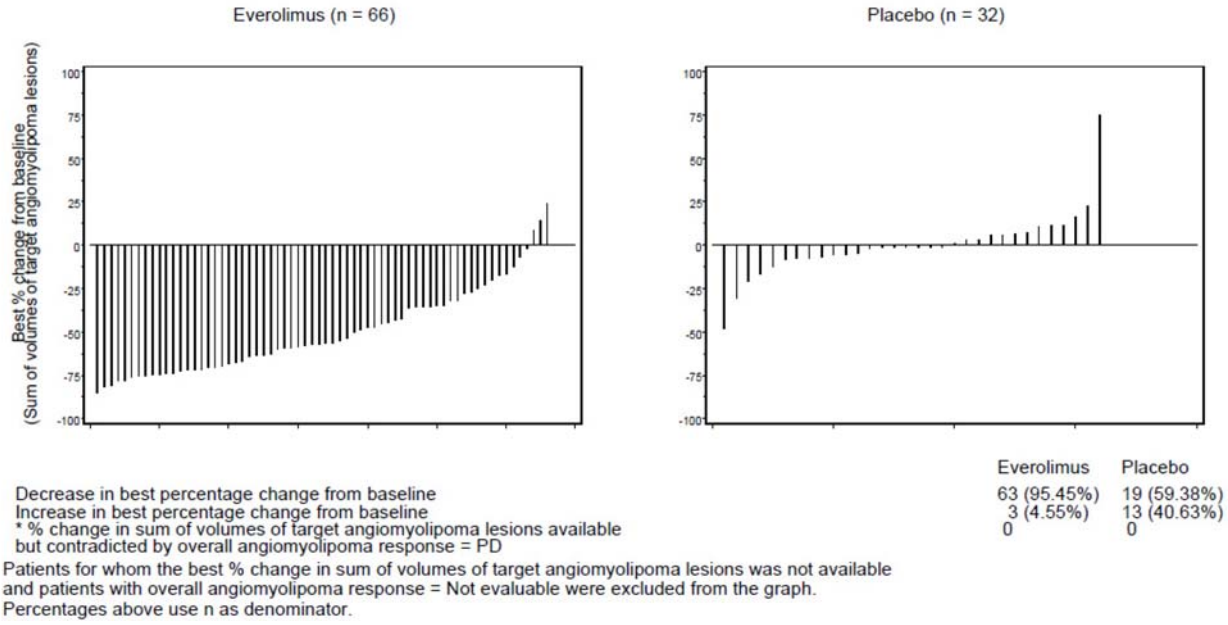
A subgroup analysis was conducted to determine whether the angiomyolipoma response in all pre-defined subgroups correlated with the results from the primary endpoint. The results are shown in Figure 6.

Figure 6: Angiomyolipoma response rates by subgroups (double-blind period) (Full Analysis Set) – Study M2302



As depicted graphically in the waterfall plots (Figure 7), 95.5% of evaluable patients in the everolimus arm experienced a reduction in the sum of volumes of target angiomyolipoma lesions relative to baseline (per central radiology review). In contrast, in the placebo arm, 59.4% of evaluable patients experienced a reduction from baseline. Conversely, only 4.6% of evaluable patients in the everolimus arm experienced an increase from baseline, whereas 40.6% of evaluable patients in the placebo arm had an increase from baseline in sum of volumes of target angiomyolipoma lesions.

Figure 7: Waterfall plot of best percentage change from baseline in the sum of volumes of target angiomyolipoma lesions as per central radiology review (Full Analysis Set) – Study M2302



The magnitude and durability of the everolimus treatment effect is shown by the changes from baseline in the sum of volumes of target angiomyolipoma lesions over time in Table 17 below.

Table 17: Change from baseline in sum of volumes of target angiomyolipoma lesions by time window (double-blind period) (Full Analysis Set) – Study M2302

	Everolimus N=79				Placebo N=39			
Sum of volumes of target angiomyolipoma lesions (cm^3)	**Week 12 n=74**	**Week 24 n=71**	**Week 48 n=27**	**Week 96 n=5**	**Week 12 n=35**	**Week 24 n=33**	**Week 48 n=10**	**Week 96 n=1**
Baseline for patients present at each respective assessment (cm^3)								
Mean	183.171	186.072	258.704	522.275	291.118	302.816	636.938	4520.070
SD	279.3697	284.4241	400.7125	621.3417	755.1058	776.7276	1372.6544	
Median	85.402	85.049	98.531	347.646	127.291	148.547	204.782	4520.070
Minimum	8.57	8.57	8.57	47.76	3.03	3.03	37.31	4520.07
Maximum	1611.54	1611.54	1611.54	1611.54	4520.07	4520.07	4520.07	4520.07
Value at the assessment (cm^3)								
Mean	107.613	104.099	137.657	365.109	298.427	311.971	685.308	5460.591
SD	184.7906	193.1776	278.6222	577.6917	797.7509	799.6156	1541.0246	
Median	44.850	38.662	41.757	96.450	117.250	127.809	199.740	5460.591
Minimum	3.25	3.11	2.94	19.59	2.53	3.01	34.64	5460.59
Maximum	1091.21	1240.12	1286.29	1387.63	4773.01	4654.14	5050.56	5460.59
Change from baseline (cm^3)								
Mean	-75.559	-81.973	-121.048	-157.166	7.309	9.155	48.369	940.521

SD	106.3470	110.6375	152.3941	129.7190	47.3772	38.1144	174.8331	
Median	-36.809	-32.627	-69.076	-223.905	-0.502	4.757	8.341	940.521
Minimum	-520.32	-615.34	-674.95	-271.63	-58.78	-102.77	-123.44	940.52
Maximum	10.58	9.08	9.18	-5.06	252.94	134.07	530.49	940.52
Percentage change from baseline								
Mean	-42.167	-47.708	-53.104	-45.150	0.883	4.411	0.215	20.808
SD	22.6386	23.9890	28.0751	34.9166	18.4363	15.3447	17.3043	
Median	-46.059	-55.416	-59.522	-58.988	-1.187	6.283	4.006	20.808
Minimum	-76.31	-79.73	-84.83	-78.13	-48.01	-31.32	-37.62	20.81
Maximum	25.64	24.16	24.44	-2.02	75.02	35.35	18.38	20.81
Percentage change from baseline [1]								
≤ -50%	31 (41.9%)	39 (54.9%)	18 (66.7%)	3 (60.0%)	0	0	0	0
≤ -30%	56 (75.7%)	57 (80.3%)	21 (77.8%)	3 (60.0%)	2 (5.7%)	1 (3.0%)	1 (10.0%)	0
< 0%	70 (94.6%)	68 (95.8%)	25 (92.6%)	5 (100.0%)	19 (54.3%)	13 (39.4%)	3 (30.0%)	0
≥ 0%	4 (5.4%)	3 (4.2%)	2 (7.4%)	0	16 (45.7%)	20 (60.6%)	7 (70.0%)	1 (100.0%)
≥ 10%	3 (4.1%)	3 (4.2%)	1 (3.7%)	0	8 (22.9%)	11 (33.3%)	4 (40.0%)	1 (100.0%)
≥ 25%	1 (1.4%)	0	0	0	1 (2.9%)	2 (6.1%)	0	0

Time to angiomyolipoma response

Time to angiomyolipoma response applies only to the 33 patients in the everolimus arm who achieved a partial response. The median time to angiomyolipoma response was 2.86 months. The proportions of angiomyolipoma responders who responded by 3 months and 6 months were 63.6% and 97.0%, respectively.

Duration of angiomyolipoma response

No progressions were observed in everolimus-treated patients who achieved a response. Angiomyolipoma responses were ongoing for between 10+ and 85+ weeks at the time of the data cut-off.

Duration of skin lesion response

There was no skin lesion progression in the 20 responding patients. Responses were ongoing for between 10+ and 84+ weeks at the time of the data cut-off.

Exploratory efficacy results

Correlation between angiomyolipoma volume and longest diameter

The purpose of this analysis was to evaluate the link between the sum of the longest diameters and the sum of volumes of target angiomyolipoma lesions. The correlation between these measures was evaluated at each assessment by the calculation of Pearson's correlation coefficient. The correlation coefficients were > 0.6 at each time point, indicating that there was a positive linear relationship between the sum of volumes and the sum of longest diameters in both treatment arms.

Incidence and reasons for angiomyolipoma surgery

No patient in either of the treatment arms reported angiomyolipoma surgery during the double-blind period.

SEGA response rate

SEGA response was evaluated in the subgroup of patients who had at least one SEGA lesion with longest diameter ≥ 1.0 cm at baseline (N=52) (Table 18).

Table 18: Best overall SEGA response as per central radiology review (double blind period) (Full Analysis Set) – Study M2302

Best overall SEGA response	Everolimus N=39 n (%)	Placebo N=13 n (%)
Response	4 (10.3)	0
Stable disease	29 (74.4)	12 (92.3)
Progression	0	0
Not evaluable	6 (15.4)	1 (7.7)
SEGA Response Rate	10.3	0
95% CI for SEGA Response Rate[1]	[2.9; 24.2]	[0.0; 24.7]

[1] Exact 95% CI obtained from the Clopper-Pearson method.
Source: Table 14.2-4.1

Change from baseline in pulmonary function

In the 5 patients with sporadic LAM and 29 patients with TSC-associated LAM, changes from baseline in pulmonary function (FEV1, FVC, and DLCO) were assessed over the course of the trial.

For FEV1, the median percentage change from baseline at Week 24 was:

- -1.43% in the everolimus arm
- -3.70% in the placebo arm

For FVC, the median percentage change from baseline at Week 24 was:

- -1.25% in the everolimus arm
- 0% in the placebo arm

For DLCO, the median percentage change from baseline at Week 24 was:

- -2.73% in the everolimus arm
- -7.57% in the placebo arm

Change from baseline in neuropsychological assessments

Results from the neuropsychological assessment analysis were not interpretable because the scales used were not validated in several countries that enrolled patients in the trial (Germany, The Netherlands, Poland, and Russia).

Change from baseline in the severity of seizures

Changes from baseline in the severity of seizures using the SSQ were assessed in those patients who were taking antiepileptic drugs at baseline. A total of 10 patients in the everolimus arm and 5 patients in the placebo arm filled out the SSQ. There was no difference in median global change score between everolimus- and placebo treated patients at Week 24, 3.50 (range: 2.00-4.75) and 3.88 (range: 3.50-4.75), respectively.

Analysis of open-label efficacy

Seven patients that had progressed on placebo entered into the open-label treatment with everolimus phase. In these patients, one subject (14.3%) had an angiomyolipoma response, with a time to response of 85 days (dating from the start of everolimus treatment) and the duration of response of

92+ days. Five patients (71.4%) had a best response of stable disease and one patient was not evaluable as of the cut-off date. All patients continued to receive everolimus.

Mutational analysis of TSC1 and TSC2

The results of the TSC1 and TSC2 mutational analyses are presented below:

Table 19: Mutation status of TSC1 and TSC2 – Study M2302

Nature of mutation	Everolimus N=79 n (%)	Placebo N=39 n (%)	All patients N=118 n (%)
TSC1 gene	2 (2.5)	2 (5.1)	4 (3.4)
TSC2 gene	60 (75.9)	27 (69.2)	87 (73.7)
Both TSC1 and TSC2 genes	0	0	0
No mutation detected in either gene	14 (17.7)	9 (23.1)	23 (19.5)
Not evaluated for mutation status	3 (3.8)	1 (2.6)	4 (3.4)

In the everolimus arm, patients with mutations in TSC2 had an angiomyolipoma response rate of 48.3% compared to 35.7% in patients with no mutation. In the placebo arm, disease progression was seen in patients with TSC2 mutations (3 of 27, or 11.1%) and in patients with no mutation identified (5 of 9, or 55.6%). The three patients who experienced disease progression on the everolimus arm all had a mutation in the TSC2 gene.

Angiogenic markers

The effects of everolimus on tumour vascularisation were examined through the measurement of angiogenic growth factors and their corresponding soluble receptors (VEGF, VEGFD, soluble VEGF receptor 1 (sVEGFR1), soluble VEGF receptor 2 (sVEGFR2), basic fibroblast growth factor (bFGF), placental growth factor (PLGF), c-Kit and collagen type IV). Samples were collected at screening, week 4, week 12, every 12 weeks until week 48 and at the end of treatment visit, when applicable during the double-blind period. Samples were collected immediately prior to drug administration. Results demonstrated an initial and sustained decrease of approximately 60% in VEGF-D, an approximate 45% decrease in collagen type IV, and an initial and sustained increase in VEGF levels in everolimus-treated patients compared to placebo-treated patients.

Summary of main study

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

Table 20 Summary of Efficacy for trial M2303

Title: A randomized, double-blind, placebo-controlled study of RAD001 in the treatment of angiomyolipoma in patients with either Tuberous Sclerosis Complex (TSC) or Sporadic Lymphangioleiomyomatosis (LAM)	
Study identifier	**CRAD001M2302**
Design	**double-blind, 2:1 randomized, parallel group, placebo-controlled, multicenter**

	Duration of main ("core") phase: Duration of Run-in phase: Duration of (open label) Extension phase:		Core phase was defined as start of the trial up to the time when the results of the final primary analysis were known. First patient first visit 28-Apr-2009, primary analysis cut-off date 30-Jun-2011 (defined as 6 months after last patient randomized), report date of primary analysis 02-Nov-2011 not applicable ongoing, projected last patient visit 30-Dec-2014
Hypothesis	Superiority		
Treatments groups	everolimus		Treatment: Everolimus administered by continuous oral daily dosing of two 5 mg tablets. Duration: No fixed treatment duration was specified. Treatment continued until angiomyolipoma progression, unacceptable toxicity, or discontinuation for any other reason Number randomized: 79
	placebo		Treatment: Placebo administered by continuous oral daily dosing of two 5 mg matching placebo tablets. Duration: End of core phase, all patients who had not progressed and were still receiving study treatment was be given the option of starting open-label everolimus. Number randomized: 39
Endpoints and definitions	Primary endpoint (see section Outcome/end points)		angiomyolipoma response rate
	Main secondary endpoints (with adjustment for multiplicity testing)	TTAP	- Time to angiomyolipoma progression -Skin lesion response rate
Database lock	set to a not further specified date after cut-off date 30-Jun-2011		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	everolimus	placebo	
	Number of subject	79	39	
	AML response rate	41.8%	0%	

	95% CI	30.8, 53.4	0.0, 9.0	
	Time to AML progression	n/a	11.37 months	
	95% CI	n/a, n/a	11.07, n/a	
	Duration of AML response	Response ongoing at time of cut-off (between 10+ and 85+ weeks)	No response observed	
	95% CI	n/a, n/a	n/a, n/a	
	Skin lesion response rate in 114 patients	26.0%	0%	
	95% CI	16.6, 37.2	0.0, 9.5	

Supportive study

Study M2301

Study M2301 was a prospective, double-blind, randomised, parallel-group, placebo-controlled, multicentre Phase-III trial evaluating treatment with everolimus vs. placebo in patients with TSC who had SEGA. The primary efficacy endpoint of the trial was the SEGA response rate and the 3 key secondary endpoints were seizure frequency reduction, time to SEGA progression, and skin lesion response rate. The majority of patients were enrolled from the paediatric population and a flexible dosing regimen was employed (dose titrated to a trough concentration of 5 - 15 ng/mL).

Results

Angiomyolipoma response was an exploratory endpoint and was evaluated in the subgroup of patients who had at least one angiomyolipoma lesion with the longest diameter ≥ 1.0 cm at baseline (N=44). Angiomyolipoma response in the everolimus arm was 53.3% (95% CI: 34.3, 71.7). There were no responses in the placebo arm.

1.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The Study M2302 was designed as a randomized, placebo controlled phase III study investigating the efficacy and safety of everolimus in the treatment of AML, specifically to measure angiomyolipoma response rate. The study had 2 distinct parts, a core phase and an open-extension phase. The design of the trial followed CHMP scientific advice and was generally well conducted.

Concerning the conduct of trial M2302, the definitions of progression were changed, mostly with amendment 1. The change of the definition of progression did not have a relevant impact on the interpretation of the results or the outcome of the study.

Efficacy data and additional analyses

Patients with TS and angiomyolipoma greater than 4 cm have a high risk for the development of symptoms and may require surgery. In the pivotal trial, patients were required to have at least one lesion ≥ 3 cm in longest diameter. Most of the patients in the everolimus arm (84.8%) and patients in the placebo arm (79.5%) presented with angiomyolipomas with a longest diameter ≥ 4 cm; such patients are considered to be at increased risk for hemorrhagic rupture. Therefore the study population represented an AML population which is at risk of complications from AML growth and at at significant risk of renal morbidity.

The study reached its primary endpoint where there was a statistically significant difference between the angiomyolipoma response rate in the everolimus arm compared to the placebo arm (41.8% vs 0%, respectively; 95% CI 23.5-58.4; p-value <0.0001). The effect observed is robust and was supported by the subgroups analyses.

Results of the key secondary endpoints support the observed benefit in the primary analysis. Treatment with everolimus was associated with a statistically significant difference with respect to prolongation of time to angiomyolipoma progression compared to placebo (HR 0.08; 95% CI: 0.02, 0.37; p<0.0001). The proportions of angiomyolipoma responders who responded by 3 months was 63.6% and by 6 months was 97.0%. Angiomyolipoma progressions were observed in 3 patients (3.8%) in the everolimus arm and 8 patients (20.5%) in the placebo arm. Median time to angiomyolipoma progression was 11.4 months in the placebo arm and was not reached in the everolimus arm. Skin lesion response rate showed a statistically significant difference, the overall effect, a 26.0% response rate in the everolimus arm during an observation time of about 10 months. No progression of any skin lesion was observed in the placebo arm during this observation time. None of the 41.8% of patients in the everolimus arm who experienced an angiomyolipoma response reported disease progression prior to the data cut-off. Responses were ongoing for between 10+ and 85+ weeks at the time of the data cut-off. Both the proportion of responses and duration of response were considered clinically impressive. Prevention of further tumor growth in these patients was considered to reflect a relevant clinical benefit.

1.5.4. Conclusions on the clinical efficacy

The CHMP considered the study acceptable and adequately designed to support the proposed claimed indication. The clinical efficacy of everolimus in TSC patients with angiomyolipoma has been demonstrated. The study M2302 clearly showed a reduction in the size of angiomyolipomas and changes in the growth kinetics of AML target lesions in the observation period.

The CHMP considered the following measure necessary to further ascertain the long-term benefit of treatment with everolimus such as improvement of disease-related symptoms, prevention of bleeding and reduction of embolization/nephrectomy. The measure was included as part of an Annex II condition:

- Submission of the clinical study report comprising the extension phase of Study M2302

1.6. Clinical safety

Safety evaluation in the claimed indication is based on data from 118 patients enrolled into study M2302. This includes 79 in the everolimus arm (10 mg dose) and 39 in the placebo arm. The safety population consisted of all patients who received ≥ 1 dose of study treatment and had ≥ 1 post-baseline assessment.

Patient exposure

The median duration of therapy with everolimus was 38.1 weeks (range: 2 to 105) with 26 patients (32.9%) exposed to everolimus for a period of ≥ 48 weeks compared to 34.0 weeks (range: 9-112 weeks) for placebo. Overall exposure was 67.7 patient-years for everolimus and 29.9 patient-years for placebo.

Table 21: Duration of exposure to study drug – Study M2302

Exposure	Everolimus N=79	Placebo N=39
Exposure categories (weeks) - n (%)		
< 12	2 (2.5)	1 (2.6)
12 to < 24	4 (5.1)	3 (7.7)
24 to < 36	28 (35.4)	17 (43.6)
36 to < 48	19 (24.1)	7 (17.9)
≥ 48	26 (32.9)	11 (28.2)
Duration of exposure (weeks)		
Mean (standard deviation)	44.7 (22.17)	40.0 (20.43)
Median	38.1	34.0
Range	2 to 105	9 to 112
Total patient-year exposure	67.7	29.9

Adverse events

Adverse events (AEs) were reported in the vast majority of patients. The tables below summarise the adverse events derived from study M2302 and M2301:

Table 22: Summary of adverse event categories – Study M2302

Category	Study M2302		Study M2301	
	Everolimus N=79 n (%)	Placebo N=39 n (%)	Everolimus N=78 n (%)	Placebo N=39 n (%)
Adverse events (AEs)[1]	**79 (100.0)**	**38 (97.4)**	**75 (96.2)**	**35 (89.7)**
AEs Suspected to be drug-related	76 (96.2)	25 (64.1)	65 (83.3)	17 (43.6)
Grade 3-4 AEs	23 (29.1)	3 (7.7)	26 (33.3)	9 (23.1)
Suspected to be drug-related	15 (19.0)	1 (2.6)	13 (16.7)	3 (7.7)
All deaths	**1 (1.3)**	**0**	**0**	**0**
On-treatment deaths[2]	1 (1.3)	0	0	0
Serious adverse events (SAEs)	**15 (19.0)**	**7 (17.9)**	**15 (19.2)**	**3 (7.7)**
Suspected to be drug-related	6 (7.6)	2 (5.1)	4 (5.1)	0
AEs leading to discontinuation	**3 (3.8)**	**4 (10.3)**	**0**	**0**
Suspected to be drug-related	2 (2.5)	1 (2.6)	0	0
Other significant AEs				
AEs requiring dose interruption and/or reduction	**38 (48.1)**	**8 (20.5)**	**38 (48.7)**	**4 (10.3)**
AEs requiring additional therapy[3]	73 (92.4)	33 (84.6)	73 (93.6)	31 (79.5)
Clinically notable AEs[4]	**73 (92.4)**	**29 (74.4)**	**73 (93.6)**	**29 (74.4)**
Suspected to be drug-related	67 (84.8)	17 (43.6)	61 (78.2)	11 (28.2)

[1] Only AEs occurring on or after the start of study treatment and no more than 28 days after the discontinuation of study treatment and before start of open-label everolimus are summarized.

[2] On-treatment deaths are deaths which occurred up to 28 days after the discontinuation of study treatment, and before start of open-label everolimus.

[3] Additional therapy includes all non-drug therapy and concomitant medications.

[4] The AE groupings of clinically notable AEs consist of events for which there is a specific clinical interest in connection with everolimus.

Patients on the everolimus arm experienced more events in several SOCs as compared to placebo.

SOCs with a higher proportion of everolimus-treated patients reporting events (≥ 10% difference relative to placebo) included:

- +45.0% Gastrointestinal disorders (stomatitis, aphthous stomatitis, mouth ulceration and vomiting)
- +11.0% Investigations
- +20.1% Metabolism and nutrition disorders (hypercholesterolemia and hypophosphatemia)
- +11.0% Nervous system disorders
- +17.7% Reproductive system and breast disorders (amenorrhea)
- +32.6% Skin and subcutaneous tissue disorders (acne)

SOCs with a higher proportion of placebo-treated patients reporting events (≥10% difference relative to everolimus included:

- +14.4% Musculoskeletal and connective tissue disorders (back pain and flank pain)
- +11.6% Renal and urinary disorders (proteinuria)

The following AEs were reported more frequently in the everolimus arm (differences relative to placebo):

- Stomatitis (+40.4%)
- Hypercholesterolemia (+17.7%)
- Acne (+16.4%)
- Mouth ulceration (+11.4%)
- Hypophosphataemia (+11.4%)
- Vomiting (+10.1%)
- Anaemia (+10.1%)

Table 23: Adverse events by system organ class irrespective of causality – Study M2302 supported by M2301 (Safety set)

Category	Study M2302		Study M2301	
	Everolimus N=79 n (%)	Placebo N=39 n (%)	Everolimus N=78 n (%)	Placebo N=39 n (%)
Any system organ class	**79 (100.0)**	**38 (97.4)**	**75 (96.2)**	**35 (89.7)**
Gastrointestinal disorders	70 (88.6)	17 (43.6)	59 (75.6)	19 (48.7)
Infections and infestations	51 (64.6)	28 (71.8)	56 (71.8)	26 (66.7)
Skin and subcutaneous tissue disorders	44 (55.7)	9 (23.1)	30 (38.5)	6 (15.4)
Nervous system disorders	35 (44.3)	13 (33.3)	28 (35.9)	17 (43.6)
Investigations	31 (39.2)	11 (28.2)	18 (23.1)	6 (15.4)
Respiratory, thoracic and mediastinal disorders	31 (39.2)	12 (30.8)	22 (28.2)	8 (20.5)
General disorders and administration site conditions	26 (32.9)	12 (30.8)	32 (41.0)	12 (30.8)
Metabolism and nutrition disorders	24 (30.4)	4 (10.3)	15 (19.2)	5 (12.8)
Musculoskeletal and connective tissue disorders	19 (24.1)	15 (38.5)	13 (16.7)	0
Blood and lymphatic system disorders	18 (22.8)	8 (20.5)	8 (10.3)	1 (2.6)
Reproductive system and breast disorders	18 (22.8)	2 (5.1)	8 (10.3)	1 (2.6)
Psychiatric disorders	16 (20.3)	5 (12.8)	22 (28.2)	3 (7.7)
Injury, poisoning and procedural complications	11 (13.9)	4 (10.3)	11 (14.1)	5 (12.8)
Vascular disorders	11 (13.9)	8 (20.5)	3 (3.8)	1 (2.6)
Eye disorders	7 (8.9)	1 (2.6)	4 (5.1)	1 (2.6)
Renal and urinary disorders	7 (8.9)	8 (20.5)	2 (2.6)	0
Ear and labyrinth disorders	4 (5.1)	2 (5.1)	1 (1.3)	2 (5.1)
Immune system disorders	4 (5.1)	1 (2.6)	2 (2.6)	1 (2.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (5.1)	2 (5.1)	0	4 (10.3)
Cardiac disorders	2 (2.5)	3 (7.7)	0	0
Endocrine disorders	2 (2.5)	0	0	1 (2.6)
Hepatobiliary disorders	1 (1.3)	0	0	0
Congenital, familial and genetic disorders	0	1 (2.6)	0	0

System organ classes are sorted by a descending frequency in the M2302 everolimus group

A patient with multiple AEs within a system organ class is counted only once.

Only AEs occurring on or after the start of study treatment and no more than 28 days after the discontinuation of study treatment and before start of open-label everolimus are summarized.

Table 24: Grading (severity) of adverse events by PT, irrespective of relationship to study drug (double-blind period) – Study M2302 Safety set

	Everolimus N=79			Placebo N=39		
MedDRA Preferred Term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Any preferred term	79 (100.0)	19 (24.1)	4 (5.1)	38 (97.4)	2 (5.1)	1 (2.6)
Amenorrhoea	7 (8.9)	2 (2.5)	0	1 (2.6)	0	0
Aphthous stomatitis	15 (19.0)	2 (2.5)	0	4 (10.3)	0	0
Blood phosphorus decreased	4 (5.1)	2 (2.5)	0	0	0	0
Convulsion	3 (3.8)	1 (1.3)	1 (1.3)	4 (10.3)	0	0
Mouth ulceration	13 (16.5)	2 (2.5)	0	2 (5.1)	0	0
Angioedema	1 (1.3)	1 (1.3)	0	0	0	0
Bile duct stenosis	1 (1.3)	1 (1.3)	0	0	0	0
Blood fibrinogen decreased	1 (1.3)	1 (1.3)	0	0	0	0
Blood uric acid increased	1 (1.3)	0	1 (1.3)	0	0	0
Bronchospasm	2 (2.5)	1 (1.3)	0	0	0	0
Caecitis	1 (1.3)	1 (1.3)	0	0	0	0
Decreased appetite	5 (6.3)	1 (1.3)	0	0	0	0
Fatigue	14 (17.7)	1(1.3)	0	7 (17.9)	0	0
Hypersensitivity	2 (2.5)	1 (1.3)	0	0	0	0
Hypertensive crisis	1 (1.3)	0	1 (1.3)	0	0	0
Inflammation	1 (1.3)	1 (1.3)	0	0	0	0
Ingrowing nail	1 (1.3)	1 (1.3)	0	0	0	0
Irritability	2 (2.5)	1 (1.3)	0	0	0	0
Joint sprain	1 (1.3)	1 (1.3)	0	0	0	0
Lymphopenia	5 (6.3)	1 (1.3)	0	3 (7.7)	0	0
Myalgia	5 (6.3)	1 (1.3)	0	1 (2.6)	0	0
Neutropenia	5 (6.3)	0	1 (1.3)	4 (10.3)	0	0
Presyncope	1 (1.3)	1 (1.3)	0	0	0	0
Stomatitis	38 (48.1)	1 (1.3)	0	3 (7.7)	0	0
Abdominal pain	9 (11.4)	0	0	3 (7.7)	1 (2.6)	0
Affective disorder	0	0	0	2 (5.1)	1 (2.6)	0
Back pain	5 (6.3)	0	0	5 (12.8)	1 (2.6)	0
Headache	17 (21.5)	0	0	7 (17.9)	1 (2.6)	0
Volvulus	0	0	0	1 (2.6)	0	1 (2.6)
Wound infection	0	0	0	1 (2.6)	1 (2.6)	0

AEs are presented in descending order of frequency of (grade 3 + grade 4) AEs for the everolimus group.
The event with maximum severity is counted for patients who experienced multiple episodes of an event.

Most AEs suspected by the investigator to be related to study drug are consistent with the known safety profile of everolimus. The most common adverse drug reactions (AEs suspected to be related to treatment by the investigator) are listed below. The more common reactions in the everolimus arm were:

- Stomatitis
- Hypercholesterolemia
- Aphthous stomatitis

- Mouth ulceration
- Acne
- Fatigue
- Anaemia
- Blood lactate dehydrogenase increased
- Leukopenia
- Nausea

The most common Grade 3 adverse drug reactions (incidence ≥ 2%) in the everolimus arm were:

- Amenorrhoea
- Aphthous stomatitis
- Mouth ulceration

No Grade 4 adverse drug reactions were reported in either treatment arm. Table 25 shows ADRs by grade of severity.

Table 25: Adverse drug reactions occurring in at least 5% of patients in either treatment arm – Study M2302

System organ class MedDRA preferred term	Everolimus N=79			Placebo N=39		
	All %	Grade 3 %	Grade 4 %	All %	Grade 3 %	Grade 4 %
Gastrointestinal disorders						
Stomatitis	77.2	6.3	0	15.4	0	0
Nausea	10.1	0	0	2.6	0	0
Diarrhoea	8.9	0	0	2.6	0	0
Vomiting	7.6	0	0	2.6	0	0
Abdominal pain	6.3	0	0	0	0	0
Flatulence	6.3	0	0	0	0	0
Metabolism and nutrition disorders						
Hypercholesterolaemia	20.3	0	0	2.6	0	0
Hypophosphataemia	8.9	0	0	0	0	0
Hyperlipidaemia	7.6	0	0	0	0	0
Decreased appetite	5.1	1.3	0	0	0	0
Iron deficiency	5.1	0	0	2.6	0	0
Skin and connective tissue disorders						
Acne	15.2	0	0	5.1	0	0
Dermatitis acneiform	7.6	0	0	0	0	0
Dry skin	7.6	0	0	2.6	0	0
Papule	5.1	0	0	2.6	0	0
General disorders and administration site conditions						
Fatigue	12.7	1.3	0	7.7	0	0
Oedema peripheral	1.3	0	0	5.1	0	0

System organ class MedDRA preferred term	Everolimus N=79			Placebo N=39		
	All %	Grade 3 %	Grade 4 %	All %	Grade 3 %	Grade 4 %
Blood and lymphatic system disorders						
Anaemia	11.4	0	0	2.6	0	0
Leukopenia	10.1	0	0	7.7	0	0
Thrombocytopenia	7.6	0	0	0	0	0
Lymphopenia	6.3	1.3	0	7.7	0	0
Neutropenia	6.3	0	0	10.3	0	0
Investigations						
Blood lactate dehydrogenase increased	10.1	0	0	5.1	0	0
Alanine aminotransferase increased	2.5	0	0	5.1	0	0
Reproductive system and breast disorders						
Amenorrhoea	7.6	2.5	0	2.6	0	0
Menstruation irregular	5.1	0	0	0	0	0
Nervous system disorders						
Headache	7.6	0	0	2.6	2.6	0
Dizziness	5.1	0	0	7.7	0	0
Infections and infestations						
Urinary tract infection	8.9	0	0	7.7	0	0
Sinusitis	5.1	0	0	0	0	0
Upper respiratory tract infection	5.1	0	0	0	0	0
Bronchitis	1.3	0	0	5.1	0	0
Tonsillitis	0	0	0	5.1	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	5.1	0	0	0	0	0
Oropharyngeal pain	3.8	0	0	5.1	0	0

An integrated analysis of safety comprising of the safety of only TSC patients in trial C2485, M2301 and M2302 was performed at the request of the CHMP. Adverse events with a suspected relationship to study drug (as assessed by the investigator) in Studies C2485, M2301, and M2302 were pooled and subsequently summarised in a single table by preferred term and grading (severity) (Table 26).

The methodology used to assess all ADRs for inclusion in SmPC section 4.8 was the following:

• Higher incidence in the everolimus arm than for placebo (with a clinically relevant difference evident)

• Related ADRs combined (i.e. hypercholesterolaemia and blood cholesterol increased, acne and dermatitis acneiform, etc). This included those categories where events have previously been grouped (e.g. stomatitis/related events covers stomatitis, mouth ulceration, aphthous stomatitis, etc)

• Clinical relevance

• For ADRs with a reported frequency below 1%, terms were added based on medical assessment.

In addition, changes have been made to text in section c) Description of selected adverse reactions, to reflect those ADRs which have been reported in oncology studies and have been included as identified risks in the RMP i.e. haemorrhage, cardiac failure, pulmonary embolism, deep vein thrombosis, impaired wound healing and hyperglycaemia.

Table 26: Adverse drug reactions, by preferred term,maximum grade and treatment setting – Pooled data from Study C2485, M2301 and M2302

Preferred term	Placebo All grades N=78 n (%)	Placebo Grade 3/4 N=78 n (%)	Afinitor S.A. All grades N=247 n (%)	Afinitor S.A. Grade 3/4 N=247 n (%)
-Any adverse event	44 (56.4)	5 (6.4)	203 (82.2)	42 (17.0)
Stomatitis	6 (7.7)	1 (1.3)	105 (42.5)	11 (4.5)
Mouth ulceration	3 (3.8)	0 (0.0)	48 (19.4)	3 (1.2)
Upper respiratory tract infection	0 (0.0)	0 (0.0)	35 (14.2)	1 (0.4)
Hypercholesterolaemia	2 (2.6)	0 (0.0)	27 (10.9)	1 (0.4)
Acne	2 (2.6)	0 (0.0)	21 (8.5)	0 (0.0)
Fatigue	4 (5.1)	0 (0.0)	18 (7.3)	1 (0.4)
Sinusitis	0 (0.0)	0 (0.0)	18 (7.3)	1 (0.4)
Otitis media	0 (0.0)	0 (0.0)	17 (6.9)	1 (0.4)
Aphthous stomatitis	3 (3.8)	0 (0.0)	16 (6.5)	2 (0.8)
Blood cholesterol increased	1 (1.3)	0 (0.0)	16 (6.5)	0 (0.0)
Diarrhoea	2 (2.6)	0 (0.0)	16 (6.5)	0 (0.0)
Cough	0 (0.0)	0 (0.0)	15 (6.1)	0 (0.0)
Pyrexia	1 (1.3)	0 (0.0)	15 (6.1)	1 (0.4)
Dermatitis acneiform	0 (0.0)	0 (0.0)	14 (5.7)	0 (0.0)
Anaemia	1 (1.3)	0 (0.0)	13 (5.3)	0 (0.0)
Nasopharyngitis	3 (3.8)	0 (0.0)	13 (5.3)	0 (0.0)
Nausea	1 (1.3)	0 (0.0)	13 (5.3)	0 (0.0)
Neutropenia	4 (5.1)	1 (1.3)	13 (5.3)	4 (1.6)
Blood lactate dehydrogenase increased	1 (1.3)	0 (0.0)	11 (4.5)	0 (0.0)
Blood triglycerides increased	1 (1.3)	0 (0.0)	11 (4.5)	0 (0.0)
Headache	2 (2.6)	1 (1.3)	11 (4.5)	0 (0.0)
Leukopenia	3 (3.8)	0 (0.0)	11 (4.5)	0 (0.0)
Pharyngitis	0 (0.0)	0 (0.0)	11 (4.5)	0 (0.0)
Urinary tract infection	3 (3.8)	0 (0.0)	11 (4.5)	0 (0.0)
Vomiting	2 (2.6)	0 (0.0)	11 (4.5)	0 (0.0)
Cellulitis	1 (1.3)	0 (0.0)	10 (4.0)	0 (0.0)
Decreased appetite	2 (2.6)	0 (0.0)	10 (4.0)	1 (0.4)
Dry skin	1 (1.3)	0 (0.0)	10 (4.0)	0 (0.0)
Gastroenteritis	0 (0.0)	0 (0.0)	10 (4.0)	0 (0.0)
Neutrophil count decreased	1 (1.3)	0 (0.0)	10 (4.0)	3 (1.2)
Amenorrhoea	1 (1.3)	0 (0.0)	9 (3.6)	4 (1.6)
Hyperlipidaemia	0 (0.0)	0 (0.0)	8 (3.2)	0 (0.0)
Low density lipoprotein increased	0 (0.0)	0 (0.0)	8 (3.2)	0 (0.0)
Menstruation irregular	0 (0.0)	0 (0.0)	8 (3.2)	0 (0.0)
Thrombocytopenia	0 (0.0)	0 (0.0)	8 (3.2)	0 (0.0)
Abdominal pain	0 (0.0)	0 (0.0)	7 (2.8)	0 (0.0)

Preferred term	Placebo All grades N=78 n (%)	Placebo Grade 3/4 N=78 n (%)	Afinitor S.A. All grades N=247 n (%)	Afinitor S.A. Grade 3/4 N=247 n (%)
Furuncle	0 (0.0)	0 (0.0)	7 (2.8)	0 (0.0)
Hypertriglyceridaemia	1 (1.3)	0 (0.0)	7 (2.8)	0 (0.0)
Hypophosphataemia	0 (0.0)	0 (0.0)	7 (2.8)	0 (0.0)
Otitis externa	0 (0.0)	0 (0.0)	7 (2.8)	0 (0.0)
Pneumonia	0 (0.0)	0 (0.0)	7 (2.8)	2 (0.8)
Rash	0 (0.0)	0 (0.0)	7 (2.8)	0 (0.0)
Skin infection	0 (0.0)	0 (0.0)	7 (2.8)	0 (0.0)
Blood alkaline phosphatase increased	1 (1.3)	1 (1.3)	6 (2.4)	2 (0.8)
Oral pain	0 (0.0)	0 (0.0)	6 (2.4)	0 (0.0)
Rhinitis	0 (0.0)	0 (0.0)	6 (2.4)	0 (0.0)
Alanine aminotransferase increased	2 (2.6)	0 (0.0)	5 (2.0)	0 (0.0)
Body tinea	0 (0.0)	0 (0.0)	5 (2.0)	0 (0.0)
Dizziness	3 (3.8)	0 (0.0)	5 (2.0)	0 (0.0)
Flatulence	0 (0.0)	0 (0.0)	5 (2.0)	0 (0.0)
Folliculitis	0 (0.0)	0 (0.0)	5 (2.0)	0 (0.0)
Gastroenteritis viral	0 (0.0)	0 (0.0)	5 (2.0)	3 (1.2)
Irritability	0 (0.0)	0 (0.0)	5 (2.0)	1 (0.4)
Lymphopenia	3 (3.8)	0 (0.0)	5 (2.0)	1 (0.4)
Oropharyngeal pain	2 (2.6)	0 (0.0)	5 (2.0)	0 (0.0)
Proteinuria	1 (1.3)	0 (0.0)	5 (2.0)	0 (0.0)
Rash pustular	0 (0.0)	0 (0.0)	5 (2.0)	0 (0.0)
Aspartate aminotransferase increased	1 (1.3)	0 (0.0)	4 (1.6)	1 (0.4)
Blood luteinising hormone increased	0 (0.0)	0 (0.0)	4 (1.6)	0 (0.0)
Bronchitis	2 (2.6)	0 (0.0)	4 (1.6)	0 (0.0)
Conjunctivitis	0 (0.0)	0 (0.0)	4 (1.6)	0 (0.0)
Constipation	0 (0.0)	0 (0.0)	4 (1.6)	0 (0.0)
Epistaxis	1 (1.3)	0 (0.0)	4 (1.6)	0 (0.0)
Gastric infection	0 (0.0)	0 (0.0)	4 (1.6)	0 (0.0)
Gastritis	0 (0.0)	0 (0.0)	4 (1.6)	0 (0.0)
Gingivitis	0 (0.0)	0 (0.0)	4 (1.6)	0 (0.0)
Hypertension	0 (0.0)	0 (0.0)	4 (1.6)	0 (0.0)
Iron deficiency	1 (1.3)	0 (0.0)	4 (1.6)	0 (0.0)
Papule	1 (1.3)	0 (0.0)	4 (1.6)	0 (0.0)
Platelet count decreased	0 (0.0)	0 (0.0)	4 (1.6)	0 (0.0)
Pruritus	0 (0.0)	0 (0.0)	4 (1.6)	0 (0.0)
Weight decreased	0 (0.0)	0 (0.0)	4 (1.6)	0 (0.0)
White blood cell count decreased	0 (0.0)	0 (0.0)	4 (1.6)	0 (0.0)

Preferred term	Placebo All grades N=78 n (%)	Placebo Grade 3/4 N=78 n (%)	Afinitor S.A. All grades N=247 n (%)	Afinitor S.A. Grade 3/4 N=247 n (%)
Alopecia	0 (0.0)	0 (0.0)	3 (1.2)	0 (0.0)
Convulsion	0 (0.0)	0 (0.0)	3 (1.2)	0 (0.0)
Dysgeusia	0 (0.0)	0 (0.0)	3 (1.2)	0 (0.0)
Ear infection	0 (0.0)	0 (0.0)	3 (1.2)	0 (0.0)
Impetigo	0 (0.0)	0 (0.0)	3 (1.2)	0 (0.0)
Menorrhagia	0 (0.0)	0 (0.0)	3 (1.2)	0 (0.0)
Migraine	0 (0.0)	0 (0.0)	3 (1.2)	0 (0.0)
Oedema peripheral	2 (2.6)	0 (0.0)	3 (1.2)	0 (0.0)
Pharyngitis streptococcal	0 (0.0)	0 (0.0)	3 (1.2)	0 (0.0)
Tooth abscess	1 (1.3)	0 (0.0)	3 (1.2)	0 (0.0)
Vaginal haemorrhage	0 (0.0)	0 (0.0)	3 (1.2)	0 (0.0)
Viral infection	0 (0.0)	0 (0.0)	3 (1.2)	0 (0.0)
Abdominal pain upper	2 (2.6)	0 (0.0)	2 (0.8)	0 (0.0)
Abscess limb	0 (0.0)	0 (0.0)	2 (0.8)	1 (0.4)
Activated partial thromboplastin time prolonged	1 (1.3)	0 (0.0)	2 (0.8)	0 (0.0)
Aggression	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Arthralgia	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Blood creatine phosphokinase increased	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Blood fibrinogen decreased	2 (2.6)	0 (0.0)	2 (0.8)	1 (0.4)
Blood fibrinogen increased	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Blood follicle stimulating hormone increased	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Blood immunoglobulin G decreased	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Blood phosphorus decreased	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Blood testosterone decreased	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Cystitis	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Eczema	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Enteritis	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Erythema	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Gait disturbance	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Haematuria	1 (1.3)	0 (0.0)	2 (0.8)	0 (0.0)
Haemoglobin decreased	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Hypokalaemia	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Infection	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Influenza	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Influenza like illness	1 (1.3)	0 (0.0)	2 (0.8)	0 (0.0)
Insomnia	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)

Preferred term	Placebo All grades N=78 n (%)	Placebo Grade 3/4 N=78 n (%)	Afinitor S.A. All grades N=247 n (%)	Afinitor S.A. Grade 3/4 N=247 n (%)
Localised infection	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Menstruation delayed	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Ocular hyperaemia	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Oral candidiasis	1 (1.3)	0 (0.0)	2 (0.8)	0 (0.0)
Pain in extremity	1 (1.3)	0 (0.0)	2 (0.8)	0 (0.0)
Peripheral sensory neuropathy	1 (1.3)	0 (0.0)	2 (0.8)	0 (0.0)
Pharyngeal inflammation	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Pneumonitis	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Prothrombin time prolonged	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Rash erythematous	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Rash macular	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Rash maculo-papular	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Rash papular	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Rhinorrhoea	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Seborrhoeic dermatitis	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Skin ulcer	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Somnolence	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Tooth infection	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Vulvovaginal mycotic infection	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Abdominal discomfort	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Activated partial thromboplastin time shortened	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Ageusia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Agitation	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Anal inflammation	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Anger	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Angioedema	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)
Anorectal disorder	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Anxiety	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Aura	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Back pain	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Bacterial infection	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Bile duct stenosis	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)
Biliary tract disorder	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Blood bilirubin increased	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Blood creatinine increased	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Blood phosphorus increased	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Body temperature decreased	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Bronchitis viral	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)

Preferred term	Placebo All grades N=78 n (%)	Placebo Grade 3/4 N=78 n (%)	Afinitor S.A. All grades N=247 n (%)	Afinitor S.A. Grade 3/4 N=247 n (%)
Bronchopneumonia	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)
Bronchospasm	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)
Caecitis	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)
Carbon monoxide diffusing capacity decreased	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Catheter site cellulitis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Cheilitis	1 (1.3)	0 (0.0)	1 (0.4)	0 (0.0)
Chest X-ray abnormal	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Cold sweat	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Complex partial seizures	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)
Complex regional pain syndrome	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Dehydration	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)
Dermatitis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Dermatitis allergic	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Dermatitis diaper	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Drug effect decreased	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Dysphagia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Dysphonia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Dyspnoea	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Ear infection bacterial	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)

Preferred term	Placebo All grades N=78 n (%)	Placebo Grade 3/4 N=78 n (%)	Afinitor S.A. All grades N=247 n (%)	Afinitor S.A. Grade 3/4 N=247 n (%)
Eosinophil count decreased	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Erythema multiforme	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Erythema of eyelid	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Eye swelling	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Eyelid infection	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Face injury	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Face oedema	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Febrile infection	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)
Fibroma	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Frequent bowel movements	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Fungal skin infection	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Gamma-glutamyltransferase increased	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Gastrointestinal infection	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Genital infection bacterial	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Genital lesion	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Genital ulceration	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Gingival pain	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Glossitis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Glucose tolerance impaired	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Haematochezia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Haematocrit decreased	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Helicobacter infection	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Hepatic enzyme increased	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Herpes zoster	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Hidradenitis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
High density lipoprotein decreased	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Hyperaesthesia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Hyperglycaemia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Hyperphosphataemia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Hypersensitivity	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)
Hypomagnesaemia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Impaired healing	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Increased upper airway secretion	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Inflammation	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)
Ingrowing nail	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
International normalised ratio increased	1 (1.3)	0 (0.0)	1 (0.4)	0 (0.0)
Iron deficiency anaemia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)

Preferred term	Placebo All grades N=78 n (%)	Placebo Grade 3/4 N=78 n (%)	Afinitor S.A. All grades N=247 n (%)	Afinitor S.A. Grade 3/4 N=247 n (%)
Joint effusion	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Joint instability	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Laryngitis	1 (1.3)	0 (0.0)	1 (0.4)	0 (0.0)
Leukocytosis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Libido decreased	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Lip blister	1 (1.3)	0 (0.0)	1 (0.4)	0 (0.0)
Lip ulceration	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Lower respiratory tract infection	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Lung neoplasm	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Lymph gland infection	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Lymphocyte count decreased	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Metrorrhagia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Migraine with aura	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Molluscum contagiosum	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Monocyte count decreased	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Mood swings	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Muscle spasms	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Muscular weakness	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Myalgia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Nasal abscess	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Nasal congestion	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Neutrophil count abnormal	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Oedema mouth	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Oligomenorrhoea	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Oral herpes	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Oral mucosal blistering	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Otorrhoea	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Ovarian cyst	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Periodontitis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Periorbital cellulitis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Pityriasis rosea	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Polycystic ovaries	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Presyncope	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)
Protein urine present	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Rash generalised	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Rash pruritic	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Respiratory tract infection	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Respiratory tract infection viral	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)

Preferred term	Placebo All grades N=78 n (%)	Placebo Grade 3/4 N=78 n (%)	Afinitor S.A. All grades N=247 n (%)	Afinitor S.A. Grade 3/4 N=247 n (%)
Respiratory tract inflammation	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Rhabdomyolysis	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)
Rhinitis allergic	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Salivary gland calculus	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Salivary hypersecretion	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Sialoadenitis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Sinus tachycardia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Skin exfoliation	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Sleep disorder	2 (2.6)	0 (0.0)	1 (0.4)	0 (0.0)
Swelling face	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Throat lesion	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Tic	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Tongue blistering	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Tongue dry	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Tonsillitis	2 (2.6)	1 (1.3)	1 (0.4)	0 (0.0)
Urine analysis abnormal	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Uterine haemorrhage	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Vaginal infection	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Vaginitis bacterial	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Viral rash	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Visual acuity reduced	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Wheezing	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Wound infection	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Abscess	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Asthenia	2 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
Balanitis	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Blood fibrinogen abnormal	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Blood glucose increased	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Choking	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Dermal cyst	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Fungal infection	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Gingival bleeding	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Hallucination	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Leukocyturia	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Transferrin decreased	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)

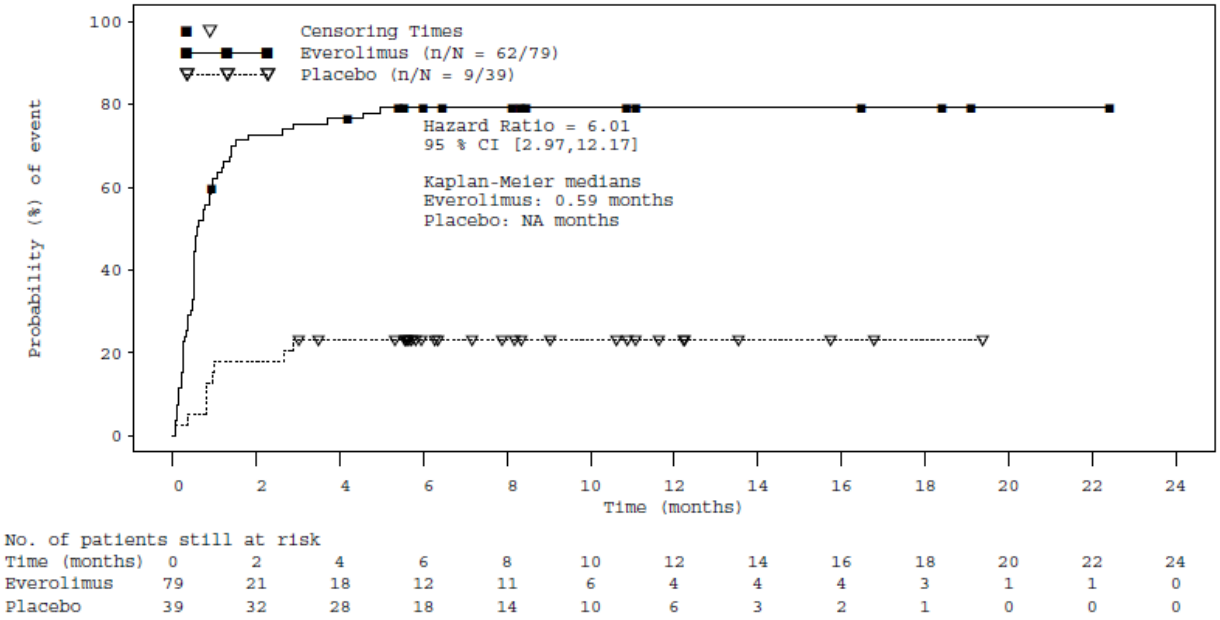
Adverse events of special interest

Stomatitis/related events

Stomatitis/related events (primarily stomatitis, aphthous stomatitis, and mouth ulceration) were reported more commonly among patients in the everolimus arm (78.5%) relative to placebo (23.1%). In the everolimus arm, most episodes were of grade 1-2 intensity (Figure 8).

The median time to first occurrence of stomatitis was 0.59 months in the everolimus arm and was not reached in the placebo arm.

Figure 8: Time to first occurrence of stomatitis – Study M2302 (double-blind period)

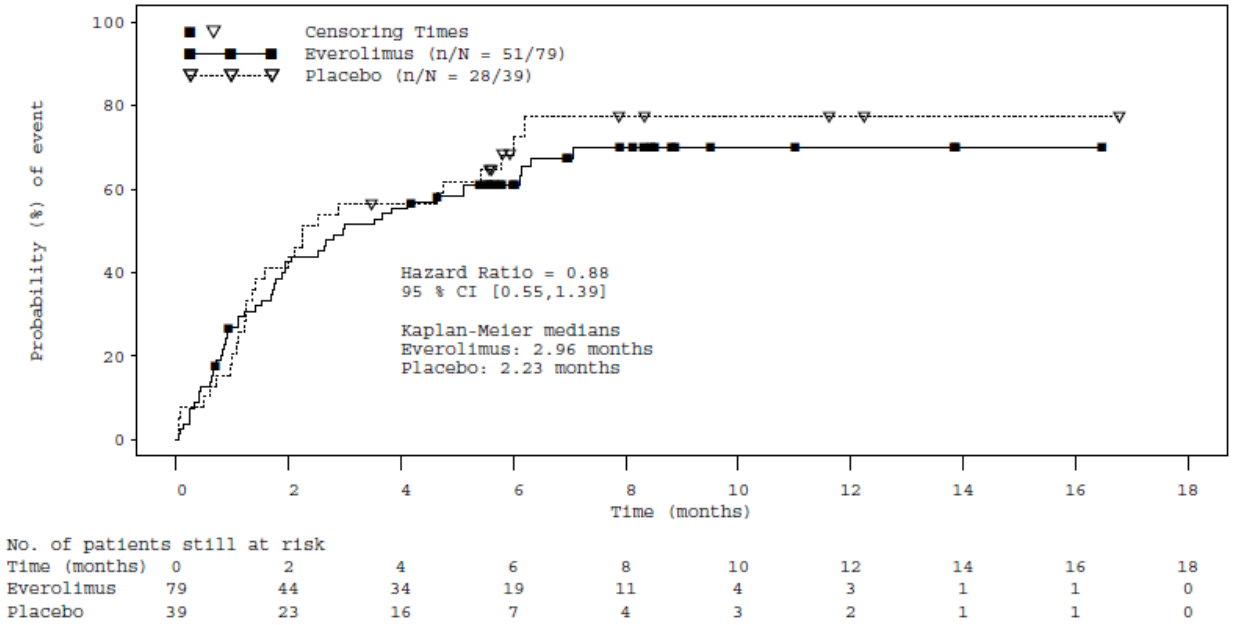


Although stomatitis/related events are one of the most clinically important side effects associated with everolimus, most either resolved without treatment or were effectively managed by following protocol guidelines, including dose adjustments/interruptions. In all, 14 (17.7%) patients experienced stomatitis/related events (primarily stomatitis, aphthous stomatitis, and mouth ulceration) in the everolimus arm that required a dose adjustment/interruption. No episodes of grade 4 stomatitis/related events were observed and no patients discontinued from the study or experienced an SAE due to a stomatitis/related event.

Infections

Although infection was an identified risk associated with everolimus therapy (median follow-up of 9.5 months), an increased risk of infection when taking everolimus was not evident for these patients with TSC (Figure 9). The incidence of infections was similar among patients in the everolimus arm (64.6%) compared with patients in the placebo arm (71.8%). The majority of the infections occurred primarily in the respiratory tract (e.g., nasopharyngitis, upper respiratory tract, sinusitis, and bronchitis) and incidences of pneumonia were uncommon (2.5% with everolimus; 2.6% with placebo). There were no Grade 3 or 4 infections in the everolimus arm.

Figure 9: Time to first occurrence of infections (double-blind period) - Study M2302



Renal events

Renal events were observed in 5.1% of patients in the everolimus arm and 15.4% of patients in the placebo arm. Increases in blood creatinine occurred less frequently in the everolimus arm (1.3%) than in the placebo arm (7.7%). Acute renal failure of grade 2 intensity occurred in the everolimus arm (2.5%) and both episodes, considered to be SAEs, resolved with treatment. Proteinuria was reported in both the everolimus (3.8%) and placebo (7.7%) arms. Two cases of Grade 2 acute renal failure were reported in the everolimus arm.

Table 27: Grading (severity) of renal events by preferred term irrespective of causality – Study M2302 supported by Study M2301

Preferred term	Study M2302						Study M2301					
	Everolimus N=79			Placebo N=39			Everolimus N=78			Placebo N=39		
	All (%)	G3 (%)	G4 (%)	All (%)	G3 (%)	G4 (%)	All (%)	G3 (%)	G4 (%)	All (%)	G3 (%)	G4 (%)
Renal events	**5.1**	**0**	**0**	**15.4**	**0**	**0**	**1.3**	**0**	**0**	**0**	**0**	**0**
Proteinuria	3.8	0	0	7.7		0	0	0	0	0	0	0
Renal failure acute	2.5	0	0	0	0	0	0	0	0	0	0	0
Blood creatinine increased	1.3	0	0	7.7	0	0	0	0	0	0	0	0
Renal impairment	0	0	0	0	0	0	1.3	0	0	0	0	0

All = All grades; G3 = Grade 3; G4 = Grade 4.
A patient with multiple AEs within a grouping is counted only once in the total row.
A patient with multiple grades for an AE while on a treatment is only counted under the maximum grade.
Only AEs occurring on or after the start of study treatment and no more than 28 days after the discontinuation of study treatment and before start of open-label everolimus are summarized.

Haemorrhages

Haemorrhages were reported in 26.6% of patients in the everolimus arm (epistaxis (8.9%), menorrhagia (5.1%) and vaginal haemorrhage (5.1%)) and in 15.4% of patients in the placebo arm (haematuria (7.7%) and haematoma (5.1%)). All were Grade 1-2. One patient (1.3%) in the everolimus arm required a dose reduction or interruption due to a haemorrhage-related event

(menorrhagia). No patients discontinued from the trial or experienced an SAE due to a hemorrhagic event.

Table 28: Grading (severity) of haemorrhage by preferred term irrespective of relationship to study drug (double-blind period) (Safety Set) – Study M2302

	Everolimus N=79		Placebo N=39	
	All grades n (%)	Grade 3 and 4 n (%)	All grades n (%)	Grade 3 and 4 n (%)
Hemorrhage				
Total	21 (26.6)	0	6 (15.4)	0
Epistaxis	7 (8.9)	0	1 (2.6)	0
Menorrhagia	4 (5.1)	0	0	0
Vaginal haemorrhage	4 (5.1)	0	0	0
Haematochezia	1 (1.3)	0	0	0
Haematoma	1 (1.3)	0	2 (5.1)	0
Haematuria	1 (1.3)	0	3 (7.7)	0
Metrorrhagia	1 (1.3)	0	0	0
Petechiae	1 (1.3)	0	0	0
Rectal haemorrhage	1 (1.3)	0	0	0
Uterine haemorrhage	1 (1.3)	0	0	0
Haemoptysis	0	0	1 (2.6)	0

A patient with multiple occurrences of an AE is counted only once in the AE category.
A patient with multiple adverse events within a grouping is counted only once in the total row.

Cytopenia

Initiation of everolimus therapy is frequently associated with a reduction in blood cell counts. Clinically notable cytopenias were reported in 22.8% of patients in the everolimus arm and 20.5% of patients in the placebo arms. Most were Grade 1-2. Dose interruption or adjustment was required in a number of cases in the everolimus arm, although no patient discontinued from the trial or experienced an SAE due to a cytopenia. Leukopenia occurred in both the everolimus arm (10.1%) and the placebo arm (7.7%). Neutropenia and lymphopenia occurred more frequently in the placebo arm relative to everolimus.

Rash and similar events

Clinically notable rash and related events occurred only in the everolimus arm and with an incidence of 11.4%. No patients discontinued from the trial or experienced an SAE due to rash and related events and all events were classified as Grade 1-2. In all, 2.5% rash-related events in the everolimus arm required a dose adjustment/interruption. No patient discontinued study drug due to an AE of rash or similar events.

Amenorrhea

Amenorrhea was reported as an adverse event (preferred term) in 7 of 52 females (13.5%) in the everolimus treated group (including two cases of grade 3) compared to one of 26 females (3.8%) in the placebo group.. These amenorrhea events were reported as secondary since these patients had experienced normal menses previously. Although 8 patients are listed as having amenorrhea, only 7 patients had true amenorrhea, as oligomenorrhea and delayed menstruation are not considered to represent true amenorrhea. Amenorrhea was reported as an adverse reaction in 6 patients (7.6%) (see Table 25). Patients' with amenorrhea were aged 18 to 48 years with the duration of these events ranging from 1 to 66+ weeks (as of the cut-off date).

Table 29: Grading (severity) of ammenorrhea by preferred term irrespective of relationship to study drug (double-blind period) (Safety Set) – Study M2302

	Everolimus N=79		Placebo N=39	
	All grades n (%)	Grade 3 and 4 n (%)	All grades n (%)	Grade 3 and 4 n (%)
Amenorrhoea and related events				
Total	8 (10.1)	2 (2.5)	1 (2.6)	0
Amenorrhoea	7 (8.9)	2 (2.5)	1 (2.6)	0
Menstruation delayed	1 (1.3)	0	0	0
Oligomenorrhoea	1 (1.3)	0	0	0

A patient with multiple occurrences of an AE is counted only once in the AE category.
A patient with multiple adverse events within a grouping is counted only once in the total row.

Hypersensitivity

Hypersensitivity (anaphylactic) reactions were reported in 2 (2.5%) patients in the everolimus arm and 1 (2.6%) patient in the placebo arm. One of the patients in the everolimus arm experienced two concurrent Grade 3 SAEs in this grouping (angiooedema and hypersensitivity), in addition to an SAE of Grade 3 bronchospasm (resulting in study drug discontinuation).

Non-infectious pneumonitis

A single patient in the everolimus arm experienced an episode of non-infectious pneumonitis. This episode of non-infectious pneumonitis was of grade 2 intensity and was suspected of being drug related by the investigator. The patient had a medical history of partial resections of the left and right pleura and a biopsy-proven diagnosis of sporadic LAM. The episode of non-infectious pneumonitis was reported after 28 days of study drug administration and resolved within 14 days following a temporary dose reduction to 5 mg once daily; no additional treatment was needed.

Thromboembolism

A single patient in the everolimus arm experienced an episode of deep vein thrombosis. This episode of deep vein thrombosis was of grade 1 intensity and was not suspected of being drug related by the investigator; none was reported in the placebo arm.

Hyperglycemia/new onset of diabetes mellitus

There were no hyperglycemia/new onset of diabetes mellitus reported in M2302 and there were no grade 3 or grade 4 laboratory abnormalities for increased fasting blood glucose.

Serious adverse event/deaths/other significant events

Serious adverse events

Six (7.6%) patients in the everolimus arm experienced a SAEs that was suspected of being related to study drug.

Table 30: Summary of adverse event categories – Study M2302

	Everolimus	**Placebo**
Category	N=79	N=39
	n (%)	n (%)

Category	Everolimus N=79 n (%)		Placebo N=39 n (%)	
On-treatment death	1	(1.3)	0	
Serious adverse event	15	(19.0)	7	(17.9)
Suspected to be drug related	6	(7.6)	2	(5.1)
AE leading to discontinuation	3	(3.8)	4	(10.3)
Suspected to be drug related	2	(2.5)	1	(2.6)

Deaths and other serious or clinically significant adverse events

One death was reported in the everolimus arm. The patient had a long-standing medical history of intractable seizures (treated with lamotrigine and lorazepam). After about 7 months since start of everolimus treatment, the patient presented with increased seizure activity, followed by Grade 4 convulsion, generalised seizure, status epilepticus, and death. The investigator considered that the event was related to worsening underlying epilepsy and was not suspected to be related to study drug.

Laboratory findings

Clinical chemistry

Biochemical abnormalities of any grade were more commonly reported in patients in the everolimus arm than in those in the placebo arm. Biochemical laboratory abnormalities that were more frequent in the everolimus arm compared to placebo (≥ 10%):

- Increased serum triglycerides (+40.3%)
- Increased serum total cholesterol (+39.9%)
- Decreased blood phosphorus (+30.2%)
- Increased serum alkaline phosphatase (+20.1%)
- Increased serum AST (+13.8%)

Renal function

Severe renal impairment (as assessed by a worst post-baseline GFR < 30 ml/min/1.73m2) was observed in 2.5% of patients in the everolimus arm and 7.7% of patients in the placebo arm. Grade 1 or 2 elevations in serum creatinine were observed in 7.6% of patients in the everolimus arm and 15.4% in the placebo arm. No patients in either arm experienced a post-baseline Grade 3 or 4 elevation of serum creatinine.

Table 31: Renal function – Study M2302 supported by Study M2301

	Study M2302		Study M2301	
	Everolimus	Placebo	Everolimus	Placebo
	N=79	N=39	N=78	N=39
	n (%)	n (%)	n (%)	n (%)
Renal impairment				
Glomerular filtration rate ≥ 30ml/min/1.73m^2	77 (97.5)	36 (92.3)	78 (100)	39 (100)
Glomerular filtration rate < 30 ml/min/1.73m^2	2 (2.5)	3 (7.7)	0	0
Missing values	0	0	0	0
Serum creatinine				
Grade 3 or 4	0	0	0	0
Grade 1 or 2	6 (7.6)	6 (15.4)	3 (3.8)	0
Grade 0	73 (92.4)	33 (84.6)	75 (96.2)	39 (100)

Glomerular filtration rate is calculated using the Modification of Diet in Renal Disease formula.
Patients are counted only for the worst post-baseline value (lowest value for GFR, highest grade for creatinine).
Grade 0 = below grade 1

Haematology

Haematologic abnormalities were common in the everolimus arm (predominantly Grade 1-2). More than 10% of patients experienced clinically relevant decreases in red cells, white cells, neutrophils, lymphocytes and platelets. One episode of Grade 3 lymphopenia and one episode of Grade 4 neutropenia were observed in the everolimus arm.

Haematological abnormalities that were more frequent in the everolimus arm compared to placebo (≥ 10%):

- Decreased haemoglobin (+17.2%)
- Decreased platelet count (+15.1%)
- Decreased white blood cells (+15.0%)
- Decreased lymphocytes (+11.3%)

Table 32: Selected laboratory abnormalities – Study M2302

Laboratory parameter	**Everolimus N=79**			**Placebo N=39**		
	All %	**Grade 3 %**	**Grade 4 %**	**All %**	**Grade 3 %**	**Grade 4 %**
Clinical chemistry						
Cholesterol increased	83.5	0	0	43.6	0	0
Triglycerides increased	50.6	0	0	10.3	0	0
Phosphate decreased	45.6	5.1	0	15.4	0	0
Aspartate transaminase increased	21.5	1.3	0	7.7	0	0
Alanine transaminase increased	17.7	1.3	0	15.4	0	0
Glucose increased	13.9	0	0	5.1	0	0

Laboratory parameter	Everolimus N=79			Placebo N=39		
	All %	Grade 3 %	Grade 4 %	All %	Grade 3 %	Grade 4 %
Creatinine increased	7.6	0	0	15.4	0	0
Bilirubin (total) increased	2.5	0	0	2.6	0	0
Haematology						
Haemoglobin decreased	60.8	0	0	43.6	0	0
White cell count decreased	32.9	0	0	17.9	0	0
Neutrophils decreased	21.5	0	1.3	23.1	0	0
Lymphocytes decreased	19.0	1.3	0	7.7	0	0
Platelets decreased	17.7	0	0	2.6	0	0

The majority of patients in Study M2302 did not have any notable abnormalities in blood, glucose, ketones, leukocytes, or protein levels in urine in either treatment arm.

Safety in special populations

There were no analyses of safety in special populations.

Safety related to drug-drug interactions and other interactions

There was no safety analysis related to drug-drug interactions and other interactions.

Discontinuation due to adverse events

Overall, patient discontinuations from study drug were infrequent, however more patients discontinued treatment in the placebo arm (10.3%) than in the everolimus arm (3.8%) (Table 33).

Table 33: AEs leading to study drug discontinuation, regardless of causality – Study M2302 supported by Study M2301

Preferred term	Study M2302		Study M2301	
	Everolimus N=79 n (%)	Placebo N=39 n (%)	Everolimus N=78 n (%)	Placebo N=39 n (%)
Any AE leading to study drug discontinuation	3(3.8)	4(10.3)	0	0
Angioedema	1(1.3)	0	0	0
Blood phosphorus decreased	1(1.3)	0	0	0
Bronchospasm	1(1.3)	0	0	0
Convulsion	1(1.3)	0	0	0
Hypersensitivity	1(1.3)	0	0	0
Angiomyolipoma	0	1(2.6)	0	0
Hallucination	0	1(2.6)	0	0
Lymphangioleiomyomatosis	0	1(2.6)	0	0
Volvulus	0	1(2.6)	0	0

A patient with multiple AEs within a grouping is counted only once in the total row.

Only AEs occurring on or after the start of study treatment and no more than 28 days after the discontinuation of study treatment and before start of open-label everolimus are summarized.

The most frequently reported reasons for discontinuation were disease progression, which was reported only in the placebo arm (9 patients, 23.1%) and adverse events. Adverse events leading to discontinuation occurred in 3 patients (3.8%) in the everolimus arm and 4 patients (10.3%) in the placebo arm. Adverse events leading to study drug discontinuation in the everolimus arm were:

- One patient with concurrent SAEs of Grade 3 hypersensitivity, Grade 3 angiooedema and Grade 3 bronchospasm that occurred on Day 15 of treatment (study drug-related)
- One patient had a SAE of convulsion on Day 240 that led to death due (not study drug-related)
- One patient with an AE of Grade 2 blood phosphorus decreased that was ongoing from Day 98 to Day 134 of treatment (study drug-related)

None of the patients in the everolimus arm had disease progression as the reason for discontinuation. Three patients met the criteria for angiomyolipoma progression according to central radiology review but have not discontinued from the trial. Discontinuation for disease progression was at investigator discretion and not mandatory. As per investigator's judgment, these patients were still receiving clinical benefit (e.g., reduction in volume for some but not all lesions or discordance between target lesion response and kidney volume increase judged by the investigator to represent clinical benefit) from everolimus.

Adverse events leading to discontinuation in the placebo arm included 2 cases of angiomyolipoma/ LAM-related conditions: one patient required hospitalisation for elective bilateral angiomyolipoma embolization and one Grade 2 lymphangioleiomyomatosis.

Three patients discontinued the study treatment for reasons other than AE/abnormal laboratory value, disease progression, or death:

- One patient randomised to everolimus withdrew consent on Day 14 due to fear of potential adverse events (no ongoing AEs suspected to be related at the time of withdrawal)
- One patient randomised to everolimus discontinued on Day 133 due to protocol deviation (the patient did not have angiomyolipoma target lesion by central radiologic review)
- One patient randomised to everolimus discontinued on Day 168 due to administrative reason (inability to comply with protocol visits)

Adverse events requiring dose interruption and/or dose reduction

Adverse events requiring dose interruptions or dose reductions were more frequent in the everolimus arm (53.2%) than in the placebo arm (33.3%). Per protocol, investigators were required to interrupt study treatment for Grade 2 AEs suspected to be related to study drug. The most commonly occurring AEs leading to everolimus dose adjustment were:

- Stomatitis (11.4%)
- Aphthous stomatitis (5.1%)
- Diarrhoea (+3.8%)
- Mouth ulceration (+3.8%)
- Nausea (+3.8%)
- Sinusitis (+3.8%)
- Thrombocytopenia (+3.8%)
- Hypercholesterolemia (+3.8%)

Table 34: Number of patients requiring dose interruptions and/or reductions of study drug – Study M2302

Interruptions and/or reductions	Everolimus N=79	Placebo N=39
Number of patients requiring dose interruption and/or reduction	42 (53.2)	13 (33.3)
1 dose interruption and/or reduction	9 (11.4)	8 (20.5)
≥ 2 dose interruptions and/or reductions	33 (41.8)	5 (12.8)
Reason for dose interruption and/or reduction		
Adverse event	37 (46.8)	8 (20.5)
Dosing error	7 (8.9)	6 (15.4)
Lab test abnormality	1 (1.3)	0
Scheduling conflict	2 (2.5)	0

Post marketing experience

Everolimus (as Afinitor, Votubia and Certican) is commercially available within European Union and other markets worldwide for the treatment of patients with advanced RCC and advanced NET, for SEGA associated with TSC and for the prophylaxis of allograft rejection following renal or cardiac transplantation. The Applicant estimates an overall exposure to the drug in excess of 14,550 patient-years.

1.6.1. Discussion on clinical safety

Common adverse reactions in the everolimus arm were stomatitis, hypercholesterolaemia, aphthous stomatitis, acne, fatigue, anaemia, blood lactate dehydrogenase increased, leukopenia and nausea. The incidence of infections was similar in both treatment arms when both trials are compared (71.8% and 64.6% of patients in the everolimus arm and 66.7% and 71.8% in the placebo arm for study M2301 and M2302 respectively). Renal events were observed less frequently in the everolimus arm (5.1% of patients) than in the placebo arm (15.4%). Hypercholesterolaemia was observed in a high

proportion of patients in the everolimus arm. An important identified risk in the RMP, regarding preventability of dyslipidemia includes 'Monitoring of blood cholesterol/triglycerides and potential concomitant treatment with lipid-lowering agent' as part of the routine risk minimisation for this risk. Thus, the current information in section 4.4 of the SmPC under the subheading 'Blood glucose and lipids' was updated to reflect this advice.

Everolimus can be associated with an increased risk of haemorrhage. Epistaxis (8.9%) accounted for the majority of haemorrhagic events in the everolimus arm compared with 2.6% of patients in the placebo arm. One patient in the everolimus arm (1.3%) had haematuria compared with 3 patients (7.7%) in the placebo arm. There were no AEs, SAEs or discontinuations from study drug for bleeding-related events from angiomyolipoma in the everolimus arm.

Secondary amenorrhea in post-adolescent females was 13.5% of patient in the everolimus arm (two cases of Grade 3) versus 3.8% of patients in the placebo arm. A single Grade 2 case of non-infectious pneumonitis was reported in the study. Information on 'haemorrhage' in section 4.8 of the SmPC for Votubia was updated to reflect the higher incidence of haemorrhages in the everolimus arm (26.6%) compared to placebo arm (15.4%). In addition, a warning regarding haemorrhage and any appropriate monitoring/management was included in section 4.4 of the SmPCs.

Grade 3-4 AEs were reported in 29.1% of everolimus-treated patients and 7.7% of placebo treated patients. Grade 3 treatment-related events reported ≥ 2% in the everolimus arm included amenorrhea, aphthous stomatitis and mouth ulceration. Four grade 4 AEs (each with an incidence of 1.3%) were reported in the everolimus arm, two of which were laboratory abnormalities (blood uric acid increased and neutropenia) reported by the central laboratory; the other two being convulsion and hypertensive crisis. No Grade 4 ADRs were reported. Clinically notable AEs, especially stomatitis-related AEs in the everolimus arm and infections in both the everolimus and placebo arms were most commonly observed and these events were managed with dose adjustments/interruptions or other treatment modalities.

An integrated analysis of safety comprising of the safety of everolimus in TSC patients in trial C2485, M2301 and M2302 was requested in order to better assess the ADRs in this specific and selected patient population which could be diluted if pooled with a patient population in the oncology setting of renal cell carcinoma, neuroendocrine tumours and breast cancer. The safety of these trials (C2485, M2301 and M2302) was compared with safety of trials C2324, C2240 and Y2301 (pivotal trials for the current indications of Afinitor). The safety information for TSC patients was updated in section 4.8 of the SmPC.

Serious adverse events were consistent with the known safety profile of everolimus. Serious adverse events were reported in similar proportions of patients in the everolimus (19.0%) and placebo treatment arms (17.9%) while AEs leading to discontinuation were reported more frequently in the placebo arm (10.3% vs 3.8%). Stomatitis and aphthous stomatitis were the most common reasons leading to dose reduction and/or temporary interruptions of therapy.The CHMP requested to include recommendation for dose adjustment and management in the treatment of ADRs in the SmPC. A single death was reported in the everolimus arm. This event was considered to be the result of a worsening of underlying intractable epilepsy and was not suspected by the investigator to be related to study drug.

The potential of everolimus to affect male fertility, which has been included in the RMP as a safety concern, was not addressed in the application as no further data was provided in this submission. Given that most patients with TSC and AML are of reproductive age, the risk of everolimus affecting male fertility will be subject to additional monitoring in the PhV plan and has been highlighted in the SmPC in section 4.6 with the following wording "Based on non-clinical findings, male fertility may be compromised by treatment with everolimus (see section 5.3)." Furthermore, to provide information to

further characterise other risks and missing information identified in the RMP, particularly reproductive toxicity, infertility and long-term safety, the MAH, at the request of the CHMP, proposed to implement a registry (CRAD001MICO3) to collect data on manifestations, interventions and outcome in patients with TSC.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

1.6.2. Conclusions on the clinical safety

The safety assessment of trial M2302 does not reveal any new safety concerns. The safety and tolerability of everolimus is consistent with previous experience. The events reported are typically mild to moderate in severity and were generally manageable with dose interruption, dose modification, and/or supportive intervention.

1.7. Risk management plan

The MAH submitted an updated Risk Management Plan within this variation procedure.

Table 33 Summary of the risk management plan (including the changes related to the application presented highlighted)

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
Important identified risks		
Non-infectious pneumonitis	Routine pharmacovigilance. **Additional activities** Targeted follow-up of all serious spontaneous reports, post-marketing surveillance study reports, reports from other programs where data are being handled as solicited and all clinical trial SAE reports using a targeted product questionnaire/checklist.	Warning in SPC Section 4.4: "Non-infectious pneumonitis is a class effect of rapamycin derivatives, including Afinitor. Non-infectious pneumonitis (including interstitial lung disease) was described in 12% of patients taking Afinitor (see section 4.8). Some cases were severe and on rare occasions, a fatal outcome was observed. A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnoea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations. Patients should be advised to report promptly any new or worsening respiratory symptoms. Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue Afinitor therapy without dose adjustments. If symptoms are moderate, consideration should be given to interruption of therapy until symptoms improve. The use of corticosteroids may be indicated. Afinitor may be reinitiated at 5 mg

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
		daily. For cases where symptoms of non-infectious pneumonitis are severe, Afinitor therapy should be discontinued and the use of corticosteroids may be indicated until clinical symptoms resolve. Therapy with Afinitor may be reinitiated at 5 mg daily depending on the individual clinical circumstances." Pneumonitis is included as ADR in SPC Section 4.8.
Severe infections	Routine pharmacovigilance. **Additional activities** Targeted follow-up of all serious spontaneous reports, post-marketing surveillance study reports, reports from other programs where data are being handled as solicited and all clinical trial SAE reports using targeted product questionnaire/checklist.	Warning in SPC Section 4.4: "Afinitor has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoal infections, including infections with opportunistic pathogens (see section 4.8). Localised and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections such as aspergillosis or candidiasis, and viral infections including reactivation of hepatitis B virus, have been described in patients taking Afinitor. Some of these infections have been severe (e.g., leading to respiratory or hepatic failure) and occasionally fatal. Physicians and patients should be aware of the increased risk of infection with Afinitor. Pre-existing infections should be treated appropriately and should have resolved fully before starting treatment with Afinitor. While taking Afinitor, be vigilant for symptoms and signs of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of Afinitor. If a diagnosis of invasive systemic fungal infection is made, Afinitor treatment should be promptly and permanently discontinued and the patient treated with appropriate antifungal therapy." Infections are included as ADR in SPC Section 4.8.
Hypersensitivity (anaphylactic reactions)	Routine pharmacovigilance. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-serious marketing surveillance study reports, reports from other programs where data is being	Contraindication in SPC Section 4.3: "Hypersensitivity to the active substance, to other rapamycin derivatives or to any of the excipients." Warning in SPC Section 4.4: "Hypersensitivity reactions manifested by symptoms including,

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
	handled as solicited and all clinical trial SAE reports, using a targeted event questionnaire/checklist.	but not limited to, anaphylaxis, dyspnoea, flushing, chest pain or angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus (see section 4.3)." Dyspnoea, flushing, angioedema, chest pain are included as ADRs in SPC Section 4.8.
Stomatitis	Routine pharmacovigilance.	Warning in SPC Section 4.4: "Mouth ulcers, stomatitis and oral mucositis have been observed in patients treated with Afinitor (see section 4.8). In such cases topical treatments are recommended, but alcohol- or peroxide-containing mouthwashes should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless fungal infection has been diagnosed (see section 4.5)." Stomatitis is included as ADR in SPC Section 4.8.
Wound healing complications	Routine pharmacovigilance.	Warning in SPC Section 4.4: "Impaired wound healing is a class effect of rapamycin derivates, including Afinitor. Caution should therefore be exercised with the use of Afinitor in the peri-surgical period." Impaired wound healing is included as an ADR in SPC Section 4.8.
Increased creatinine/proteinuria/ renal failure	Routine pharmacovigilance. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, serious reports from other programs where data is being handled as solicited and all clinical trial SAE reports, using a targeted event questionnaire/checklist.	Warning in SPC Section 4.4: Elevations of serum creatinine, usually mild, and proteinuria have been reported in clinical trials (see section 4.8). Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein or serum creatinine, is recommended prior to the start of Afinitor therapy and periodically thereafter. Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with Afinitor (see section 4.8). Renal function of patients should be monitored particularly where patients have additional risk factors that may further impair renal function." Increased creatinine, proteinuria, and renal failure are included as ADRs in SPC Section 4.8.
Hyperglycaemia/new onset diabetes mellitus	Routine pharmacovigilance.	Warning in SPC Section 4.4: "Hyperglycaemia, hyperlipidaemia and hypertrigylceridaemia have been reported in clinical trials (see

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
		section 4.8). Monitoring of fasting serum glucose is recommended prior to the start of ~~Afinitor~~ everolimus therapy and periodically thereafter. When possible optimal glycaemic control should be achieved before starting a patient on ~~Afinitor~~ everolimus." Glucose increased, triglycerides increased, and new-onset diabetes mellitus are included as ADRs in SPC Section 4.8.
Dyslipidaemia	Routine pharmacovigilance.	Warning in SPC Section 4.4: "Hyperglycaemia, hyperlipidaemia and hypertrigylceridaemia have been reported in clinical trials (see section 4.8)." Cholesterol increased and triglycerides increased are included as ADRs in SPC Section 4.8. Relevant information included in Votubia SPC Section 4.4: "Monitoring of blood cholesterol and triglycerides, and potential concomitant treatment with a lipid-lowering agent is also recommended (see also Table 1 in section 4.2)."
Hypophosphataemia	Routine pharmacovigilance.	Phosphate decreased is included as ADR in SPC Section 4.8.
Cardiac failure	Routine pharmacovigilance including detailed cumulative review in the PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, serious reports from other programs where data is being handled as solicited and all clinical trial SAE reports, using a targeted event questionnaire/checklist.	Congestive cardiac failure is included as ADR in SPC Section 4.8.
Cytopenia	Routine pharmacovigilance including detailed cumulative review in the PSUR.	Warning in SPC Section 4.4: "Decreased haemoglobin, lymphocytes, neutrophils and platelets have been reported in clinical trials (see section 4.8). Monitoring of complete blood count is recommended prior to the start of Afinitor therapy and periodically thereafter." Lymphocytes decreased, platelets decreased, and neutrophils decreased are included as ADRs in SPC Section 4.8.
Hemorrhages	Routine pharmacovigilance including detailed cumulative review in the PSUR.	Warning in Votubia SPC Section 4.4: "Serious cases of haemorrhage, some with a fatal outcome, have

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
		been reported in patients treated with everolimus in the oncology setting. No serious cases of renal haemorrhage were reported in the TSC setting. Caution is advised in patients taking Votubia, particularly during concomitant use with active substances known to affect platelet function or that can increase the risk of haemorrhage as well as in patients with a history of bleeding disorders. Healthcare professionals and patients should be vigilant for signs and symptoms of bleeding throughout the treatment period, especially if risk factors for haemorrhage are combined." Haemorrhage is included as ADR in SPC Section 4.8.
Thromboembolism	Routine pharmacovigilance including detailed cumulative review in the PSUR.	Pulmonary embolism is included as ADR in SPC Section 4.8.
Secondary amenorrhea in post-adolescent females	Routine pharmacovigilance including cumulative analysis in the PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, serious reports from other programs where data is being handled as solicited and all clinical trial SAE reports, using a targeted event questionnaire/checklist. Formal amenorrhea analysis across CRAD001C2485, CRAD001M2301, and CRAD001M2302 following study completions.	Relevant information in SPC Section 4.6: "The potential for everolimus to cause infertility in male and female patients is unknown, however secondary amenorrhoea and associated luteinising hormone (LH) /follicle stimulating hormone (FSH) imbalance has been observed in female patients." Secondary amenorrhea/LH/FSH imbalance included as ADRs in SPC Section 4.8.
Pre-existing infection (reactivation, aggravation, or exacerbation)	Routine pharmacovigilance including detailed cumulative review in the PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, serious reports from other programs where data is being handled as solicited and all clinical trial SAE reports, using a targeted product questionnaire/checklist.	Warning in SPC Section 4.4: "Afinitor has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoal infections, including infections with opportunistic pathogens (see section 4.8). Localised and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections such as aspergillosis or candidiasis, and viral infections including reactivation of hepatitis B virus, have been described in patients taking Afinitor. Some of these infections have been severe (e.g., leading to respiratory or hepatic failure) and occasionally fatal.

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
		Physicians and patients should be aware of the increased risk of infection with Afinitor. Pre-existing infections should be treated appropriately and should have resolved fully before starting treatment with Afinitor. While taking Afinitor, be vigilant for symptoms and signs of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of Afinitor. If a diagnosis of invasive systemic fungal infection is made, Afinitor treatment should be promptly and permanently discontinued and the patient treated with appropriate antifungal therapy." Infections are included as ADR in SPC Section 4.8. "In clinical studies, everolimus has been associated with serious cases of hepatitis B reactivation, including fatal outcome. Reactivation of infection is an expected event during periods of immunosuppression."
Safety in patients with hepatic impairment	Routine pharmacovigilance including detailed cumulative review in the PSUR.	Appropriate dosing information in SPC Section 4.2: "• Severe hepatic impairment (Child-Pugh C) – not recommended. Relevant information in SPC Section 4.4: "Votubia should not be used in patients with severe hepatic impairment (Child-Pugh class C) Further information in SPC Section 5.2: "Hepatic impairment The safety, tolerability and pharmacokinetics of Afinitor were evaluated in a single oral dose study of everolimus in 34 subjects with impaired hepatic function relative to subjects with normal hepatic function. Compared to normal subjects, there was a 1.6-fold, 3.3-fold, and 3.6-fold increase in exposure (i.e. AUC0-inf) for subjects with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment, respectively. Simulations of multiple dose pharmacokinetics support the dosing recommendations in hepatic impaired subjects based on their Child Pugh status. Dose adjustment

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
		is recommended for patients with hepatic impairment."
Important potential risks		
~~Developmental~~ Postnatal developmental toxicity	Routine pharmacovigilance including detailed cumulative review in the PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, and serious reports from other programs where data are being handled as solicited and all clinical trial SAE reports, using a targeted event questionnaire/checklist. Study CRAD001M2301: A randomized, double-blind, placebo-controlled study of RAD001 in the treatment of patients with subependymal giant cell astrocytomas (SEGA) associated with tuberous sclerosis complex (TSC). Study CRAD001C2485: Everolimus (RAD001) therapy of giant cell astrocytomas in patients with tuberous sclerosis complex (including children). Both studies: • Mandated evaluation of endocrine hormonal levels in all patients: LH, FSH, testosterone (males only), estradiol (females only) at screening and every 24 weeks thereafter through the end of the study; Tanner classification until stage V or until the age of 15 (females) or 16 (males) • Weight and height	Relevant information included in SPC Section 5.3: "In rats, everolimus caused embryo/ foetotoxicity at systemic exposure below the therapeutic level. This was manifested as mortality and reduced foetal weight. The incidence of skeletal variations and malformations (e.g. sternal cleft) was increased at 0.3 and 0.9 mg/kg. In rabbits, embryotoxicity was evident in an increase in late resorptions."
Reproductive (teratogenicity) toxicity	Routine pharmacovigilance including detailed cumulative review in the PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, and serious reports from other programs where data are being handled as solicited and all clinical trial SAE reports, using a targeted event and pregnancy questionnaire/checklist.	Relevant information in SPC Section 4.6: "There are no or limited data from the use of everolimus in pregnant women. Studies in animals have shown reproductive toxicity effects (see section 5.3). Everolimus is not recommended during pregnancy and in women of childbearing potential not using contraception." Relevant information included in SPC Section 5.3: "In a male fertility study in rats, testicular morphology was affected at 0.5 mg/kg and above, and sperm motility, sperm head count, and plasma testosterone levels were

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
		diminished at 5 mg/kg, which is within the range of therapeutic exposure (52 ng•hr/mL and 414 ng•hr/mL, respectively, compared to 560 ng•hr/mL human exposure at 10 mg/day) and which caused a reduction in male fertility. There was evidence of reversibility. Female fertility was not affected, but everolimus crossed the placenta and was toxic to the foetus."
Intestinal obstruction/ileus	Routine pharmacovigilance including detailed cumulative review in the PSUR.	None.
Male infertility	Routine pharmacovigilance including detailed cumulative review in the PSUR. **Additional activities** • TSC patients Disease registry CRAD001MIC03: An international disease registry collecting data on manifestations, interventions, and outcomes in patients with tuberous sclerosis complex – TOSCA Safety assessments include safety monitoring and reporting (e.g. SAE). Document fertility in male patients at baseline when available; sex hormone values at baseline and yearly updates for male and female patients.	Relevant information in SPC Section 4.6: "Studies in animals have shown reproductive toxicity effects (see Section 5.3). Based on non-clinical findings, male fertility may be compromised by treatment with everolimus (see section 5.3)." Relevant information included in SPC Section 5.3: "In a male fertility study in rats, testicular morphology was affected at 0.5 mg/kg and above, and sperm motility, sperm head count, and plasma testosterone levels were diminished at 5 mg/kg, which is within the range of therapeutic exposure and which caused a reduction in male fertility. There was evidence of reversibility. Female fertility was not affected, but everolimus crossed the placenta and was toxic to the foetus."
Pancreatitis	Routine pharmacovigilance including detailed cumulative review in the PSUR.	None
Cholelithiasis	Routine pharmacovigilance including detailed cumulative review in the PSUR.	None
Important identified interaction		
Strong CYP3A4 inhibitors and PgP inhibitors	Routine pharmacovigilance.	Relevant information in SPC Section 4.4: "Co-administration with inhibitors and inducers of CYP3A4 and/or the multidrug efflux pump P-glycoprotein (PgP) should be avoided. If co-administration of a moderate CYP3A4 and/or PgP inhibitor or inducer cannot be avoided, dose adjustments of Afinitor can be taken into consideration based on predicted AUC (see section 4.5). Concomitant treatment with potent

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
		CYP3A4 inhibitors result in dramatically increased plasma concentrations of everolimus (see section 4.5). There are currently not sufficient data to allow dosing recommendations in this situation. Hence, concomitant treatment of Afinitor and potent inhibitors is not recommended." Relevant information in SPC Section 4.5: "Substances that are inhibitors of CYP3A4 or PgP may increase everolimus blood concentrations by decreasing the metabolism or the efflux of everolimus from intestinal cells. Interaction by and recommendations regarding concomitant administration of specific CYP3A4 and PgP inhibitors is included in Table 1 in the same SPC section." Relevant information in SPC Section 5.2: "The results of a meta-analysis of pharmacokinetic data from blood samples collected from several clinical studies including 945 patients demonstrated that concomitant administration of CYP3A4 inducers and inhibitors did not appear to have a significant effect on the Cmin exposure of everolimus beyond the limits of variability. Moderate and strong inhibitors increased Cmin exposure by 5% and 10%, respectively, and potent inducers increased Cmin exposure by 7%."
Moderate CYP3A4 inhibitors and PgP inhibitor	Routine pharmacovigilance.	Relevant information in SPC Section 4.4: "Co-administration with inhibitors and inducers of CYP3A4 and/or the multidrug efflux pump P-glycoprotein (PgP) should be avoided. If co-administration of a moderate CYP3A4 and/or PgP inhibitor or inducer cannot be avoided, dose adjustments of Afinitor can be taken into consideration based on predicted AUC (see section 4.5). Concomitant treatment with potent CYP3A4 inhibitors result in dramatically increased plasma concentrations of everolimus (see section 4.5). There are currently not sufficient data to allow dosing recommendations in this situation. Hence, concomitant treatment of

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
		Afinitor and potent inhibitors is not recommended." Relevant information in SPC Section 4.5: "Substances that are inhibitors of CYP3A4 or PgP may increase everolimus blood concentrations by decreasing the metabolism or the efflux of everolimus from intestinal cells. Interaction by and recommendations regarding concomitant administration of specific CYP3A4 and PgP inhibitors is included in Table 1 in the same SPC section." Relevant information in SPC Section 5.2: "The results of a meta-analysis of pharmacokinetic data from blood samples collected from several clinical studies including 945 patients demonstrated that concomitant administration of CYP3A4 inducers and inhibitors did not appear to have a significant effect on the Cmin exposure of everolimus beyond the limits of variability. Moderate and strong inhibitors increased Cmin exposure by 5% and 10%, respectively, and potent inducers increased Cmin exposure by 7%."
Strong CYP3A4 inducers and PgP inducers	Routine pharmacovigilance.	Relevant information in SPC Section 4.4: "Co-administration with inhibitors and inducers of CYP3A4 and/or the multidrug efflux pump P-glycoprotein (PgP) should be avoided. If co-administration of a moderate CYP3A4 and/or PgP inhibitor or inducer cannot be avoided, dose adjustments of Afinitor can be taken into consideration based on predicted AUC (see section 4.5)." Relevant information in SPC Section 4.5: "Substances that are inducers of CYP3A4 or PgP may decrease everolimus blood concentrations by increasing metabolism or the efflux of everolimus from intestinal cells." Interaction by and recommendations regarding concomitant administration of specific CYP3A4 and PgP inducers is included in Table 1 in the same SPC section." Relevant information in SPC

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
		Section 5.2: "The results of a meta-analysis of pharmacokinetic data from blood samples collected from several clinical studies including 945 patients demonstrated that concomitant administration of CYP3A4 inducers and inhibitors did not appear to have a significant effect on the Cmin exposure of everolimus beyond the limits of variability. Moderate and strong inhibitors increased Cmin exposure by 5% and 10%, respectively, and potent inducers increased Cmin exposure by 7%."
CYP3A4 substrates and PgP substrates	Routine pharmacovigilance.	Relevant information in SPC Section 4.5: "Based on in vitro results, the systemic concentrations obtained after oral daily doses of 10 mg make inhibition of PgP, CYP3A4 and CYP2D6 unlikely. However, inhibition of CYP3A4 and PgP in the gut cannot be excluded; hence everolimus may affect the bioavailability of co-administered substances which are CYP3A4 and/or PgP substrates."
Important potential interaction		
Not applicable		None
Important missing information		
Pediatric patients less than 3 years old	Routine pharmacovigilance including cumulative analysis in PSUR.	Appropriate dosing information in SPC Section 4.2: "The safety and efficacy of Afinitor in children aged 0 to 18 years have not been established. No data are available." Relevant information in SPC Section 5.1: "The EMA has waived the obligation to submit the results of studies with Afinitor in all subsets of paediatric population in renal cell carcinoma (see section 4.2 for information on paediatric use)."
Off-label use in pediatric and adolescent patients	Routine pharmacovigilance including cumulative analysis in PSUR.	Appropriate dosing information in SPC Section 4.2: "The safety and efficacy of Afinitor in children aged 0 to 18 years have not been established. No data are available." Relevant information in SPC Section 5.1: "The EMA has waived the obligation to submit the results of studies with Afinitor in all subsets of paediatric population in renal cell carcinoma

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
		(see section 4.2 for information on paediatric use)."
Pregnant or breast-feeding women	Routine pharmacovigilance including cumulative analysis in PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, and serious reports from other programs where data are being handled as solicited and all clinical trial SAE reports, using a targeted event and pregnancy questionnaire/checklist.	Relevant information included in SPC Section 4.6: "There are no or limited amount of data from the use of everolimus in pregnant women. Everolimus is not recommended during pregnancy and in women of childbearing potential not using contraception. It is not known whether everolimus is excreted in breast milk. However, in rats, everolimus and/or its metabolites readily pass into the milk. Therefore, women taking everolimus should not breast-feed."
Hormonal contraceptive use	Routine pharmacovigilance.	Relevant information included in Afinitor SPC Section 4.6: "Women of childbearing potential must use effective method of contraception while receiving everolimus." Relevant information included in Votubia SPC Section 4.6: "Women of childbearing potential must use highly effective method of contraception (e.g. oral, injected, or implanted non-oestrogen-containing hormonal method of birth control, progesterone-based contraceptives, hysterectomy, tubal ligation, complete abstinence, barrier methods, intrauterine device [IUD], and/or female/male sterilisation) while receiving everolimus, and for up to 8 weeks after ending treatment."
Patients with renal impairment	Routine pharmacovigilance. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, and serious reports from other programs where data are being handled as solicited and all clinical trial SAE reports, using a targeted event questionnaire/ checklist.	Information in SPC Section 4.2: "No dose adjustment is required (see section 5.2)." Further information in SPC Section 5.2: "In a population pharmacokinetic analysis of 170 patients with advanced solid tumors, no significant influence of creatinine clearance (25-178 mL/min) was detected on CL/F of everolimus. Post-transplant renal impairment (creatinine clearance range, 11-107 mL/min) did not affect the pharmacokinetics of everolimus in transplant patients."
Long-term safety	Routine pharmacovigilance. **Additional activities** • TSC patients CRAD001M2301: A randomized, double-blind, placebo-controlled	None

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
	study of RAD001 in the treatment of patients with subependymal giant cell astrocytomas (SEGA) associated with tuberous sclerosis complex (TSC). CRAD001C2485: Everolimus (RAD001) therapy of giant cell astrocytomas in patients with tuberous sclerosis complex (including children). CRAD001M2302: A randomized double-blinded study of RAD001 10 mg/d versus placebo in the treatment of angiomyolipomata in patients with tuberous sclerosis complex and/or sporadic lymphangioleiomyomatosis All studies: Mandated evaluation of endocrine hormonal levels in all patients: LH, FSH, testosterone (males only), estradiol (females only) at screening and every 24 weeks thereafter through the end of the study; Tanner classification until stage V or until the age of 15 (females) or 16 (males) Weight and height Disease registry CRAD001MIC03: An international disease registry collecting data on manifestations, interventions, and outcomes in patients with tuberous sclerosis complex – TOSCA ~~(draft protocol in progress)~~ Safety assessments include dose/regimen changes, treatment discontinuation of mTOR inhibitors and other TSC therapies excluding symptomatic therapies (e.g. antiepileptics), frequency and type of follow-up visits (e.g. hospitalization, emergency room visit), frequency of surgical procedures, other safety outcomes (e.g. death), and safety monitoring and reporting (e.g. SAE, pregnancy). • ~~Breast cancer patients~~ ~~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~~ ~~CRAD001W2301: A randomized,~~	

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
	~~phase III, double-blind, placebo-controlled multicenter trial of daily everolimus in combination with trastuzumab and vinorelbine, in pretreated women with HER2/neu over-expressing locally advanced or metastatic breast cancer~~ ~~CRAD001Y2301: A randomized, double-blind, placebo-controlled study of everolimus in combination with exemestane in the treatment of postmenopausal women with estrogen receptor positive locally advanced or metastatic breast cancer who are refractory to letrozole or anastrozole~~	
Patients with CNS metastases Patients with uncontrolled or cardiac disease Patients with impairment of GI function Patients undergoing chronic treatment with steroids or another immunosuppressive agent Carcinogenicity Product impurities	Routine pharmacovigilance.	None

The RMP has been updated to reflect the pharmacovigilance activities related to the patient population with SEGA associated with TSC. Therefore, pharmacovigilance activities related to the oncologic indication were removed (e.g. breast cancer studies). The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activity in addition to the use of routine pharmacovigilance was needed to investigate further some of the long-term safety concerns:

- TSC patients

Disease registry CRAD001MIC03: An international disease registry collecting data on manifestations, interventions, and outcomes in patients with tuberous sclerosis complex – TOSCA

Safety assessments include safety monitoring and reporting (e.g. SAE). Document fertility in male patients at baseline when available; sex hormone values at baseline and yearly updates for male and female patients.

No additional risk minimisation activities were required beyond those included in the product information.

In addition, the CHMP considered that the applicant should take the following minor points into consideration when an update of the Risk management Plan is submitted:

- Amendment of the current version the CRAD001MIC03 (TOSCA) protocol and eCRF: Expand the collection of adverse events information in line with the expectation described in the new EU GPV guidance and collect information about important identified risks and potential risks identified in the RMP. The proposed updated protocol of this PASS should be submitted no later than 60 days after the conclusion of this procedure.

1.8. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), to which the CHMP agreed. The changes are listed in track changes in Annex I.

No full user consultation with target patient groups on the package leaflet has been performed on the basis that the changes to the PL were limited and a user consultation was deemed not necessary.

2. Overall conclusion and impact on the benefit/risk balance

Benefits

Beneficial effects

The study met its primary endpoint where a 50% volume reduction in the sum of target angiomyolipoma lesions was observed in 41.8% patients compared to 0% of patient in the placebo arm (95% CI: 23.5 – 58.4; p-value<0.0001). The secondary endpoints as well as subgroup analyses confirmed the robustness of the results. The CHMP considered the results adequate to demonstrate the clinical benefit of everolimus treatment.

Although not prospectively identified as an efficacy outcome, a higher incidence of renal events was observed in the placebo arm. Fewer patients in the everolimus arm (2.5%) compared with the placebo arm (7.7%) experienced severe renal impairment as assessed by a worst post-baseline glomerular filtration rate < 30 mL/min/1.73 m^2. In addition, no patient in the everolimus arm required surgery or embolization during the course of the study, while 1 patient (2.6%) who received placebo required bilateral renal embolization; and only patients in the placebo arm (9 patients, 23.1%) versus none in the everolimus arm discontinued treatment because disease progression.

Uncertainty in the knowledge about the beneficial effects

Uncertainties in the knowledge of the beneficial effects of everolimus treatment in a patient with angiomyolipoma are related to the uncertainty about the long-term benefit. The results from the open label phase of the study and the TSC registry will be important in order to determine the long term benefit from systemic everolimus treatment in AML.

Risks

Unfavourable effects

The main AEs in the everolimus safety database are infections and stomatitis which were manageable and were not considered serious. The events reported were typically mild to moderate in severity and were generally manageable with dose interruption, dose modification, and/or supportive intervention. The most common adverse drug reactions in the everolimus treated group were stomatitis, hypercholesterolemia, aphthous stomatitis, mouth ulceration, acne, fatigue, anemia, blood lactate dehydrogenase increased, leukopenia, and nausea. No new emergent safety concerns have been identified for the population in the proposed indication.

Uncertainty in the knowledge about the unfavourable effects

The potential of everolimus to affect male fertility is a concern given that no further data has been provided in this submission and there is insufficient data to exclude this risk. Given that most patients with TSC and AML are of reproductive age, the risk of everolimus affecting male fertility will be subject to additional monitoring in the PhV plan and has been highlighted in the SmPC.

There is remaining uncertainty on the long term effects of everolimus treatment are adequately addressed through routine and additional pharmacovigilance measures, as detailed in the pharmacovigilance plan.

Benefit-risk balance

Importance of favourable and unfavourable effects

Untreated AML lesions invariably increase in size over time and are associated with major complications such as haemorrhage and, in some cases renal failure. Patients with TS and angiomyolipoma greater than 4 cm have a high risk for the development of complications and may require surgery. Patients with significant risk of renal morbidity and increased risk of hemorrhagic rupture may benefit from the reduction in tumour volume and disease progression from everolimus treatment.

Overall the pivotal study provided compelling results with regards to its primary endpoint (AML response rate and decreased tumour volume) and safety in the proposed indication. The evidence of efficacy is based on analysis of change in sum of angiomyolipoma volume. None of the patients in the everolimus arm who experienced an angiomyolipoma response reported disease progression prior to the data cut-off. Both the proportion of responses and duration of response were considered clinically impressive. Prevention of further tumour growth in these patients is considered to reflect a clinical benefit. This is the first prospective clinical trial to demonstrate the benefit of a pharmacotherapeutic approach to treatment for this population.

The adverse drug reactions reported were typically mild to moderate in severity and were generally manageable with dose interruption, dose modification, and/or supportive intervention.

Benefit-risk balance

Based on the results of the pivotal trial M2302, the benefits of everolimus treatment in patients with AML associated TSC (AML response rate of 41.8% for everolimus treated group vs 0% for placebo treated group and reduction in angiomyolipoma volume in the everolimus treated group) outweighed the generally mild to moderate toxicity. Therefore, the CHMP considered that the benefit-risk balance for everolimus in the indication "Votubia is indicated for the treatment of adult patients with renal angiomyolipoma associated with tuberous sclerosis complex (TSC) who are at risk of complications (based on factors such as tumour size or presence of aneurysm, or presence of multiple or bilateral tumours) but who do not require immediate surgery. The evidence is based on analysis of change in sum of angiomyolipoma volume." was positive.