19 September 2013
EMA/CHMP/39285/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Votubia

International non-proprietary name: EVEROLIMUS

Procedure No EMEA/H/C/002311/X/0008/G

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Table of contents

List of abbreviations

ADR	adverse drug reaction
AED	anti-epileptic drugs
AUC	area under the curve
AE	adverse event
BBB	blood-brain-barrier
BE	bioequivalence
BHT	butylhydroxytoluene
BSA	body surface area
CI	confidence interval
CL/F	oral clearance
C_{min}	minimum blood/plasma concentration
C_{mav}	maximum blood/plasma concentration
CMH	Cochran-Mantel-Haenszel
CSF	cerebral spinal fluid
CPU	clinical pharmacology unit
CT	computed tomography
CYP3A4	cytochrome P450 3A4
EIAED	enzyme-inducing antiepileptic drug
EURD	European union reference date
FMI	Final Market Image
HR	hazard ratio
IDMC	Independent Data Monitoring Committee
LC-MS	Liquid Chromatography-Mass Spectrometry
LC-MS/MS	Liquid Chromatography with Tandem Mass Spectrometry
LAM	lymphangioleiomyomatosis
LOCF	last observed carried forward
LoQ	limit of quantification
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MF	Marketed Formulation
MRT	mean resistance time
mTOR	mammalian target of rapamycin
mTORC1	mTOR signal transduction complex 1
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PDCO	Paediatric Committee
P-gP	P-glycoprotein
PK	pharmacokinetic
PIP	paediatric investigation planp
PL	package leaflet
PSUR	periodic safety update report
SAE	serious adverse event
SEGA	subependymal giant cell astrocytoma
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SEN	subependymal nodule
SSC	study steering committee
TSC	tuberous sclerosis complex

TTSP	time to SEGA progression
T1/2	half-life
Tmax	time to reach C max
λz	terminal elimination rate constant
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
Vd/F	volume of distribution

Background information on the procedure

1.1. Submission of the dossier

Pursuant to Article 7.2(b) of Commission Regulation (EC) No 1234/2008, Novartis Europharm Ltd submitted to the European Medicines Agency (EMA) on 27 July 2012 an application for a Grouping of a line extension to add a new pharmaceutical form and three new strengths with a type II variation to add a paediatric indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Votubia	Everolimus	See Annex A

The group consisted of:

Extension of the Marketing Authorisation for the above mentioned medicinal product

concerning new strengths: 2, 3 and 5 mg dispersible tablets and the following variations:

Variation requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Grouping of a line extension to add a new pharmaceutical form and three new strengths with a type II to add a paediatric indication.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/127/2011 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMA/169079/2012 (EMEA C2-00019-PIP02-07-M02) was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Votubia was designated as an orphan medicinal product EU/3/10/764 on August 4, 2010. Votubia was designated as an orphan medicinal product in the following indication: Treatment of tuberous sclerosis" (TS) [1, 2].

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

Similarity

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

[1] http://ec.europa.eu/health/documents/community-register/html/o764.htm
[2] http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2010/08/WC500095727.pdf

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on October 18, 2007. The Protocol Assistance pertained to clinical aspects of the dossier.

Licensing status

Votubia has been given a Marketing Authorisation in the EU on 2 September 2011.

1.2. Manufacturers

Manufacturers responsible for batch release

Novartis Pharma GmbH
Roonstrasse 25
D-90429 Nuernberg
Germany

1.3. Steps taken for the assessment of the product

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

Rapporteur:	Dr Harald Enzmann
Co-Rapporteur:	Dr Ian Hudson

- The application was received by the EMA on 27 July 2012.
- The procedure started on 15 August 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 2 November 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 6 November 2012.
- During the meeting on 13 December 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 13 December 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 27 March 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 24 May 2013.
- During the CHMP meeting on 30 May 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 15 August 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 2 September 2013.
- During the meeting on 19 September 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting of an extension of the Marketing Authorisation for Votubia.

2. Scientific discussion

2.1. Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant condition involving the TSC1 (encoding hamartin, chromosome 9) and/or TSC2 genes (encoding tuberin, chromosome 16) and has a prevalence of approximately 1 in 6,000 live births. Mutations in either TSC1 or TSC2 are found in 80% to 85% of patients and a wide spectrum of mutations results in mTOR hyperactivity. When either TSC1 or TSC2 are deficient, mTORC1 is constitutively upregulated, leading to the formation of hamartomas throughout the body. Lesions can occur in the kidneys, brain, heart, liver, lungs and skin.

The disease expression is highly variable, with manifestations ranging from mild skin findings to seizures, learning disabilities, mental retardation, autism and fatal renal, cardiac or pulmonary disease. TSC patients most often present with neurologic symptoms and up to 90% of patients experience seizures. Half of patients experience cognitive impairment, autism or other behavioural disorders and renal disease is the leading cause of death or disability in adults with TSC (haemorrhage or renal failure). Benign skin lesions occur in nearly all patients. A limited number of features are responsible for the decreased life expectancy and these include:

- Neurologic disorders (SEGAs and seizures)
- Renal disease (angiomyolipomas)
- Pulmonary disease (lymphangioleiomyomatosis and bronchopneumonia)
- Cardiovascular disease (rhabdomyoma and aneurysm)

SEGA and its treatment

Subependymal giant cell astrocytomas (SEGAs) are typically slow-growing, glioneuronal tumours arising near the foramen of Monro which develop in 5% to 20% of patients with TSC. SEGAs represent 25% of the excess mortality due to TSC and represent a significant medical risk for this population, including the potential for sudden death secondary to acute hydrocephalus which is directly proportional to tumour volume. As SEGAs enlarge, symptoms of increased intracranial pressure, new neurologic deficits, or deterioration of seizure control are observed. Asymptomatic lesions can progress to obstructing the foramen of Monro in as little as 18 months.

Surgical removal of SEGA lesions is currently the treatment of choice, although the timing of surgery is considered to be controversial. It has been noted that major complications tend to occur more frequently in patients who are symptomatic for raised intracranial pressure or major hydrocephalus before surgery. The rationale for early surgery appears to be to avoid the complications of raised intracranial pressure and hydrocephalus. In the majority of cases with a macroscopically complete resection, the surgery can be considered curative as the lesion does not recur.

SEGAs may in some cases prove to be non-resectable due to their location, (e.g., in the region of the hypothalamus or pineal gland), the presence of peritumoural oedema, or invasion of surrounding normal brain tissue. Surgery, even when successful, can result in a significant risk of peri- and post-operative complications including meningitis, haematomas, hemiparesis, adhesions and incomplete resection.

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), subependymal giant cell astrocytoma (SEGA) associated TSC and renal angiomyolypoma associated with TSC. The product Votubia (everolimus) has been approved for the following indications:

- Renal angiomyolipoma associated with tuberous sclerosis complex (TSC)

  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.

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

  Votubia is indicated for the treatment of patients aged 3 years and older with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not amenable to surgery.

  The evidence is based on analysis of change in SEGA volume. Further clinical benefit, such as improvement in disease-related symptoms, has not been demonstrated.

This application concerns a grouped type II variation and a line extension.

The scope of the **variation** was to:

- Update the SmPC based on data from the phase-III randomized placebo-controlled trial in patients with TSC who have SEGA (Study M2301), and longer-term follow-up from the phase-II trial (Study C2485).
- Provide new information in patients < 3 years of age (approximately 17% of patients in Study M2301).
- Revise the indication to “Votubia is indicated for the treatment of patients with SEGA associated with TSC who require therapeutic intervention and who are not likely to require surgery” to more accurately reflect the population studied.
- Revise the starting dose (from 3 mg/m^2 to 4.5 mg/m^2) as well as the target trough range (from 5 to 15 ng/mL to 3 to 15 ng/mL) for patients with TSC who have SEGA.

Changes were proposed to SmPC sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2. Minor revisions were also proposed to SmPC section 4.4.

Consequential changes were proposed to PL sections 1 and 2.

The purpose of the **line extension** was to:

- Seek marketing approval for an age-appropriate formulation (Votubia 2 mg, 3 mg and 5 mg dispersible tablets) for satisfying the agreement for an age appropriate formulation (i.e. dispersible tablets) in the Paediatric Investigational Plan (PIP).

Changes specific to the line extension are proposed to SmPC sections 1, 2, 3, 4.2, 6 and 8. Consequential changes are proposed to PL sections 3, 5 and 6. In addition, a new section "Instructions for Use" has been added.

2.2. Quality aspects

The medicinal product is presented as dispersible tablets containing 2mg, 3mg and 5mg of everolimus as active substance. Other ingredients are crospovidone, lactose monohydrate, mannitol, microcrystalline cellulose, magnesium stearate, silica colloidal anhydrous, hypromellose and Butylhydroxytoluene (BHT).

The dispersible tablets are packed in double-sided aluminium blisters with PA/AL/PVC as forming foil and aluminium with a vinyl/acryl resin based heat seal lacquer as lidding foil.

2.2.1. Active Substance

The active substance everolimus used for the manufacture of Votubia 2mg, 3mg and 5mg dispersible tablets is of the same quality as that one used for the already marketed Afinitor and Votubia tablets, as well as Certican tablets and dispersible tablets.

Information concerning the active substance of this line extension reference can be found in the published EPAR of Votubia EMEA/H/C/2311.

2.2.2. Finished Medicinal Product

Pharmaceutical development

The active substance everolimus (40-O-(2-hydroxyethyl)-rapamycin) is a macrocyclic lactone with potent anti-proliferative and immunosuppressant properties which is derived by chemical modification from the natural product rapamycin. Its physico-chemical properties were taken into account to prepare the intermediate (solid dispersion) and the finished product (tablets). Everolimus is hydrophobic, practically insoluble in water, soluble in organic solvents, chemically unstable above room temperature, and sensitive to light. Particle size of the active substance was considered not relevant for the quality of the finished product, since the amorphous active substance is dissolved to prepare the intermediate solid dispersion.

All excipients are well known pharmaceutical ingredients and their quality compliant with Ph. Eur. Standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

As the formulation of everolimus dispersible tablets is compositionally similar to everolimus immediate release tablets, the same formulation principle was employed. The main difference of the dispersible form is that it contains microcrystalline cellulose, mannitol and silica colloidal anhydrous and no lactose anhydrous.

The ideal dosage form for a hydrophobic, poorly soluble and chemically instable active substance is a solid dispersion where the active substance is dispersed in a water-soluble carrier.

The same solid dispersion was used for everolimus 2.5mg, 5mg and 10mg immediate release tablets.

The formulation used during the clinical studies was the same as the final formulation.

With regard to dissolution, the dissolution method selected for everolimus 2mg, 3mg and 5mg dispersible tablets was the same as the one authorised for everolimus immediate release tablets. It was demonstrated during the validation studies that the proposed method was suitable for analysis of dissolution samples of all strengths. All three dosage strengths released more than 85% of the active substance in 15 minutes. According to current Guidance on waivers of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system, for release profiles reaching 85% in 15 minutes, no similarity factor should be calculated. Therefore, the dissolution profiles of 2 mg, 3 mg and 5 mg dispersible tablets were considered similar without f2 factor calculation and the claimed biowaiver for the 3mg accepted. Comparative dissolution studies were carried out in the Bioequivalence (BE) study, and compared the immediate release tablets and the dispersible tablets. The dissolution profiles were found to be different. Therefore the BE result as well as the comparative dissolution shows that the proposed

dispersible tablets are not interchangeable with the authorised immediate release tablets. This fact has been stated in the proposed SmPC.

During pre-validation, three full scale batches were manufactured to prove operational ranges and to establish in-process controls and specifications. Moreover, potentially critical process parameters which have been identified during process development were studied in detail.

The pre-validation results demonstrate that the manufacturing process of everolimus 2mg, 3mg and 5mg dispersible tablets is robust and consistently yields to products meeting the pre-determined quality characteristics. Furthermore, the chosen in-process tests have been shown to be suitable for monitoring the manufacturing process.

Based on experience gained from the registration stability studies, everolimus 2 mg, 3 mg and 5 mg dispersible tablets will be packed in double-sided aluminium blisters with PA/AL/PVC as forming foil and aluminium with a vinyl/acryl resin based heat seal lacquer as lidding foil. The blisters are then packed in a cardboard based pack. The suitability of the container closure system for packaging everolimus tablets is demonstrated in stability studies. The materials were in line with the EU guidelines on plastic primary packaging materials.

Adventitious agents

The only excipient from animal origin is lactose monohydrate. Magnesium stearate is of vegetable origin. Lactose is derived from milk suitable for human consumption and is prepared from calf rennet only in accordance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMEA/410/01/01 Rev. 3). Therefore no TSE risk is anticipated.

Manufacture

The manufacture of everolimus 2mg, 3mg and 5mg dispersible tablets is a two-step process. The first step is the preparation of the solid dispersion of the active substance (i.e. pharmaceutical intermediate) which is processed, in a second step, with the other excipients to obtain the everolimus dispersible tablets (i.e. medicinal product).

The manufacture of this dispersion consists of standard processes with appropriate in-process control testing. Process parameters are either fixed or easily met operational ranges are established. The dispersion is tested in accordance with an intermediate monograph. All testing procedures are described and validated.

Batch results of ten production batches of everolimus solid dispersion consistently met the specified acceptance criteria of the solid dispersion.

The dispersible tablets are proportional and are manufactured from the same solid dispersion and tabletting blend. The tabletting mixture is prepared with conventional mixing and sieving procedures and final compression. Appropriate in process controls and limits during tabletting such as average mass, hardness, friability and disintegration time were carried out.

The manufacturing process and in-process controls meet the current standards of pharmaceutical technology and are suitable to guarantee an appropriate quality of the medicinal product.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this pharmaceutical form.

Specification

The finished product release and shelf-life specification for the 2 mg, 3 mg and 5 mg everolimus dispersible tablets include appropriate tests for appearance-shape, colour, debossment (visual), identification of everolimus (UV and HPLC), identification of BHT (GC), mean mass, disintegration time(Ph. Eur.), fineness of dispersion (Ph.Eur.), dissolution after 15 min (HPLC), water content by Karl Fischer, degradation products (HPLC), microbial enumeration tests (plate-count method, Ph.Eur. harmonised ICH method), uniformity of dosage units by content uniformity (HPLC, Ph. Eur. 2.9.40), assay of BHT (GC), assay of everolimus (HPLC). Analytical methods were described and non compendial methods were validated in line with ICH guidelines.

The specification was justified and the limits for the degradation products do not raise any safety concern and are in line with ICH guideline Q6A 'Specifications: Test procedures and acceptance criteria for new active substances and new medicinal products: Chemical substances' and ICH guideline Q3B (R2) 'Impurities in new medicinal products'.

Batch analysis results on six production-scale batches of each strength confirm consistency and uniformity of the manufacture and indicate that the process is under control.

Stability

The stability study for everolimus solid dispersion is not included in this dossier. However, the data were presented during assessment of the already approved everolimus immediate release tablets (Afinitor, Votubia). Based on the stability data, a satisfactory shelf life can be assigned for the everolimus solid dispersion.

Stability results on three production-scale batches of each strength of everolimus dispersible tablets stored under long term (25°C / 60%RH, 12 months), intermediate (30°C / 75%RH, 12 months), accelerated (40°C / 75%RH, 6 months), high temperature (50°C, 3 months) according to ICH conditions were presented. The tablets were kept in the commercial packaging. Stability testing parameters included appearance, water content, disintegration time, fineness of dispersion, dissolution, assay of everolimus, BHT and degradation products, hardness testing and microbiological quality (initial and end time points). The analytical methods were stability indicating.

The proposed dispersible tablets were also exposed to freeze/thaw condition. One batch of each strength was exposed to four freeze/thaw cycles with freezing at -20°C. Analysis after 28 days following the cycles shows no significant effect on assay, impurities and physical stability parameter including tablet disintegration.

Photostability data in line with ICH requirement has been carried out for two batches of 2mg, 3mg and 5mg dispersible tablets. Significant difference was observed between tablets exposed to light stress condition and unexposed control samples stored in the blisters. Therefore it can be concluded that everolimus tablets is sensitive to light and should be stored protected from light. The proposed commercial packaging was shown to provide adequate protection.

In accordance with the Note for Guidance on Start of Shelf-life of the Finished Dosage form, the shelf-life of the medicinal product will start with the production date of everolimus solid dispersion.

Based on the available data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.3. Discussion on chemical, pharmaceutical and biological aspects

Data on development, manufacture and control of these dispersible tablets containing 2mg, 3mg and 5mg of everolimus has been presented in a satisfactory manner. The ideal dosage form for a hydrophobic poorly soluble and chemically instable active substance is a solid dispersion where the drug substance is dispersed in a water-soluble carrier. As the formulation of everolimus dispersible tablets is compositionally similar to everolimus immediate release tablets, the same formulation principle was employed. The compendial excipients selected for the formulation are commonly used in pharmaceutical tablet formulations. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the medicinal product should have a satisfactory and uniform clinical performance.

Conclusions on the chemical, pharmaceutical and biological aspects

Based on the data provided, the quality of this medicinal product is considered to be acceptable. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.4. Recommendation(s) for future quality development

Not applicable

2.3. Non-clinical aspects

2.3.1. Introduction

To support this new application, the MAH has provided an overview with the known pharmacodynamics, pharmacokinetics and toxicology of everolimus supplemented by one additional pharmacokinetic study investigating the brain distribution of everolimus in rats after oral administration of 3 mg/kg everolimus with and without oral co-administration of 10 mg/kg cyclosporine.

2.3.2. Pharmacology

The MAH did not submit pharmacology studies with this application.

The MAH presented evidence on the development of the blood-brain barrier in response to questions from the CHMP. The majority of the literature indicates that the blood-brain-barrier (BBB) develops during foetal life and is well formed by birth, especially to proteins and macromolecules although for non-human mammals born in a relatively immature state (such as rat and mouse), many transport mechanisms may continue to mature after birth[3].

2.3.3. Pharmacokinetics

Study R1000720: Brain distribution of RAD001 in rats after oral administration of 3 mg/kg RAD001 with and without oral co-administration of 10 mg/kg Cyclosporine

[3] Abbott NJ, Patabendige AAK, Dolman DEM, et al (2010). Structure and function of the blood-brain barrier.Neurobiol of Disease; 37: 13-25

Study R1000720 examined the distribution of everolimus to brain cortex and CSF in rats after oral administration of 3 mg/kg everolimus with and without oral co-administration of 10 mg/kg cyclosporine.

Assay methods

Everolimus was stated to have been determined in human and animal blood by HPLC coupled to LC-MS or by specific ELISA. The limit of quantification (LoQ) was stated to be 0.3 to 1ng/ml and 2ng/mL respectively. The ELISA method was stated to have been validated against LC-MS and correlated within a 95% confidence interval. Everolimus was stated to be stable in human and animal blood over the time of sample processing and analysis.

Distribution

The determination of the test compound in the blood, CSF and brain cortex homogenates was by LC-MS/MS. In the rat, the blood-brain passage of everolimus and/or its metabolites was found to be dose dependent, consistent with saturation of an efflux pump at the blood-brain barrier. After administration there was a rapid uptake of everolimus in the brain cortex followed by a slow efflux. The co-administration of the P-gp inhibitor cyclosporine enhanced the exposure of everolimus in the brain cortex (2.62-fold increase in AUC_{last}), which is consistent with the inhibition of P-gp at the blood-brain-barrier. There was also a rapid uptake of everolimus in CSF, although the exposure of everolimus in CSF was less than that in the brain cortex with individual cortex/CSF concentration ratios ranging from 3.49 to 5.0. Co-administration of cyclosporine did not enhance the exposure of everolimus in the CSF in terms of AUC_{last}. Mean concentrations at 0.25, 1, and 4 hours were consistently higher in the everolimus plus cyclosporine arm than in the everolimus arm. The similar AUC_{last} between the arms was due to the lower mean concentration at the 24 h time point in the everolimus plus cyclosporine arm. Results of the study are presented in Tables 1-4.

Table 1: Concentrations (ng/mL or ng/g) in blood, brain cortex, and CSF after oral administration of 3 mg/kg everolimus (n = 3)

Time (h)	Blood	Brain cortex	CSF
0.25	23.7 ± 6.85	0	0
1	54.5 ± 6.50	5.41 ± 0.843	0
4	27.9 ± 4.34	7.24 ± 1.83	1.22 ± 1.11
24	7.02 ± 3.54	8.65 ± 3.43	2.07 ± 0.820

Table 2: Concentrations (ng/mL or ng/g) in blood, brain cortex, and CSF after oral administration of 3 mg/kg everolimus with oral co-administration of 10 mg/kg cyclosporine (n = 3)

Time (h)	Blood	Brain cortex	CSF
0.25	30.7 ± 7.30	0	0.650 ± 1.13
1	62.9 ± 54.9	7.73 ± 6.82	1.17 ± 1.20
4	35.9 ± 8.22	15.3 ± 5.51	2..07 ± 1.90
24	19.5 ± 3.22	28.1 ± 4.51	0.314 ± 0.544

Table 3: Pharmacokinetic parameters after oral administration of 3 mg/kg everolimus (n = 3)

Parameter	Blood	Brain cortex	CSF
Tmax (h)	1	24	24
Cmax (ng/mL or ng/mL)	54.5	8.65	2.07
AUClast (ng/mL·h or ng/g·h)	505	180	34.7
Tissue/Blood	1.00	0.356	0.0688

Table 4: Pharmacokinetic parameters after oral administration of 3 mg/kg everolimus with oral co-administration of 10 mg/kg Cyclosporine (n = 3)

Parameter	Blood	Brain cortex	CSF
Tmax (h)	1	24	4
Cmax (ng/mL or ng/mL)	62.9	28.1	2.07
AUClast (ng/mL·h or ng/g·h)	741	471	29.8
Tissue/Blood	1.00	0.636	0.0402

2.3.4. Toxicology

The MAH did not submit toxicology studies with this application.

The MAH submitted a review which re-evaluated the adverse treatment-related findings in a juvenile rat development study. In this study there were no juvenile animal-specific systemic effects. The lenticular findings (also reported in studies in adult rat studies) were considered a species-specific response in rats, since they were not observed in any of the other species studied (mice, monkey, rabbits, minipigs). Neurological development parameters were assessed. Although there were delays in pre-weaning evaluations (i.e., eye opening, testes descent), all criteria were met by the end of the assessment periods. Post-weaning evaluations revealed no everolimus-related effects on acoustic startle, pupillary reflex, open field motor activity, or passive avoidance tests.

In males, the results of the water maze evaluation revealed a statistically significant increase in the total latency time during the learning phase at 0.5 and 1.5 mg/kg/day everolimus, and during the memory phase at 1.5 mg/kg/day everolimus relative to the concurrent controls. There were no effects in females in the water maze evaluation, and no alterations in males or females in the passive avoidance test. There was absence of effects on reflex evaluations during the dosing period and the absence of microscopic changes in the brain.

The potential effects of everolimus on brain development were also assessed in the pre- and post-natal development (PPND) study in rats, the results of which indicated that fetal exposure during in utero development and pup exposure via nursing did not result in effects on reflex or learning/memory evaluations. The expression of P-gP in rat brain is age-dependent: it is undetectable in the embryo and

newborn rat brain, became detectable at Day 7 postpartum, gradually increased and reached a plateau at postpartum Day 28[4]. In contrast, the expression of P-gP is detectable at early stage of development for human fetal brain (8- to 12-weeks of gestation), and with increasing intensity during fetal development[5], [6]. The expression of MDR1 (the gene for P-gP) in human fetal brain at 21 weeks of gestation appeared to be similar to that of adult brain[7]. Therefore, it is expected, that elimination of everolimus from the brain of a human child would be more efficient than from a juvenile rat brain.

2.3.5. Ecotoxicity/environmental risk assessment

The calculation of the predicted environmental concentration (PEC) was based on the prevalence of the entire TCS- SEGA population including all age ranges in the procedures Votubia EMEA/H/C/2311 and Votubia EMEA/H/C/2311/II/04 resulting in a PEC clearly below the action limit of 0.01µg/L for a Phase II environmental risk assessment.

Table 5: Summary of main study results

Substance (INN/Invented Name):Everolimus			
CAS-number (if available): 159351-69-6			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD117	4.0	Potential PBT N
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined (prevalence)	0.00057	µg/L	> 0.01 threshold N
Other concerns (e.g. chemical class)			N

2.3.6. Discussion on non-clinical aspects

To support this application, the MAH provided an overview of the known pharmacodynamics, pharmacokinetics and toxicology of everolimus supplemented by one additional pharmacokinetic study investigating the brain distribution of everolimus in rats after oral administration of 3 mg/kg everolimus with and without oral co-administration of 10 mg/kg cyclosporine.

The time profile of the blood and brain concentrations of everolimus demonstrated a rapid uptake of the test compound in the brain followed by a slow efflux. The mean peak concentration of everolimus in the brain cortex occurred at the last sampling time point of 24 h. The co-administration of the P-gp inhibitor cyclosporine enhanced the exposure of everolimus in the brain cortex (2.62-fold increase in AUC_{last}), which is consistent with the inhibition of P-gp at the blood-brain-barrier.

There was also a rapid uptake of everolimus in CSF, although the exposure of everolimus in CSF was less than that in the brain cortex with individual cortex/CSF concentration ratios ranging from 3.49 to 5.0. Co-administration of cyclosporine did not enhance the exposure of everolimus in the CSF in terms of AUC_{last}. It should be noted that mean concentrations at 0.25, 1, and 4 hours were consistently higher in the everolimus plus cyclosporine arm than in the everolimus arm. The similar AUC_{last} between

[4] Matsuoka Y, Okazaki M, Kitamura Y, et al (1999). Developmental expression of P-glycoprotein (multiresistance gene product) in the rat brain. J Neurobiol; 39:383-392
[5] Schumacher U. Mollgard K (1997). The multidrug-resistance P-glycoprotein (Pgp, MDR1) is an early marker of blood-brain barrier development in the microvessels of the developing human brain. Histochem Cell Biol; 108:179-182
[6] Virgintino D, Errede M, Girolamo F, et al (2008). Fetal blood-brain barrier P-glycoprotein contributes to brain protection during human development. J Neuropathol. & Exp Neurol; 67:50-61
[7] Miki Y, Suzuki T, Tazawa C, et al (2005). Steroid and xenobiotic receptor (SXR), cytochrome P450 3A4 and multidrug resistance gene 1 in human adult and fetal tissues. Mol Cell Endocrinol; 231: 75-85

the arms was due to the lower mean concentration at the 24 h time point in the everolimus plus cyclosporine arm.

The therapeutic relevance of the findings on blood-brain passage was considered relevant for the intended expansion of the indication to children < 3 years of age. There was uncertainty as to whether the BBB was fully developed at birth and if the distribution of everolimus into the brain of patients younger than three years of age compared to that of older patients. The MAH submitted a discussion on the development of the BBB. Extrapolating from the non-clinical pharmacology and toxicology studies into humans, there is the presumption that everolimus may also penetrate the BBB in humans and the response of SEGA lesions in the clinical Study M2301 may be derived from the effect of everolimus. Thus, given that the main efflux mechanism of everolimus from the brain is via PgP transportation and that this mechanism develops in-utero in humans and post-partum in rats, extrapolation of exposure to everolimus in the juvenile rats to children age < 3 years was accepted. In addition, the MAH presented an adequate discussion to the extrapolation of exposure data from the juvenile toxicology studies to the paediatric population. Although there were delays in pre-weaning evaluations (i.e., eye opening, testes descent), all criteria were met by the end of the assessment periods. Post-weaning evaluations revealed no everolimus-related effects on acoustic startle, pupillary reflex, open field motor activity, or passive avoidance tests. The effects of everolimus in TSC animal models reported in the published literature indicate no evidence of adverse effects on brain development in juvenile animals.

As requested by the CHMP, the following information was added in section 5.2 of the SmPC concerning everolimus distribution across the BBB:

“Nonclinical studies in rats indicate:
- A rapid uptake of everolimus in the brain followed by a slow efflux.
- The radioactive metabolites of [3H]everolimus do not significantly cross the blood-brain barrier.
- A dose-dependent brain penetration of everolimus, which is consistent with the hypothesis of saturation of an efflux pump present in the brain capillary endothelial cells.
- The co-administration of the PgP inhibitor, cyclosporine, enhances the exposure of everolimus in the brain cortex, which is consistent with the inhibition of PgP at the blood-brain barrier.

There are no clinical data on the distribution of everolimus in the human brain. Non-clinical studies in rats demonstrated distribution into the brain following administration by both the intravenous and oral routes.”

An acceptable explanation for not providing an updated ERA was submitted. Everolimus PEC surfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. Thus, everolimus is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

All the concerns over the distribution of everolimus in the brain as well as neurotoxicity in the developing brain have been addressed. The study results of the brain distribution of everolimus with or without the co-administration of the P-gp inhibitor in the rat provided evidence of the passage of everolimus and/or its metabolites into the brain cortex and CSF in a dose-dependent manner. In addition, the results of the juvenile toxicity studies in rats and monkeys, safety pharmacology studies and the pre- and post-natal development study in rats, as well as the effects of everolimus in TSC animal models reported in the published literature indicate no evidence of permanent adverse effects on brain development. The overall conclusion that the non-clinical studies do not indicate any

permanent adverse effects on brain development was accepted. These results supported the extension of the indication of everolimus in the treatment of SRGA patients to children < 3 years of age.

2.4. Clinical aspects

2.4.1. Introduction

The MAH submitted a population PK report and a report describing a PK/PD model for everolimus in patients with TSC who have SEGA. Data on clinical pharmacology was provided from 4 studies, updated data from studies M2301 (cut-off date , 21 March 2011) and C2485 (cut-off date, 31 December 2010) and new studies X2105 and X2106, which were requested by the CHMP as part of post-authorisation commitments at the time of marketing authorisation.

Furthermore, the MAH submitted a report entitled 'First Available Results (FAR) Clinical Trial Protocol CRAD001X2111.' This abbreviated clinical study report reported on a BE trial investigating BE of 2x5 vs. 5x2 mg dispersible tablets.

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

Study	Description	Clinical pharmacology data
M2301 (data cut-off date 02-Mar-2011)	A randomized, double-blind, placebo-controlled phase III study of everolimus to evaluate the safety and efficacy of everolimus in patients with TSC who have SEGA, irrespective of age. Everolimus was administered orally at a starting dose of 4.5mg/m^2/day, and subsequently titrated, subject to tolerability, to attain whole blood trough concentrations of 5-15 ng/mL.	C_{min} and exposure-response relationships in patients with TSC who have SEGA
C2485 (data cut-off 31-Dec-2010)	A prospective, non-randomized, open-label, investigator-initiated, phase-II study designed to evaluate the safety and efficacy of everolimus therapy in patients ≥3 years with TSC who have SEGA. Everolimus was administered orally at a starting dose of 3.0 mg/m^2/day (once-daily or on an alternate day regimen) and subsequently titrated, subject to tolerability, to attain whole blood trough concentrations of 5-15 ng/mL.	C_{min} and exposure-response relationships in patients with TSC who have SEGA
X2105	A single-center, open-label, randomized, two-way cross-over study with 2 treatment periods and 2 treatment sequences conducted in 54 healthy subjects (male and female), aged 18 to 55 years. The subjects were randomly assigned to one of the 2 treatment sequences to receive the following treatments in two study periods: 1 × 5-mg dispersible tablet and the 5 × 1-mg MF tablets. Treatment periods were separated by a washout interval of 8 days. The study drug was administered to subjects under fasting conditions.	To determine the bioequivalence between the dispersible tablet and the 1-mg MF tablet.
X2106	A single-center, open-label, randomized, two-way cross-over study with 2 treatment periods and 2 treatment sequences conducted in 54 healthy subjects (male and female), aged 18 to 55 years. The subjects were randomly assigned to one of the 2 treatment sequences to receive the following treatments in two study periods: 1 × 5-mg dispersible tablet and the 1 × 5-mg FMI tablets. Treatment periods were separated by a washout interval of 8 days. The study drug was administered to subjects under fasting conditions.	To determine the bioequivalence between the dispersible tablet and the 5-mg FMI tablet.

2.4.2. Pharmacokinetics

The new biopharmaceutic information of everolimus in humans comprised results of bioequivalence Study X2105 which compared the 5 mg dispersible tablet to the 1 mg tablet used in Study M2301 and the results of bioequivalence Study X2106 which compared the 5 mg dispersible tablet to the 5 mg tablet used in Study C2485.

Absorption

- Bioavailability

Study X2105

Study X2105 was a single centre, randomized, open-label, crossover study with two treatment periods and two possible treatment sequences. Fifty-four healthy eligible subjects (female or male subjects aged 18 to 55 years in good health condition) were enrolled in the study and randomized to one of the

two treatment sequences. Sequence 1-everolimus 1×5-mg dispersible tablet (test) and Sequence 2-everolimus 5×1-mg MF (marketed formulation) tablets (reference). In each treatment sequence the two treatment periods were preceded by baseline assessments (up to 24 h prior to study drug administration) followed by a single-dose treatment and 144 h of follow-up for pharmacokinetic (PK) samples.

Study subjects remained in the clinical pharmacology unit (CPU) for the first 72 h after study drug administration. Thereafter, subjects were released from the CPU and had three additional visits during the first and second treatment periods at 96 h (Day 5 and Day 19, respectively), 120 h (Day 6 and Day 20, respectively) and 144 h (Day 7 and Day 21, respectively) post-dose for collection of PK samples. The end of study (EOS) evaluation was done 14 (± 2) days after the study drug administration in the second treatment period. The two treatment periods were separated by an out-patient period of 8 days for thorough washout of the investigational product (the second drug administration was to be 14 days following the previous one).

Primary objective of study X2105 was to demonstrate bioequivalence between the 1 × 5-mg dispersible tablet and the 5 × 1-mg MF tablets used in the phase III SEGA study M2301. Secondary objectives were to evaluate safety and tolerability of a single dose of 5x1-mg dispersible tablets and a single 5-mg MF of everolimus.

Primary endpoints for bioequivalence analysis were $AUC_{(0\text{-}144h)}$, $AUC_{(0\text{-}inf)}$, and C_{max} of everolimus. Secondary PK variables were T_{max}, $T_{1/2}$, λ_z, CL/F, BSA-normalized CL/F and Vd/F.

Most subjects had non-quantifiable concentration values at 144 h post-dose. Therefore, sample size was small for the PK parameter $AUC_{0\text{-}144h}$ i.e. only 6 subjects with quantifiable concentrations at 144 h (C_{144h}) in each treatment arm, and only 4 subjects with quantifiable concentrations at 144 h in both treatment arms.

Table 6: Summary of statistical analysis of everolimus primary PK parameters (PK set) – Study X2105

				Treatment comparison		
PK Parameter (unit)	Treatment	n *	Adjusted Geo-mean	Comparison	Geo-mean Ratio	90% CI Lower	Upper
$AUC_{(0\text{-}inf)}$ (ng.h/mL)	A	51	255.20				
	B	51	219.88	B:A	0.86	0.802	0.926
$AUC_{(0\text{-}144h)}$ (ng.h/mL)	A	4	363.88				
	B	4	330.02	B:A	0.91	0.760	1.082
C_{max} (ng/mL)	A	51	39.81				
	B	51	25.40	B:A	0.64	0.599	0.679

For means of comparison, results from study C2121 comparing 5x1 mg 'non-dispersible' tablets administered as intact tablets or dispersed in water are displayed in Table 7 below.

Table 7: Geometric mean ratio (test/reference) and 90% confidence intervals for primary everolimus PK parameters – Study C2121

				Treatment Comparison		
PK Parameter (unit)	Trt	n	Adjusted geo-mean	Comparison(s)	Ratio of geo-mean (test/ref.)	90% CI*
C_{max} (ng/mL)	A	39	26.6			
	B	36	19.1	B:A	0.72	(0.63, 0.82)
$AUC_{(0\text{-}inf)}$ (h.ng/mL)	A	39	192.4			
	B	36	168.7	B:A	0.88	(0.80, 0.96)
$AUC_{(0\text{-}t)}$ (h.ng/mL)	A	39	170.8			
	B	36	146.2	B:A	0.86	(0.77, 0.95)
$t_{max}^{\$}$ (h)	A	39	1.0			
	B	36	1.0	B-A	0.00	(-1.00, 1.00)

CI= confidence interval; geo-mean= geometric mean; n= number of observations; ref.= reference; Trt= treatment.

Treatment A: Ref. (5 x 1-mg intact tablets), Treatment B: Test (5 x 1-mg tablets in suspension)

* 90% CIs were based on a mixed-model with sequence, period and treatment as fixed effects and subject nested in sequence as a random effect in the model. A natural log transformation for AUC and C_{max} was used prior to the mixed model.

$: For t_{max}, median, median difference and range are presented in the columns of adjusted geometric mean, ratio of geo-mean and 90% CI columns, respectively.

Since the t_{last} for most subjects (of study X2105) was actually 72 h or 96 h, and rarely 144 h, it led to the exclusion of the primary PK parameter $AUC_{0\text{-}144h}$ for all but 4 subjects. Additional exploratory analyses on $AUC_{0\text{-}72h}$ and $AUC_{0\text{-}96h}$ were conducted.

Geometric mean ratio of the test to reference formulation, for the exploratory PK parameters $AUC_{0\text{-}72h}$ and $AUC_{0\text{-}96h}$ was 0.86 and 0.89 respectively. The 90% CIs for $AUC_{0\text{-}72h}$ and $AUC_{0\text{-}96h}$ were 0.8004-0.9290 and 0.8241-0.9661 respectively, and were completely within the bioequivalence interval for the boundaries of (0.8, 1.25).

For the secondary parameters, $T_{1/2}$, CL/F, BSA normalized CL/F, λz, Vd/F and MRT, the geometric mean ratios of test to reference formulations and the 90% CIs for the ratio of geometric means were within the interval of (0.8, 1.25).

Study X2106

Study X2106 was a single centre, randomized, open-label, crossover study with two treatment periods and two possible treatment sequences. Fifty-four (54) healthy subjects were enrolled and randomized to one of the two treatment sequences. Sequence 1-everolimus 1×5-mg dispersible tablet (test) and 1×5-mg Final Market Image (FMI) tablet (reference); Sequence 2-everolimus 1×5-mg FMI tablet (reference) and everolimus 1×5-mg dispersible tablet (test).

In each sequence the two treatment periods were preceded by baseline assessments (up to 24 h prior to study drug administration) followed by a single-dose treatment and 144 h of follow-up for PK samples.

Primary objective of study X2106 was to demonstrate bioequivalence between the 1 × 5-mg dispersible tablet and the 1 × 5-mg FMI tablets. Secondary objectives were to evaluate safety and tolerability of a single dose of a single 5-mg dispersible a single 5-mg FMI tablet of everolimus.

Primary endpoints for bioequivalence analysis were $AUC_{(0-144h)}$, $AUC_{(0-inf)}$, and C_{max} of everolimus. Secondary PK variables were T_{max}, $T_{1/2}$, λ_z, CL/F, BSA-normalized CL/F and Vd/F. Additional secondary PK variables were: $AUC_{(0-72h)}$, $AUC_{(0-96h)}$, and $AUC_{(0-tlast)}$.

Comparable to study X2105, most subjects had non-quantifiable concentration values at 144 h post-dose. There were only 6 subjects with quantifiable concentration at 144 h in the 1×5 mg FMI formulation arm and 4 subjects with quantifiable concentration at 144 h in the 1×5 mg dispersible formulation arm. There was only a single subject with valid $AUC_{(0-144h)}$ for both formulations.

Table 8: Summary of statistical analysis of everolimus primary PK parameters (PK set) – Study X2106

$AUC_{(0-inf)}$ (ng.h/mL)	A	52	254.53				
	B	52	230.95	B:A	0.91	0.862	0.955
$AUC_{(0-144h)}$ (ng.h/mL)	A	1					
	B	1		B:A			
C_{max} (ng/mL)	A	53	32.01				
	B	53	25.76	B:A	0.80	0.754	0.859

Treatment A: everolimus 1x5-mg FMI tablet, Treatment B: everolimus 1x5-mg dispersible tablet

* n is the number of subjects with non-missing PK parameter for both periods.

The estimates and 90% CIs were based on an analysis of variance (ANOVA) on log-transformed PK parameters with sequence, period, treatment and subject nested in sequence as fixed effects in the model. Results were then back-transformed to the original scale.

For the primary parameter $AUC_{(0-inf)}$, ratio of geometric means of the test to the reference formulation was 0.91, with a 90% CI lower bound of 0.862 and an upper bound of 0.955, thus lying entirely within the interval for the boundaries of (0.8, 1.25), and meeting the criteria for BE. $AUC_{(0-144h)}$, geometric mean ratio (test: reference) could not be derived due to lack of data. The geometric mean ratio (test: reference) for C_{max} was 0.80, with a 90% CI of 0.754-0.859, thus lying outside the (0.8, 1.25) boundaries for BE.

Geometric mean ratio of the test to reference formulation, for the exploratory PK parameters $AUC_{(0-tlast)}$, $AUC_{(0-72h)}$ and $AUC_{(0-96h)}$ was 0.90, 0.90 and 0.91 respectively. The 90% CIs for $AUC_{(0-tlast)}$, $AUC_{(0-72h)}$ and $AUC_{(0-96h)}$ were 0.848-0.945, 0.854-0.946 and 0.856-0.958 respectively, and were completely within the bioequivalence interval for the boundaries of (0.8, 1.25).

For the secondary parameters, $T_{1/2}$, CL/F, BSA normalized CL/F, λz, Vd/F and MRT, the geometric mean ratios of test to reference formulations and the 90% CIs for the ratio of geometric means were within the interval of (0.8, 1.25).

Dose proportionality and time dependencies

Study X2111

Study X2111 was a single center, open-label, randomised two-way cross-over study investigating the bioequivalence of everolimus (RAD001) 2 × 5-mg dispersible tablets in suspension and 5 × 2- mg dispersible tablets in suspension, in healthy male subjects. The primary objective of study X2111 was to compare the rate and extent of absorption between 2 × 5 -mg dispersible tablets in suspension and 5 × 2 -mg dispersible tablets in suspension measured by AUC_{inf}, AUC_{last} and C_{max} following a single dose of everolimus.

This study enrolled 24 healthy adult (age range 25-54 years) volunteers. Each subject was to be treated with both treatment sequences after pre-defined washout periods. Twenty-three of the 24 patients completed both treatment sequences. One patient did not complete the study due to use of prohibited concomitant medication in between treatment sequences.

The geometric mean ratios for the primary PK parameters and 90% CI comparing the 5 × 2 -mg dispersible tablets in suspension (test) and 2 × 5 -mg dispersible tablets in suspension (reference) were as follows:

AUC_{inf}: 0.97 (0.89 to 1.06) (N=23 subjects)

AUC_{last}: 0.97 (0.88 to 1.06) (N=23 subjects)

C_{max}: 0.96 (0.87 to 1.07) (N=23 subjects)

Table 9 below shows the major PK findings of the trial:

Table 9: Summary of everolimus primary parameters by treatment – PAS – Study X2111

Treatment	Statistics	AUClast (ng*h/mL)	AUCinf (ng*h/mL)	Cmax (ng/mL)
Everolimus 2 × 5 -mg dispersible tablet	n	23	23	23
	Mean (SD)	431.22 (101.322)	451.51 (104.532)	45.97 (10.314)
	CV% mean	23.50	23.15	22.43
	Geo-mean	420.94	441.10	44.81
	CV% geo-mean	22.32	21.90	23.99
	Median	413.66	434.32	45.30
	[Min; Max]	[309.6; 715.2]	[326.3; 742.2]	[24.1; 65.6]
Everolimus 5 × 2 -mg dispersible tablet	n	23	23	23
	Mean (SD)	420.33 (120.036)	443.27 (125.146)	44.60 (11.184)
	CV% mean	28.56	28.23	25.07
	Geo-mean	405.94	428.64	43.22
	CV% geo-mean	26.85	26.23	26.53
	Median	387.32	412.15	43.80
	[Min; Max]	[255.1; 739.4]	[273.9; 777.9]	[25.7; 68.5]

n: number of subjects with non-missing values
CV% = coefficient of variation (%) = sd/mean*100,
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100.

Special populations

Population PK and PK/PD model

A population PK report and a report describing a PK/PD model for everolimus in patients with TSC who have SEGA were submitted.

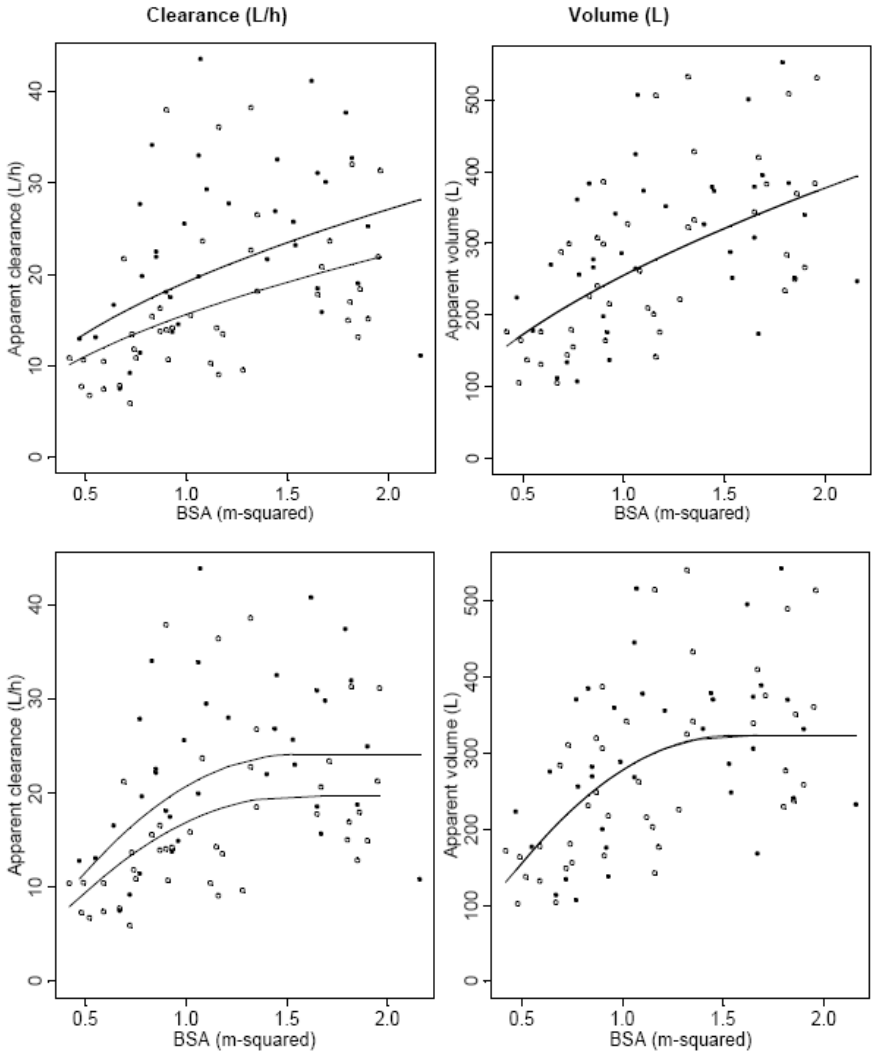
The model used data from only the double blinded treatment phase of study M2301 up to the 02 March 2011 cut-off date. NONMEM with METHOD=1 INTERACTION was used for modelling. The NONMEM objective function values and diagnostic plots were used to assess goodness of fit, to suggest covariates to add to the model, and to evaluate the model. Covariates age, BSA, BMI, baseline SEGA volume, sex, and concomitant medications were also examined graphically for trends and their reduction of variability by plotting individual estimates versus the covariates. A visual predictive check was also used as part of the model evaluation. The recommended starting dose for the SEGA indication was 4.5 mg/m^2 using either the dispersible tablets or the regular tablets. Simulations of steady-state C_{min} were conducted separately based on the recommended starting dose rounded to feasible mg doses for both the regular and dispersible tablets to assess the relative frequency of C_{min}'s within and outside of the newly proposed target range of 3-15 ng/mL.

Seventy-eight patients ranging from 1.0 to 23.9 years and 0.4 m^2 to 2.2 m^2 body surface area contributed 810 everolimus blood concentrations to the population pharmacokinetic analysis. The samples were generally a trough and a peak sample collected from the patient on the same day. A one compartment model adequately characterized the data. Due to the limited sampling the absorption rate constant was set to 6.07 h-1 for all patients.

The initial modelling to explain variability identified body surface area and presence of CYP3A or PgP enzyme inducers as significant covariates. The individual estimates of oral clearance and volume from the best of these models were examined closely at the lowest BSA. The population oral clearance was

higher than the corresponding individual estimates of oral clearance suggesting some lack of fit of the population model (top panel of Figure 1). For the final model, piecewise differentiable functions (smooth splines) for oral clearance and oral volume were selected to provide less bias, especially for individual oral clearance at the lowest BSA. For the final model (bottom panel of Figure 1), the estimates of clearance and volume were lower at the data limits than the initial models so as to infer slightly lower (potentially safer) doses when extrapolated compared to the initial models (based on BSA normalised clearance, bottom panel of Figure 2).

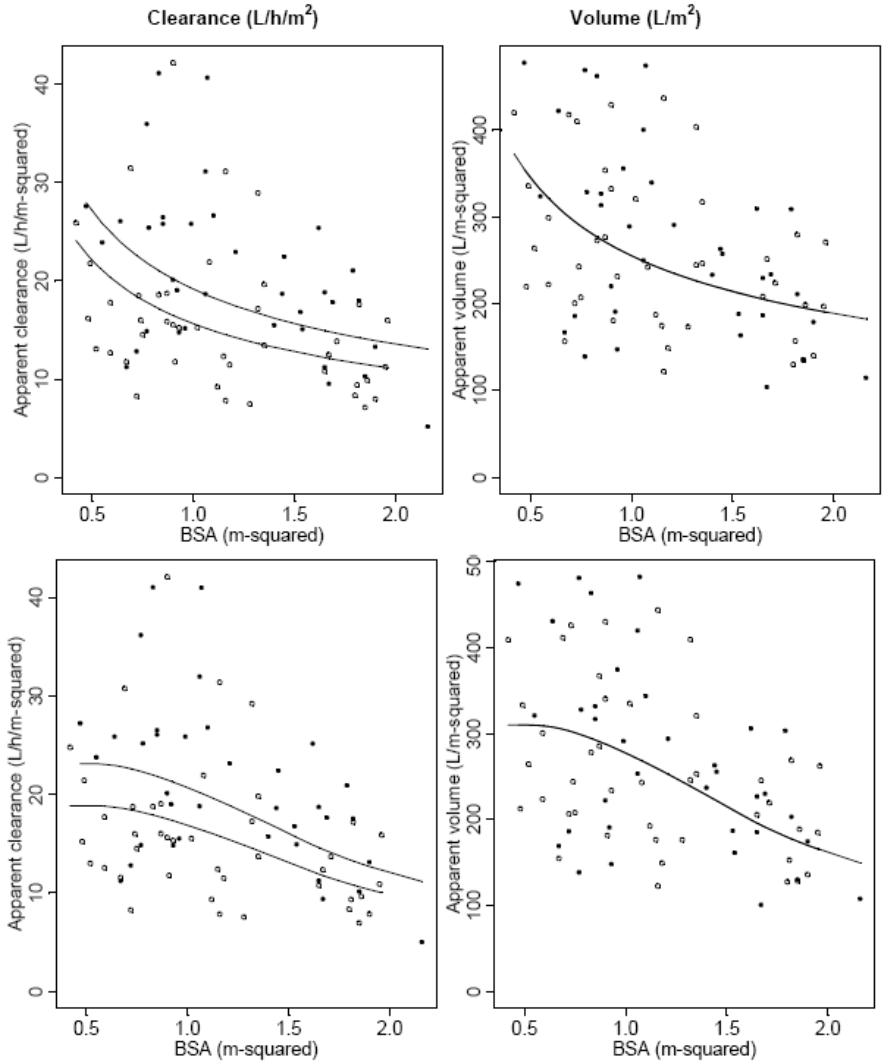
Figure 1: Individual and typical clearance and volume versus BSA by presence (closed circles, upper curves) and absence (open circles, lower curves) of inducers at baseline



Presence of inducers was a covariate only for clearance. The population estimate of volume versus BSA was not dependent on inducers and so the curves on the right for presence and absence of inducers coincide. Model 12 upper panel; Model 19 (final model) lower panel; N=78.

In the final model, at BSA ≤ 0.542 m^2 the estimates of typical normalized oral clearance and normalized oral volume were 18.9 L/h/m^2 and 310 L/m^2, respectively, and at BSA ≥1.542 m^2 the estimates of typical unnormalized oral clearance and unnormalized oral volume were 19.7 L/h and 323L. With the presence of CYP3A or PgP enzyme inducers, the corresponding apparent clearances (L/h) and normalized clearances (L/h/m^2) increased by 23%.

Figure 2: Individual and typical normalised clearance and volume versus BSA by presence (closed circles, upper curves) and absence (open circles, lower curves) of inducers at baseline



Presence of inducers was a covariate only for clearance. The population estimate of volume versus BSA was not dependent on inducers and so the curves on the right for presence and absence of inducers coincide. Model 12 upper panel; Model 19 (final model) lower panel; N=78.

Summaries of the model derived AUC, C_{min}, C_{max} and half-life from the final PK model based on the recommended starting dose of 4.5 mg/m^2 are shown in the Table 10 and 11.

Table 10: Summary of AUC (h x ng/mL) by age groups

Population	Subpopulation	N	Mean	SD	Min	Median	Max
All		78	299.0	143.2	105.6	270.5	923.4
Age	age<10 y	42	258.7	118.9	105.6	246.1	620.4
	10<=age<=18	26	322.3	155.5	114.0	289.6	923.4
	age>18 y	10	407.7	147.0	215.3	405.4	621.8
Inducer	Inducer off	42	333.7	132.8	105.6	292.4	621.8
	Inducer on	36	258.5	146.0	107.7	225.1	923.4
Inducer & age	Off & age<10 y	24	300.4	130.0	105.6	278.3	620.4
	Off & 10<=age<=18	12	336.9	102.7	137.4	346.1	532.1
	Off & age>18 y	6	460.6	137.8	255.6	448.1	621.8
	On & age<10 y	18	203.1	74.1	107.7	179.5	398.9
	On & 10<=age<=18	14	309.8	192.9	114.0	270.5	923.4
	On & age>18 y	4	328.3	138.3	215.3	293.6	510.6

Individual estimates from the final population PK model based on the recommended starting dose of 4.5 mg/m^2 rounded to the nearest whole number mg dose.

Table 11: Summary of steady state C_{min} (ng/mL) by age groups

Population	Subpopulation	N	Mean	SD	Min	Median	Max
All		78	5.3	3.4	1.1	4.4	21.1
Age	age<10 y	42	4.7	3.0	1.1	4.1	14.9
	10<=age<=18	26	5.5	3.8	1.5	4.5	21.1
	age>18 y	10	7.1	3.4	2.7	6.9	12.7
Inducer	Inducer off	42	6.4	3.1	1.1	5.7	14.9
Inducer	Inducer on	36	3.9	3.3	1.4	3.0	21.1
Inducer & age	Off & age<10 y	24	5.9	3.3	1.1	5.1	14.9
Inducer & age	Off & 10<=age<=18	12	6.1	2.1	2.2	5.9	9.5
Inducer & age	Off & age>18 y	6	9.0	2.9	4.5	8.6	12.7
Inducer & age	On & age<10 y	18	3.1	1.6	1.4	2.6	6.8
Inducer & age	On & 10<=age<=18	14	4.9	4.9	1.5	3.5	21.1
Inducer & age	On & age>18 y	4	4.2	1.6	2.7	4.2	5.8

Individual estimates from the final population PK model based on the recommended starting dose of 4.5 mg/m^2 rounded to the nearest whole number mg dose.

Table 12: Summary of steady C_{max} by age groups

Population	Subpopulation	N	Mean	SD	Min	Median	Max
All		78	23.7	10.0	9.2	21.5	61.7
Age	age<10 y	42	20.2	7.9	9.2	19.4	42.8
	10<=age<=18	26	26.1	10.3	10.5	24.7	61.7
	age>18 y	10	32.5	11.0	19.9	31.2	50.0
Inducer	Inducer off	42	25.0	9.2	10.7	22.3	44.5
	Inducer on	36	22.2	10.8	9.2	20.4	61.7
Inducer & age	Off & age<10 y	24	22.3	8.5	10.7	20.7	42.8
	Off & 10<=age<=18	12	26.0	7.8	11.3	27.0	42.0
	Off & age>18 y	6	33.9	9.8	19.9	33.8	44.5
	On & age<10 y	18	17.3	6.2	9.2	15.7	31.7
	On & 10<=age<=18	14	26.2	12.3	10.5	23.4	61.7
	On & age>18 y	4	30.4	14.0	20.3	25.6	50.0

Individual estimates from the final population PK model based on the recommended starting dose of 4.5 mg/m^2 rounded to the nearest whole number mg dose.

Table 13: Summary of steady half-life (h) by age groups

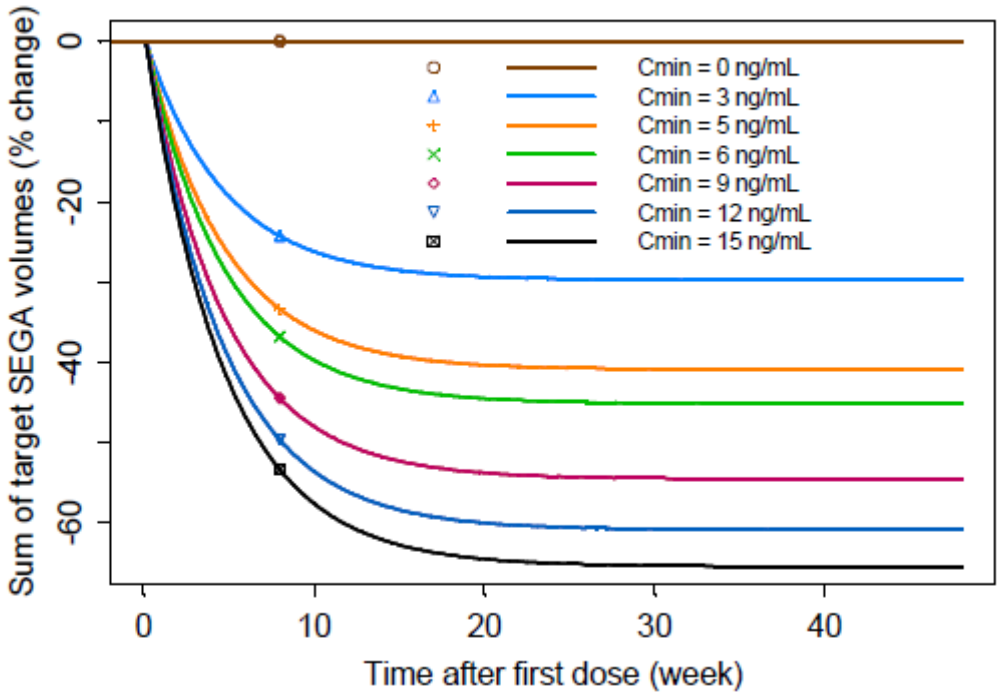
Population	Subpopulation	N	Mean	SD	Min	Median	Max
All		78	10.6	2.5	6.5	10.1	17.3
Age	age<10 y	42	10.9	2.8	6.5	10.2	17.3
	10<=age<=18	26	10.1	2.1	6.9	9.9	14.9
	age>18 y	10	10.5	2.2	7.4	11.1	13.8
Inducer	Inducer off	42	11.7	2.2	7.1	11.3	17.3
	Inducer on	36	9.2	2.1	6.5	8.9	16.7
Inducer & age	Off & age<10 y	24	11.9	2.7	7.1	11.1	17.3
	Off & 10<=age<=18	12	11.1	1.4	9.0	10.9	13.5
	Off & age>18 y	6	12.1	1.1	10.8	11.9	13.8
	On & age<10 y	18	9.5	2.2	6.5	9.1	16.7
	On & 10<=age<=18	14	9.2	2.1	6.9	8.7	14.9
	On & age>18 y	4	8.2	0.8	7.4	8.1	9.2

Individual estimates from the final population PK model based on the recommended starting dose of 4.5 mg/m^2 rounded to the nearest whole number mg dose.

The presence of inducers the percentage of patients with a steady state C_{min} less that 3 ng/mL was 44.4% as compared to 14.3% in the non-induced population.

Below is a figure with y-axis as tumour volume (percent change from baseline).While the model did not assume that patients' SEGA tumour volumes were at steady state, typical patients were estimated to be at steady state (Figure 3).

Figure 3: Percentage change in sum of target SEGA volumes over 48 weeks by steady state C_{min}



2.4.3. Pharmacodynamics

Primary and Secondary pharmacology

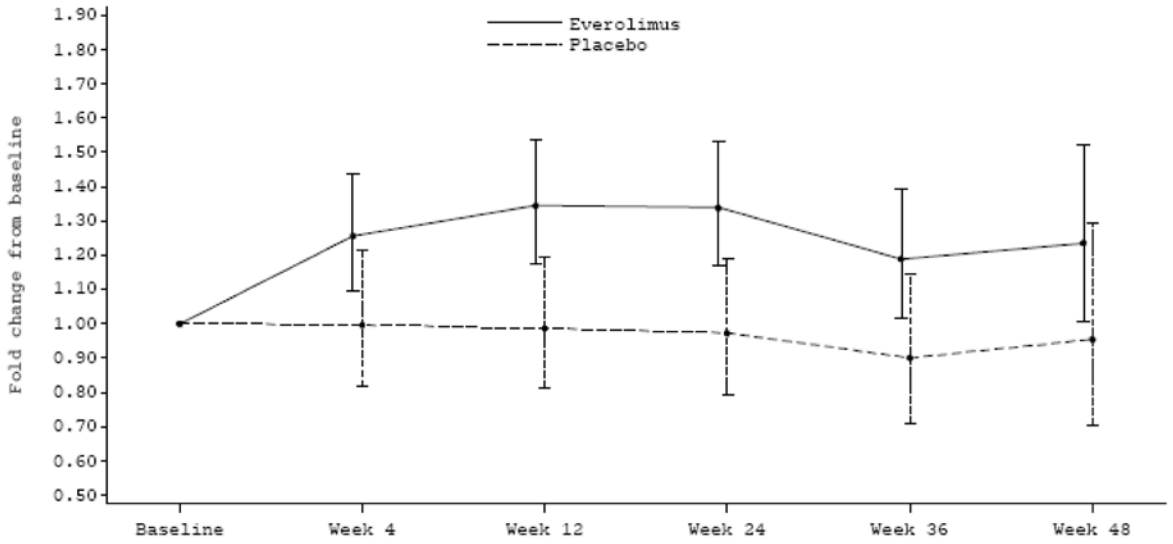
Evaluation of biomarkers were assessed in plasma samples collected during the conduct of study M2301 at screening, week 4, week 12, every 12 weeks until week 48 and at the end of treatment visit. Analyses were performed using standard enzyme-linked immunosorbent assay (ELISA) technology as well as by multiplexed MSD platform formatted as 4plex and 2plex combinations, following validation of the assay in accordance with the manufacturer's specifications.

The following biomarkers related to the angiogenesis pathway were analyzed: 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.

Figure 4 below shows longitudinal plots of 3 selected biomarkers (VEGF, soluble VEGFR-2, and collagen type 4).

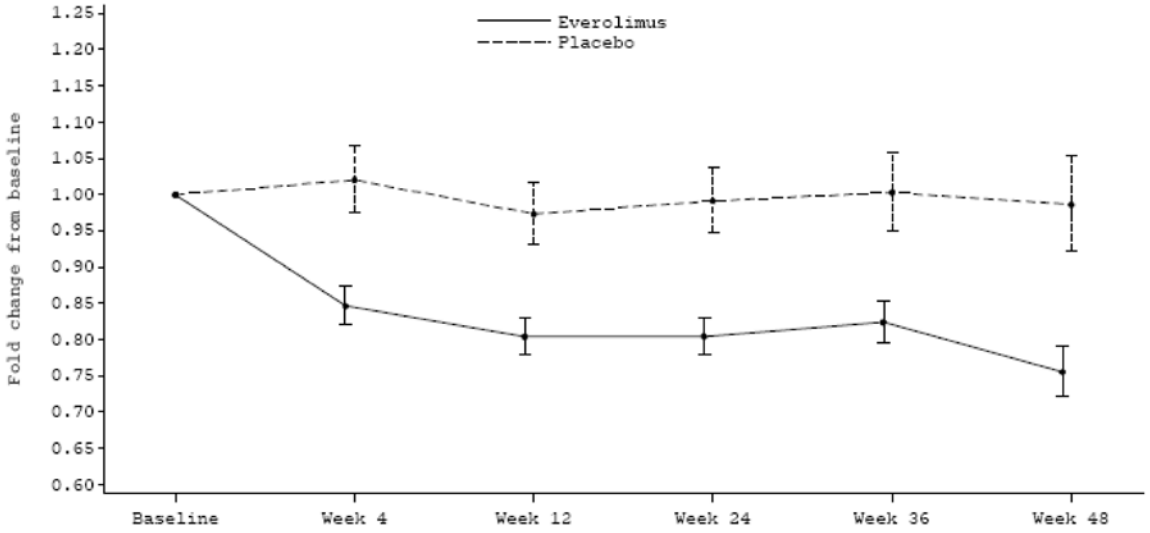
Figure 4: Longitudinal plots of mean VEGF, soluble VEGFR 2, and collagen type IV

VEGF



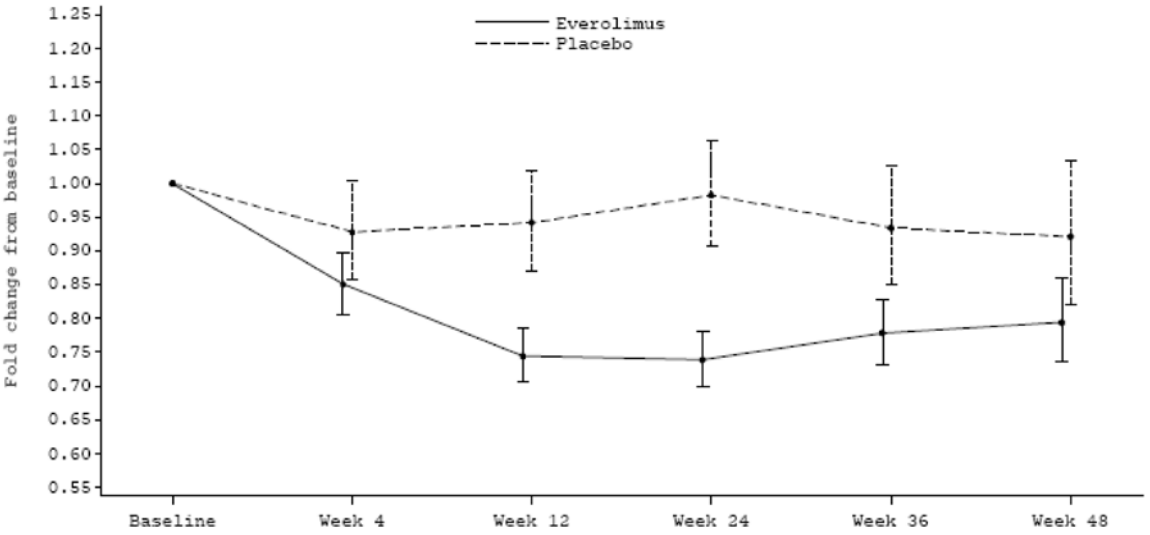
- Mean fold change and 95% confidence interval obtained using a mixed model including terms for baseline value, time and interaction between time and treatment.

Soluble VEGFR 2



- Mean fold change and 95% confidence interval obtained using a mixed model including terms for baseline value, time and interaction between time and treatment.

Collagen type IV



- Mean fold change and 95% confidence interval obtained using a mixed model including terms for baseline value, time and interaction between time and treatment.

Approximately 20% decrease in sVEGFR2 and collagen type IV and an initial and sustained increase in VEGF levels in everolimus-treated patients compared to placebo-treated patients with TSC who have SEGA has been observed.

2.4.4. Discussion on clinical pharmacology

Results of the pharmacology studies show that dissolution of intact tablets (both non-dispersible and dispersible) in water affects PK behaviour of the substance: C_{max} is significantly lower than after swallowing intact tablets although AUC does not seem to be affected. These results show that intact standard tablets and dispersible tablets cannot be used interchangeably. A statement has been included in the SmPC in section 4.2 on the interchangeability of the pharmaceutical forms. The lower C_{max} is considered to be the result of incomplete swallowing of the solution. Taken the small difference

of the AUCs into consideration, the dispersible tablets can be used in patients who cannot swallow intact tablets (such as e.g. suckling babies) provided that c_{trough} is monitored as recommended in the SmPC.

The MAH submitted a study demonstrating bioequivalence between the 5 mg and 2 mg dispersible formulations and received a biowaiver for the 3 mg tablet.

Dosing based on Body Surface Area was justified by the reduced variability in drug clearance when normalised for BSA compared to the variability observed when normalised for weight. A new section on dosing based on BSA using the Dubois formula was introduced in section 4.2 of the SmPC. Simulations based on the population pharmacokinetic model indicated that the presence of inducers increased both apparent and BSA-normalised clearance by 23%. Furthermore, in the presence of inducers the percentage of patients with a steady state C_{min} less that 3 ng/mL was 44.4% as compared to 14.3% in the non-induced population.

The MAH provided data on biomarkers related to the angiogenesis. The analysis showed an increase in VEGF and collagen type IV expression and a decrease in VEGFR2 expression in plasma of patients treated with everolimus compared to placebo treated patients. The data on the levels of VEGF was included in section 5.1 of the SmPC.

The MAH proposed a new starting dose of 4.5 mg/m^2. The results from population PK and PK/PD modelling study showed that 4.5 mg/m^2 starting dose appears acceptable across the age range. In addition, the actual starting dose of the pivotal study M2301 was also 4.5 mg/m^2 whereas study C2485 used a starting dose of 3.0 mg/m^2/day. The increase to 4.5 mg/m^2/day in study M2301 was initiated in order to enable patients to reach the target trough concentration earlier and on the observation that the maximum tolerated dose in paediatric patients[8] was 5.0 mg/m^2. The majority of the questions around the reliability of the population PK model have been sufficiently resolved to endorse the model-based justifications of the starting dose until further data and analyses are available. Thus, the new starting dose is justified.

The MAH proposed to widen the trough target range from 5-15 ng/ml to 3-15 ng/ml. This proposal was withdrawn by the MAH during the procedure.

The MAH applied for a change in the indication to “Votubia is indicated for the treatment of patients with SEGA associated with TSC who require therapeutic intervention and who are not likely to require surgery”. The MAH submitted a discussion on the need to treat patients with demonstrated SEGA growth (as measured by volume increase) regardless of the size of the lesions. Since SEGA lesions can develop by the age of below one, the MAH proposed to also include the paediatric patient population as they that may also require therapeutic intervention early in the disease. The CHMP had concerns over reports of SEGA regrowth following treatment withdrawal and the potential for complications following rapid re-bound growth and lesion progression or haemorrhage due to size fluctuation. The main concern was that this could lead to a lost opportunity for an early potentially curative neurosurgical resection. The MAH responded that they did not have clinical trial experience with the use of everolimus for the purpose of SEGA reduction with the intent of performing tumour resection. In the absence of such data, the MAH withdrew the proposal during the procedure.

[8] Fouladi M, Laningham F, Wu J, et al. (2007). Phase I study of everolimus in padiatric patients with refractory solid tumors; vol25, 30:4806-4812

2.4.5. Conclusions on clinical pharmacology

The updated data submitted for studies C2485 and M2301 confirms the previous data submitted at the time of the marketing authorisation, that there was a statistically significant correlation between C_{min} and absolute SEGA volume reduction and between C_{min} and percentage SEGA volume reduction.

The population pharmacokinetic model supports the starting dose of 4.5 mg/m^2.

The plasma angiogenesis markers did not have either prognostic or predictive values.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

- Additional data and analyses are planned to be submitted in September 2013. These will comprise 1) a subset of 20 or more patients to have PK profiles with less sparse data, 2) longer follow-up PK data through 3.5 years, and 3) up to 39 additional patients – those randomized to placebo who switched to everolimus. This should improve understanding and the accuracy and precision of estimates of clearance and of the effects of BSA and Cytochrome p450 3A4 (CYP3A4) and PgP inducers on clearance.

2.5. Clinical efficacy

2.5.1. Main study

Study M2301: 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)

Methods

Trial M2301 is an ongoing, prospective, double-blind, randomized, parallel-group, placebo-controlled, multi-centre phase III trial evaluating treatment with everolimus versus placebo in patients with TSC-associated SEGA.

The trial was separated by 3 treatment phases as follows:

- **Core treatment phase**: the period lasting from randomization of the first patient until the last randomized patient was treated with everolimus or placebo for 6 months. The core treatment phase was divided into the following:
    - Double-blind treatment period.
    - Open-label period in which patients who had been receiving placebo and experienced a SEGA progression (as per central review or unequivocal progression according to investigator assessment) during the blinded treatment phase were offered open-label everolimus.
- **Extension phase**: if superiority of everolimus was shown during the core treatment phase, an extension phase was to be launched.
- **A follow-up period**, in which all patients were to have a follow-up visit scheduled 28 days after the last dose of study treatment to assess adverse events (AEs) and serious adverse events (SAEs) that could have occurred after discontinuation from study treatment, was also conducted for both core and extension phases.

Study Participants

Main inclusion criteria selected for patients, irrespective of age, was patients with TSC associated SEGA and radiological evidence of at least one of the following three conditions prior to randomisation: (1) serial SEGA growth; (2) presence of a new SEGA lesion; (3) new or worsening hydrocephalus. Relevant exclusion criterion was patients for whom SEGA related surgery was likely to be required as per the opinion of the investigator.

Treatments

The study protocol required the titration of everolimus from an initial starting dose of 4.5 mg/m^2/day, subject to tolerability, with the objective of attaining trough concentrations in the 5-15 ng/mL range. Regular trough monitoring was to be performed throughout the study. Trough (pre-dose) blood levels of everolimus were assessed after 2 weeks of initial treatment, at each clinic visit, and 1-2 weeks after starting an increased dose at a new level, or any decrease in an enzyme-inducing drug, or any increase in an enzyme-inhibiting agent. Treatment duration was not specified and continued until SEGA progression or unacceptable toxicity. The core treatment phase corresponded to the period between the randomisation of the first patient and the last randomised patient completing 6 months of treatment.

Objectives

The primary objective of this study was to compare SEGA response rate on everolimus versus placebo in patients with TSC-associated SEGA irrespective of age.

Key secondary study objectives were to compare everolimus vs. placebo in a pre-defined sequence with respect to:

1. Change from baseline in frequency of epileptiform events

2. Time to SEGA progression

3. Skin lesion response rate

Outcomes/endpoints

The primary efficacy endpoint was SEGA response rate (as determined by independent central radiology review). SEGA response was defined as: (1) a ≥ 50% reduction in SEGA volume relative to baseline (where SEGA volume was the sum of all target SEGA lesion volumes identified at baseline); and (2) no unequivocal worsening of non-target SEGA lesions, no new SEGA lesions (≥ 1 cm in longest diameter), and no new or worsening hydrocephalus.

Key secondary efficacy endpoints included: absolute change in total seizure frequency per 24 hours from baseline to Week 24, time to SEGA progression (TTSP), and skin lesion response rate.

Safety endpoints were rate, type, severity, and causal relationship of AEs and SAEs to treatment. Safety and tolerability were assessed according to NCI CTCAE criteria.

Sample size

The planned sample size was 99 patients.

Randomisation

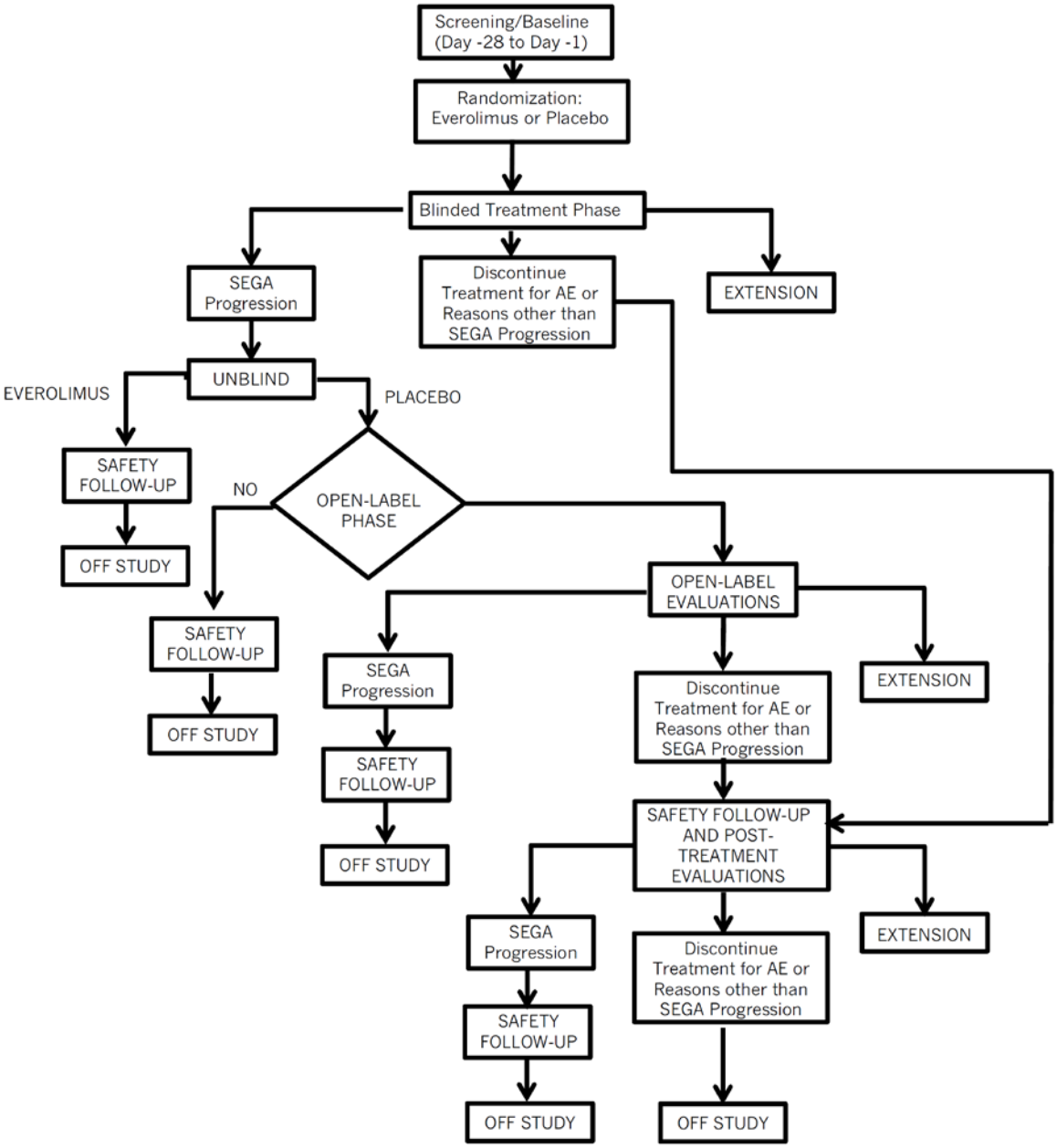
Patients were randomised in a 2:1 ratio to receive treatment with either everolimus or placebo. Randomisation was stratified by the use of enzyme-inducing anti-epileptic drugs (EIAEDs).

Blinding (masking)

The study was designed as a double-blind study. The extension and follow up phase of the study was open label.

Results

Participant flow



Safety Follow-Up: Collection of AEs and SAEs that occur within 28 days of treatment discontinuation. SAEs suspected to be related to study drug were collected for an additional 8 weeks (56 days).

Post-Treatment Evaluations: MRI of the brain (and MRI/CT of the kidneys, if applicable) annually

Open-Label Evaluations: MRI of the brain (and MRI/CT of the kidneys, if applicable) was to be done 12, 24, and 48 weeks after the start of open-label everolimus and annually thereafter. Safety and efficacy assessments were to be carried out as in the blinded treatment phase (with the exception of biomarker assessments, which were not performed in the open-label phase).

Recruitment

One-hundred-seventeen patients with SEGA associated with TSC were enrolled to this study from 24 centres in 10 countries.

Conduct of the study

Of 117 individuals enrolled in the trial, 78 were randomised to treatment with everolimus and 39 to treatment with placebo between 20 August 2009 and 02 Sepember 2010. A total of 5 patients randomised to placebo switched to open-label treatment with everolimus and were included in the open-label population. The final primary analysis used data up to the cut-off date of 02 March 2011, which was 6 months after the last patient was randomised. The database was locked and unblinded on 05 May 2011. At the end of the core treatment phase and based on the efficacy results, the Study Steering Committee (SSC) met on 13 May 2011 and recommended to unblind the study and that all patients be offered the opportunity to receive open-label treatment with everolimus. The study is currently on-going. Updated results from the 2-year analysis correspond to a cut-off date of 31 December 2010.

Table 14: Patient disposition

	Everolimus	Placebo
Randomised	78	39
Ongoing in double-blind treatment	76 (97.4%)	31 (79.5%)
Reason for discontinuation		
Withdrew consent	1	1
Lost to follow-up	1	0
Disease progression	0	6
Non-compliance with visits	0	1
Duration of exposure (weeks)		
<12	0	0
12 to <24	0	4 (10.3%)
24 to <36	28 (35.9%)	15 (38.5%)
36 to <48	23 (29.5%)	7 (17.9%)
≥48	27 (34.6%)	13 (33.3%)

Baseline data

Demographic characteristics and disease (TSC and SEGA respectively) characteristics at baseline are displayed in Table 15, Table 16, and Table 17 respectively:

Table 15: Demographic characteristics - Full Analysis Set

Demographic characteristic	Everolimus N=78	Placebo N=39
Age (years)		
Mean (standard deviation)	10.1 (5.9)	10.3 (7.3)
Median	9.5	7.1
Range	1.0 to 23.9	0.8 to 26.6
Age group (years) - n (%)		
< 3	13 (16.7)	7 (17.9)
3 - < 18	55 (70.5)	26 (66.7)
≥ 18	10 (12.8)	6 (15.4)
Gender - n (%)		
Male	49 (62.8)	18 (46.2)
Female	29 (37.2)	21 (53.8)
Weight - n (%)		
Mean (standard deviation)	38.7 (22.8)	39.5 (24.5)
Median	31.4	27.1
Range	9.0 to 107.8	7.9 to 94.0
Height - n (%)		
Mean (standard deviation)	133.9 (28.9)	133.0 (35.8)
Median	133.5	123.0
Range	76 to 182	71 to 192
Body surface area (m^2)		
Mean (standard deviation)	1.2 (0.5)	1.2 (0.5)
Median	1.1	1.0
Range	0.4 to 2.2	0.4 to 2.1
Race - n (%)		
Caucasian	73 (93.6)	36 (92.3)
Black or African American	3 (3.8)	1 (2.6)
Pacific Islander or Native Hawaiian	1 (1.3)	0
Asian	0	0
American Indian or Alaska Native	0	0
Other [a]	1 (1.3)	2 (5.1)
Ethnicity - n (%)		
Not Hispanic/Latino	76 (97.4)	35 (89.7)
Hispanic/Latino	2 (2.6)	4 (10.3)

[a] 'Other' was applied to patients who were of mixed race

Table 16: TSC characteristics at baseline - Full Analysis Set

	Everolimus N=78 n (%)		Placebo N=39 n (%)	
Diagnosis of TSC	**78**	**(100.0)**	**39**	**(100.0)**
At least two major features	78	(100.0)	39	(100.0)
TSC diagnosis criteria (modified Gomez)				
Major features				
Subependymal giant cell astrocytoma	78	(100.0)	39	(100.0)
Subependymal nodule	73	(93.6)	37	(94.9)
Cortical tuber [a]	71	(91.0)	38	(97.4)
Hypomelanotic macules (≥ 3)	70	(89.7)	36	(92.3)
Facial angiofibromas or forehead plaque	60	(76.9)	30	(76.9)
Cardiac rhabdomyoma, single or multiple	49	(62.8)	22	(56.4)
Renal angiomyolipoma [b]	47	(60.3)	28	(71.8)
Shagreen patch (connective tissue nevus)	37	(47.4)	23	(59.0)
Non-traumatic ungual or periungual fibroma	12	(15.4)	14	(35.9)
Multiple retinal nodular hamartomas	11	(14.1)	9	(23.1)
Lymphangioleiomyomatosis [b]	1	(1.3)	0	
Minor features				
Multiple renal cysts	31	(39.7)	9	(23.1)
Cerebral white matter radial migration lines [a]	14	(17.9)	6	(15.4)
Gingival fibromas	10	(12.8)	10	(25.6)
Multiple, randomly distributed pits in dental enamel	10	(12.8)	6	(15.4)
Confetti skin lesions	9	(11.5)	7	(17.9)
Non-renal hamartoma	6	(7.7)	4	(10.3)
Retinal achromic patch	4	(5.1)	3	(7.7)
Bone cysts	2	(2.6)	0	
Hamartomatous rectal polyps	0		0	

Table 17: SEGA characteristics at baseline - Full Analysis Set

	Everolimus N=78 n (%)		Placebo N=39 n (%)	
Patients with worsening SEGA compared with pre-baseline [a]	**66**	**(84.6)**	**34**	**(87.2)**
Serial growth	63	(80.8)	32	(82.1)
New SEGA lesion ≥ 1 cm in longest diameter	7	(9.0)	5	(12.8)
New or worsening hydrocephalus	5	(6.4)	0	
Number of target SEGA lesions				
0	2	(2.6)	0	
1	40	(51.3)	25	(64.1)
2	34	(43.6)	14	(35.9)
3	1	(1.3)	0	
≥ 4	1	(1.3)	0	
Number of non-target SEGA lesions				
0	46	(59.0)	20	(51.3)
1	28	(35.9)	16	(41.0)
2	2	(2.6)	2	(5.1)
3	2	(2.6)	1	(2.6)
SEGA volume (sum of volumes of target SEGA lesions [cm^3])				
n	76 [b]		39	
Mean (standard deviation)	2.83	(3.82)	1.77	(1.68)
Median	1.63		1.30	
Range	0.18 to 25.15		0.32 to 9.75	
Hydrocephalus				
Yes	8	(10.3)	0	
No	70	(89.7)	39	(100.0)
Any prior anti-SEGA medication/surgery				
Surgery	6	(7.7)	2	(5.1)

[a] Patients may satisfy more than one criterion for worsening SEGA compared with pre-baseline. The assessments are as per central review.
[b] Two patients were excluded due to the absence of target SEGA lesions

Source: Table 14.1-3.3 and Table 14.1-3.7

Numbers analysed

Four patients were excluded from the per-protocol set – two everolimus patients because their best SEGA response was 'not evaluable', one everolimus patient because of insufficient treatment exposure, and one placebo patient who received an incorrect medication packet (though it transpired after un-blinding that the incorrect packet still contained placebo).

Table 18: Subject Accountability

Analysis population	Everolimus N=78 n (%)		Placebo N=39 n (%)	
Full Analysis Set (FAS)	**78**	**(100.0)**	**39**	**(100.0)**
EIAED at randomization	15	(19.2)	7	(17.9)
No EIAED at randomization	63	(80.8)	32	(82.1)
Per Protocol Set (PPS)	**75**	**(96.2)**	**38**	**(97.4)**
EIAED at randomization	15	(19.2)	7	(17.9)
No EIAED at randomization	60	(76.9)	31	(79.5)
Safety Set	**78**	**(100.0)**	**39**	**(100.0)**
EIAED at randomization	15	(19.2)	7	(17.9)
No EIAED at randomization	63	(80.8)	32	(82.1)
Open-label everolimus population	**0**		**5**	**(12.8)**
EIAED at randomization	0		1	(2.6)
No EIAED at randomization	0		4	(10.3)

Patients in the FAS, PPS, and open-label everolimus population are presented according to the randomized treatment groups whilst those in the Safety Set are presented according to the actual treatment groups

Outcomes and estimation

Primary endpoint

Analysis of the primary endpoint demonstrated an overall SEGA response rate of 34.6% as per central radiology review, relative to 0% for placebo (p< 0.0001) (Table 19).

Table 19: Best overall SEGA response as per central radiology review – Full Analysis Set

	Everolimus N=78		Placebo N=39		p-value [a]	Difference in response rates [95% CI] [b]
Best overall SEGA response - n (%)						
Response	27	(34.6)	0			
Stable disease	49	(62.8)	36	(92.3)		
Progression	0		3	(7.7)		
Not evaluable	2	(2.6)	0			
Primary analysis						
SEGA response rate - n (%)	27	(34.6)	0		<0.0001	34.6 [15.1, 52.4]
95% CI for SEGA response rate [c]	[24.2, 46.2]		[0.0, 9.0]			

[a] p-value is obtained from the one-sided exact Cochran-Mantel-Haenszel test, stratified by the protocol stratification factor (EIAED use versus EIAED non-use)
[b] Difference in response rates (everolimus minus placebo). Exact 95% CI obtained from the exact unconditional confidence limits.
[c] Exact 95% CI obtained from the Clopper-Pearson method

Source: Table 14.2-1.1

Supportive analysis

There are several supportive analyses, of which two results are described here:

A sensitivity analysis using exact logistic regression gave similar results as did an analysis using 'worsening' instead of 'progression' (worsening requires a >25% increase from nadir but without the requirement of increasing to a volume greater than baseline – the response rates in this analysis were 26 (33.3% vs. 0)).

Table 20: Change from baseline of sum of volumes of target SEGA lesions by time window – Full Analysis Set

Sum of volumes of target SEGA lesions (cm^3)	Everolimus N=78			Placebo N=39		
	Week 12 N=74	Week 24 N=74	Week 48 N=32	Week 12 N=39	Week 24 N=34	Week 48 N=14
Baseline (cm^3)						
Mean (standard deviation)	2.779 (3.823)	2.687 (3.598)	2.814 (4.689)	1.775 (1.681)	1.859 (1.775)	2.362 (2.454)
Median	1.585	1.627	1.076	1.300	1.323	1.323
Range	0.18 to 25.15	0.18 to 25.15	0.28 to 25.15	0.32 to 9.75	0.32 to 9.75	0.43 to 9.75
Value at the assessment (cm^3)						
Mean (standard deviation)	1.458 (1.546)	1.308 (1.365)	1.153 (1.255)	1.814 (1.766)	1.873 (1.827)	2.178 (2.243)
Median	0.917	0.909	0.559	1.362	1.413	1.424
Range	0.14 to 7.41	0.10 to 6.84	0.14 to 5.28	0.21 to 10.54	0.15 to 9.69	0.31 to 8.64
Change from baseline (cm^3)						
Mean (standard deviation)	-1.320 (2.586)	-1.379 (2.571)	-1.661 (3.744)	0.039 (0.277)	0.014 (0.231)	-0.184 (0.370)
Median	-0.566	-0.650	-0.487	0.006	0.005	-0.069
Range	-18.27 to 0.17	-19.07 to 0.14	-19.88 to 0.01	-0.55 to 0.79	-0.44 to 0.49	-1.12 to 0.28
Percentage change from baseline						
Mean (standard deviation)	-38.724 (19.507)	-43.951 (20.904)	-45.946 (21.629)	2.802 (21.577)	-3.175 (20.710)	-7.091 (18.993)
Median	-39.068	-47.693	-48.028	0.914	1.610	-6.244
Range	-75.00 to 10.07	-85.23 to 22.39	-88.96 to 0.77	-42.18 to 68.64	-58.46 to 36.58	-37.54 to 21.44

Sum of volumes of target SEGA lesions (cm^3)	Everolimus N=78			Placebo N=39		
	Week 12 N=74	Week 24 N=74	Week 48 N=32	Week 12 N=39	Week 24 N=34	Week 48 N=14
Percentage change from baseline [a]						
≤ -50%	22 (29.7)	31 (41.9)	14 (43.8)	0	1 (2.9)	0
≤ -30%	54 (73.0)	58 (78.4)	26 (81.3)	3 (7.7)	5 (14.7)	2 (14.3)
< 0%	71 (95.9)	71 (95.9)	31 (96.9)	18 (46.2)	17 (50.0)	9 (64.3)
≥ 0%	3 (4.1)	3 (4.1)	1 (3.1)	21 (53.8)	17 (50.0)	5 (35.7)
≥ 10%	1 (1.4)	1 (1.4)	0	11 (28.2)	8 (23.5)	3 (21.4)
≥ 25%	0	0	0	3 (7.7)	2 (5.9)	0

[a] Percentages are calculated relative to the number of patients N evaluated at baseline and the corresponding time window

Source: Table 14.2-1.5

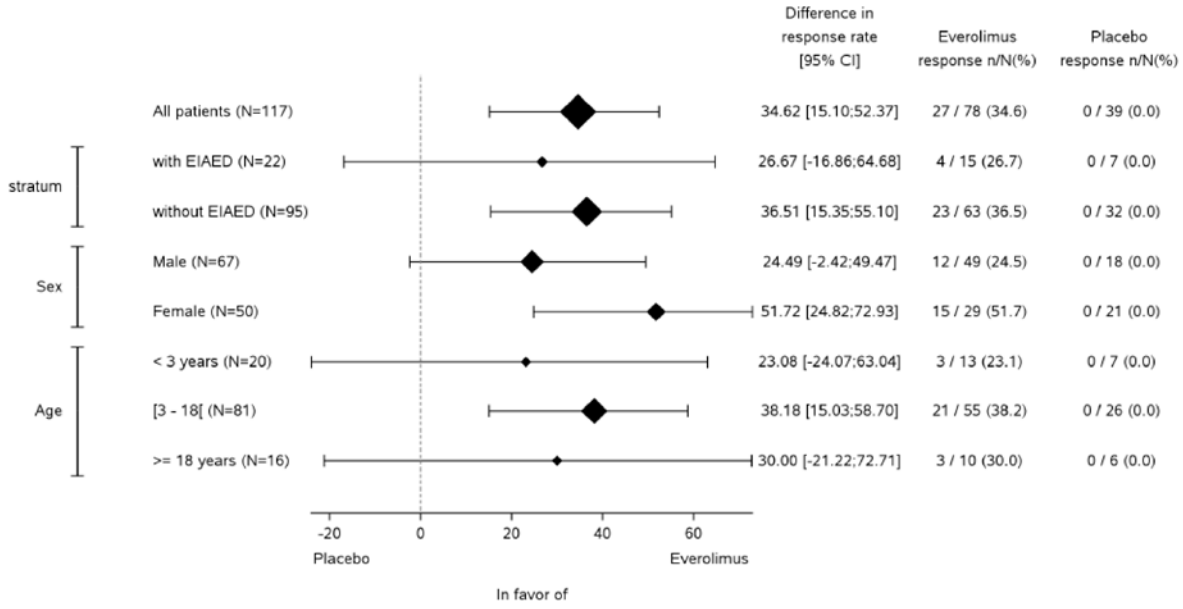
A higher proportion of patients in the everolimus arm at Weeks 12, 24, and 48 were reported with SEGA volume reductions ≥ 30% (73.0%, 78.4%, and 81.3%, respectively) and ≥ 50% (29.7%, 41.9%, and 43.8%, respectively) than those in the placebo arm (reductions ≥ 30%: 7.7%, 14.7%, and 14.3%, respectively; reductions ≥ 50%: 0%, 2.9%, and 0%, respectively).

All patients in the everolimus arm experienced a reduction in sum of volumes of target SEGA lesions relative to baseline in contrast to those on the placebo arm, where 66.7% experienced a reduction.

Change from baseline in target lesion volume (absolute and percentage change) were tabulated by treatment group. The greater decreases were seen on the everolimus group, supporting the primary findings. The change from baseline was evident at 12 weeks with a 39% mean percentage decrease at week 12 in the everolimus arm as compared to a 3% mean increase in the placebo arm. The effect was durable with a 46% mean percentage decrease in the everolimus arm at week 48 as compared to a 7% mean decrease in the placebo arm.

Concerning efficacy, Figure 5 below provides relevant information concerning the subgroup of patients younger than 3 years of age.

Figure 5: SEGA response by subgroup



Secondary efficacy results

Frequency of epileptiform events

No change in median seizure frequency was shown from baseline to Week 24 based on the last observation carried out (LOCF) approach for either treatment arm (0.00; 95% CI 0.00; 0.00), and no statistically significant difference was observed between groups (p=0.2004) (Table 21).

Table 21: Change from baseline to Week 24 (LOCF approach) in total seizure frequency per 24 hours from video EEG - Full Analysis Set

	Everolimus N=78	Placebo N=39
Baseline [a]		
N	78	39
Mean (standard deviation)	3.41 (8.36)	5.58 (14.98)
Median	0.00	0.00
Range	0.0 to 42.6	0.0 to 78.9
Week 24/LOCF [a]		
N	78	39
Mean (standard deviation)	2.17 (4.84)	5.33 (15.57)
Median	0.00	0.00
Range	0.0 to 31.6	0.0 to 91.5
Change from baseline to Week 24/LOCF		
N	78	39
Mean (standard deviation)	-1.24 (6.12)	-0.24 (5.70)
Median	0.00	0.00
Range	-34.0 to 13.0	-15.9 to 14.4
95% CI for median [b]	[0.00, 0.00]	[0.00, 0.00]
p-value for treatment effect [c]	0.2004	

Seizure frequency per 24 hours is calculated as 24*(raw count/actual duration of EEG recording [hours]) and was listed as missing if the actual EEG recording duration was < 18 hours

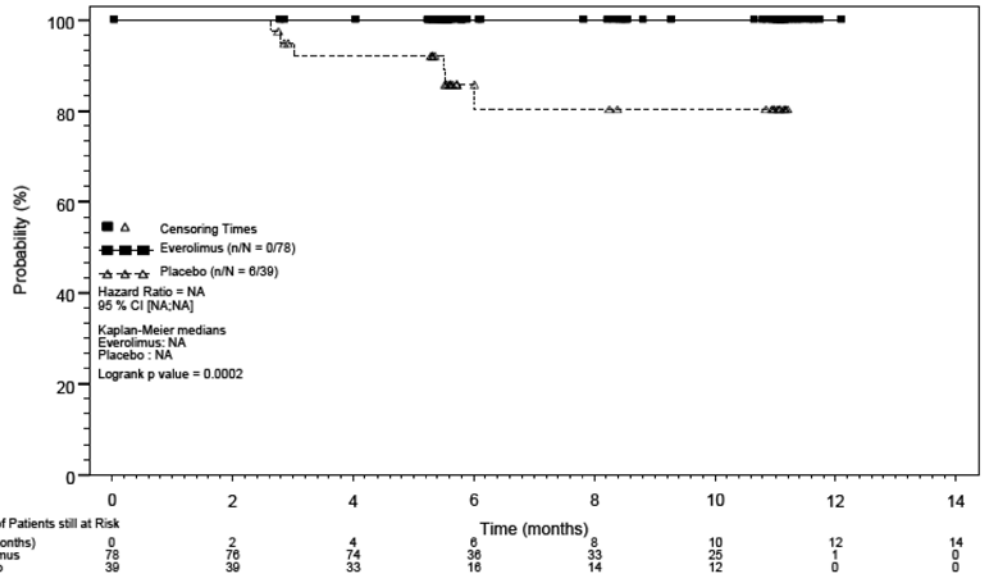
[a] Missing values were imputed as per LOCF method
[b] 95% CI of the median based on bootstrap percentiles
[c] p-value obtained from rank ANCOVA (one-sided test) with baseline seizure frequency as covariate, stratified by use of EIAED at randomization (EIAED use versus EIAED non-use)

Source: Table 14.2-2.1

Time to SEGA progression (TTSP)

The median time to SEGA progression (TTSP) based on central radiology review was not reached in either treatment arm; SEGA progressions were observed in the placebo treatment group (6 events 15.4%; stratified log-rank test p=0.0002) (Figure 6). The estimated progression-free rates at 6 months were 100% for the everolimus arm and 85.7% for placebo (P-value <0.025). However, the p-value was not statistically significant.

Figure 6: Kaplan-Meier plot of time to SEGA progression as per central radiology review - Full Analysis Set



p-value is obtained from the one-sided stratified log-rank test; hazard ratio was not estimated since all observed SEGA progressions occurred in one treatment arm

Source: Figure 14.2-2.1

Skin lesion response rate

Skin lesion response rate was 30% for everolimus treated patients compared to 4% with placebo-treated patients (p-value = 0.0004[one-sided exact CMH test]). No patient in either arm reported a complete clinical skin lesion response.

Table 22: Best overall skin lesion response as per investigator (in patients with at least one skin lesion at baseline) - Full Analysis Set

	Everolimus N=72		Placebo N=38		p-value [a]
Best overall skin lesion response					
Complete clinical response (CCR)	0		0		
Partial response (PR)	30	(41.7)	4	(10.5)	
Stable disease (SD)	42	(58.3)	33	(86.8)	
Progression	0		0		
Not evaluable	0		1	(2.6)	
Skin lesion response (CCR or PR) rate	**30**	**(41.7)**	**4**	**(10.5)**	**0.0004**
95% CI for skin lesion response rate [b]	[30.2, 53.9]		[2.9, 24.8]		

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

[b] Exact 95% CI obtained from the Clopper-Pearson method

Source: Table 14.2-4.1

Other secondary endpoints

Duration of SEGA response

No cases of SEGA progression were seen in the everolimus treatment arm. Responses were all ongoing and durations ranged from 63+ to 255+ days.

Time to SEGA response

Twenty-seven SEGA responses were reported in the everolimus treatment arm. The median time to SEGA response was 2.99 months coinciding with the time of the first assessment (95% CI: 2.79, 5.36), with a range from 77 to 179 days.

Time to SEGA worsening

The median value was not reached in either treatment arm. SEGA worsening was observed in 7 patients (9.0%) in the everolimus arm and in 8 (20.5%) in the placebo arm.

Duration of skin lesion response

Among the 30 patients with a skin lesion response in the everolimus treatment arm, there were no cases of skin lesion progression. Responses were ongoing in all cases and ranged from 70+ to 436+ days.

Interictal epileptiform discharge frequency

Overall, there was no difference observed in the change in the Awake IED frequency from baseline to Week 24 between everolimus-treated patients and those treated with placebo. This was also the case for the subset of patients with ≥ 1 Awake IED at baseline (N=62). Similar results were observed for Asleep IED frequency.

Change from baseline in plasma angiogenic markers

The evaluation of the change from baseline in plasma angiogenic molecules is currently ongoing.

Angiomyolipoma responses

Angiomyolipoma responses were observed solely in the everolimus arm (53.3%; 95% CI: 34.3, 71.7).

Table 23: Best overall angiomyolipoma response as per central review (in patients with at least one target angiomyolipoma lesion at baseline)– Full Analysis Set

	Everolimus N=30		Placebo N=14	
Best overall angiomyolipoma response				
Response	16	(53.3)	0	
Stable disease (SD)	9	(30.0)	10	(71.4)
Progression	0		3	(21.4)
Not evaluable	5	(16.7)	1	(7.1)
Angiomyolipoma response (CCR or PR) rate	**16**	**(53.3)**	**0**	
95% CI for angiomyolipoma response rate [a]	[34.3, 71.7]		[0.0, 23.2]	

[a] Exact 95% CI obtained from the Clopper-Pearson method

At Weeks 12, 24, 48, everolimus treatment resulted in greater median reductions by percentage change from baseline in the sum of target angiomyolipoma lesions (-52.2%, - 58.9%, and -68.7%, respectively) as compared to placebo (5.8%, 8.1%, and 24.0%, respectively). Only everolimus-treated patients were reported with angiomyolipoma reductions of ≥ 50% at Weeks 12, 24, and 48 (56.5%, 78.3%, and 80.0%, respectively), while higher percentages of patients in the everolimus arm were observed with angiomyolipoma reductions of ≥ 30% (82.6%, 100%, and 100%, respectively) than in those with placebo (8.3%, 18.2%, and 16.7%, respectively). These figures are based on best reductions at each time point and did not necessarily meet the criteria for response.

Hydrocephalus volume

All patients with hydrocephalus at baseline were randomised to the everolimus arm. All experienced a decrease in ventricular volume and no patients required surgical intervention for growing SEGA during the course of the study.

Ancillary analyses

- **Analysis of efficacy - open-label period for study M2301**

In the open-label period, 2 of the 5 patients who were initially treated with placebo and subsequently crossed over to the everolimus arm reported a SEGA response. The durations of response for these patients were 182+ days and 114+ days, respectively. Durations of therapy were 377 days and 204 days, respectively; prior to SEGA response, these patients received everolimus therapy for 161 days and 85 days, respectively. Both patients were female, < 10 years of age, and were not treated with EIAEDs. The remaining 3 patients were reported with stable disease, but all presented with a ≥ 40% reduction from baseline.

None of the patients were observed with new or worsening hydrocephalus, ventricular configuration changes/cap signs, or changes in CSF flow dynamics during the open-label period. None of the patients entering the open-label phase had either a target angiomyolipoma lesion or SEN lesion at baseline.

Supportive study

The MAH submitted a two years report on trial C2485 (data cut-off date 02 March 2011) as part of the renewal of Votubia. Twenty-eight patients with TSC who had SEGA were screened and subsequently enrolled between 07 January 2007 and 18 December2008. As of the 31 December 2010 data cut-off date, 25 out of 28 patients are ongoing in this study (same number of patients as the previous cut-off); all these 25 patients have ≥ 2 years of exposure.

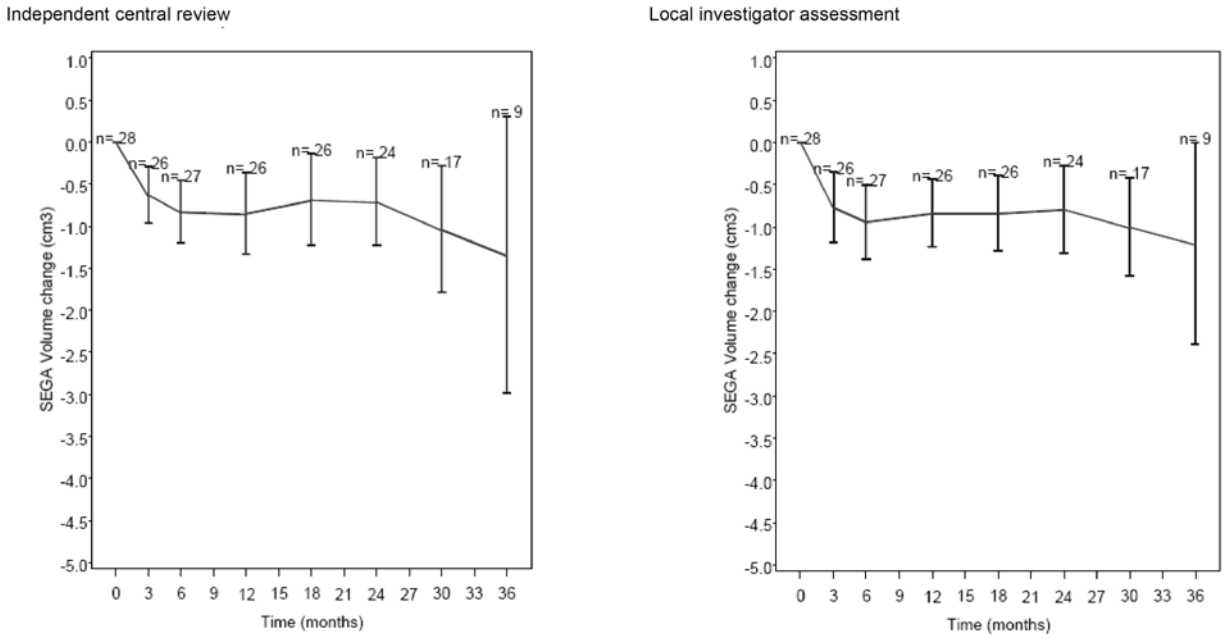
Primary endpoint: reduction in primary SEGA volume

Results from longer-term follow-up demonstrated that the positive effect on tumour burden was maintained with a median reduction in primary SEGA volume at Month 24 of 0.71 cm^3 (range: -0.55 to 9.60), with:

- 19 patients (79.2%) experiencing reductions of ≥ 30% relative to baseline
- 12 patients (50.0%) experiencing reductions of ≥ 50%

Figure 7 shows an updated median profile of primary SEGA volume shrinkage from baseline.

Figure 7: Median profile of primary SEGA volume shrinkage from baseline (FAS) - Study C2485 (data cut-off: 02 March 2011)



95% confidence intervals for the median reduction from baseline obtained by bootstrap simulation
Source: C2485 2-year Analysis – Figure 14.2-1.3

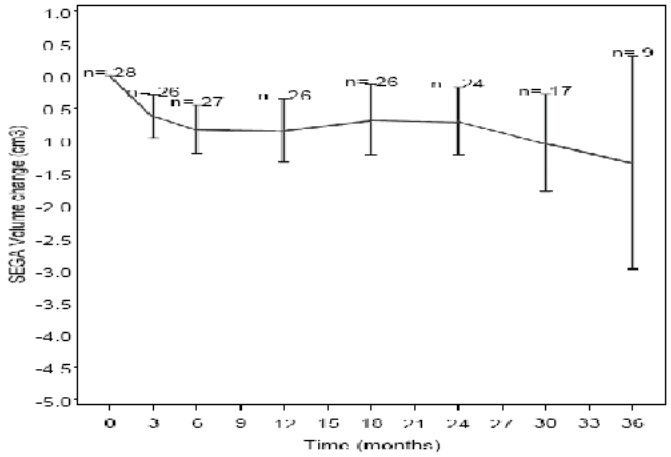
Results from the updated 2-year analysis in study C2485 are presented in Table 24 and Figure 8 and 9.

Table 24: Response of SEGA volume to everolimus therapy as per independent central review by time point in Phase II trial (FAS) – Study C2485

SEGA volume (cm^3)	Independent central review							
	Baseline N=28	Month 3 N=26	Month 6 N=27	Month 12 N=26	Month 18 N=26	Month 24 N=24	Month 30 N=17	Month 36 N=9
Primary tumor volume								
Mean (standard deviation)	2.45 (2.813)	1.47 (1.646)	1.33 (1.497)	1.26 (1.526)	1.28 (1.110)	1.19 (1.042)	1.49 (1.469)	1.17 (0.796)
Median	1.74	0.84	0.93	0.84	0.81	0.94	1.05	0.97
Range	0.49 - 14.23	0.25 - 8.32	0.31 - 7.98	0.29 - 8.18	0.33 - 5.20	0.20 - 4.63	0.40 - 6.27	0.39 - 2.70
Reduction from baseline								
Mean (standard deviation)		1.08 (1.338)	1.19 (1.433)	1.07 (1.276)	1.25 (1.887)	1.25 (1.994)	1.47 (2.123)	1.73 (1.710)
Median		0.63	0.83	0.85	0.69	0.71	1.04	1.34
Range		-0.12 - 5.91	0.06 - 6.25	0.02 - 6.05	-0.24 - 9.03	-0.55 - 9.60	-0.78 - 7.96	0.15 - 4.75
Percentage reduction from baseline, n (%)								
≥ 50%		10 (38.5)	9 (33.3)	9 (34.6)	11 (42.3)	12 (50.0)	7 (41.2)	5 (55.6)
≥ 30%		17 (65.4)	21 (77.8)	20 (76.9)	18 (69.2)	19 (79.2)	11 (64.7)	7 (77.8)
> 0%		25 (96.2)	27 (100.0)	26 (100.0)	24 (92.3)	23 (95.8)	15 (88.2)	9 (100.0)
No change		0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)
Increase		1 (3.8)	0 (0.0)	0 (0.0)	1 (3.8)	1 (4.2)	2 (11.8)	0 (0.0)
Total tumor volume								
Mean (standard deviation)	2.72 (2.815)	1.61 (1.649)	1.48 (1.506)	1.40 (1.530)	1.45 (1.141)	1.31 (1.020)	1.53 (1.455)	1.19 (0.800)
Median	1.77	1.02	1.04	0.93	0.98	1.18	1.08	0.97
Range	0.49 - 14.23	0.27 - 8.32	0.34 - 7.98	0.29 - 8.18	0.33 - 5.20	0.22 - 4.63	0.40 - 6.27	0.42 - 2.70
Reduction from baseline								
Mean (standard deviation)		1.16 (1.335)	1.31 (1.431)	1.22 (1.315)	1.37 (1.874)	1.40 (2.016)	1.51 (2.121)	1.76 (1.706)
Median		0.72	0.91	0.91	0.91	0.76	1.04	1.34
SEGA volume (cm^3)	Independent central review							
	Baseline N=28	Month 3 N=26	Month 6 N=27	Month 12 N=26	Month 18 N=26	Month 24 N=24	Month 30 N=17	Month 36 N=9
Range		-0.12 - 5.91	0.07 - 6.25	0.02 - 6.05	-0.24 - 9.03	-0.55 - 9.60	-0.78 - 7.96	0.16 - 4.75
Percentage reduction from baseline, n (%)								
≥ 50%		9 (34.6)	9 (33.3)	10 (38.5)	11 (42.3)	12 (50.0)	8 (47.1)	5 (55.6)
≥ 30%		18 (69.2)	24 (88.9)	19 (73.1)	19 (73.1)	19 (79.2)	11 (64.7)	8 (88.9)
> 0%		25 (96.2)	27 (100.0)	26 (100.0)	24 (92.3)	23 (95.8)	15 (88.2)	9 (100.0)
No change		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Increase		1 (3.8)	0 (0.0)	0 (0.0)	2 (7.7)	1 (4.2)	2 (11.8)	0 (0.0)

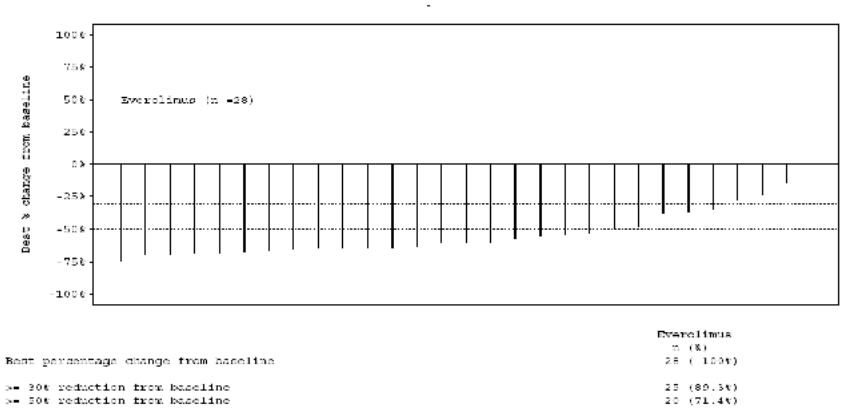
Magnetic resonance imaging assessments were assigned to time windows based on the scan date (constructed around the scheduled assessment time)
If 2 assessments were to occur within the same time window, that closest to the scheduled time of assessment was used in the analysis
Source: [C2485-2-Year CSR-Table 14.2-1.5], [C2485-2-Year CSR-Table 14.2-1.7], [C2485-2-Year CSR-Listing 14.2-1.3], and [C2485-2-Year CSR-Listing 14.2-1.4]

Figure 8: Median profile of primary SEGA volume shrinkage from baseline (independent central review) in Phase-II trial (FAS) – Study C2485



95% confidence intervals for the median reduction from baseline obtained by bootstrap simulation.

Figure 9: Tumour shrinkage: maximum percentage change from Baseline in primary SEGA volume (independent central review) in Phase-II trial (FAS) – Study C2485



Best percentage change equates to the largest tumor shrinkage at any post-baseline time point relative to baseline

At month 24, 50% of patients were still maintaining a >50% reduction in SEGA volume (n=24), whilst at month 36 this was 55.6% although fewer patients contributed to the 36 month data (n=9).

An updated 3-year analysis was presented for study C2485 in the context of the 2nd annual reassessment/renewal. Twenty-eight patients with TSC who had SEGA were screened and subsequently enrolled between 07 January 2007 and 18 December 2008. As of the 14 December 2011 data cut-off date, 24 out of 28 patients are ongoing in this study (one patient less as compared to the previous cut-off); all these 24 patients have ≥ 3 years of exposure.

The 2 years report does not provide new insights in most of the secondary endpoints (such as Seizure frequency, Quality of life, Neuropsychometric functioning etc.), except for the following:

Duration of response

Of the 25 patients with a ≥ 30% reduction in primary SEGA volume, two patients met the definition for progression (i.e., an increase from nadir of ≥ 25% to a value greater than baseline) at any later time point. The median time from first response to progression/censoring was 23.79 months (range: >0.0 to 39.4).

Response of facial angiofibromas

Responses of facial angiofibromas continue to show improvement with time. At Month 18, 7 of 9 patients showed improvement which rises to 8 of 9 patients at Month 24, and 9 of 9 patients at Month 30.

Discussion on clinical efficacy

The efficacy data was reviewed during the renewal procedure for Votubia. The MAH re-submitted two study reports from the renewal procedure, the updated 2 and 3–year analysis for the uncontrolled trial C2485 and the study report for the double bind placebo-controlled trial M2301.

M2301 has now transitioned from the placebo-controlled double-blind sequence to open–label where patients with evidence of progression were able to cross over from placebo arm to the everolimus arm. Data on best overall response rate from the double-blind sequence of the trial was available for up to 48 weeks in some patients, although the median duration of treatment was 45 weeks on everolimus and 41 weeks on placebo.

In study M2301, a reduction in SEGA volume from baseline of >50% was defined as a response. Using this definition, the best overall response rate on everolimus was 34.6% (95% CI 24.2-46.2%) as compared to 0 (95% CI 0-9%) on placebo (p<0.0001). The reduction in SEGA volume was evident by week 12 and was durable. The mean percentage decrease in SEGA volume from baseline was 39% at week 12 in the everolimus arm as compared to a 3% mean increase in the placebo arm. A 46% mean percentage decrease in the everolimus arm was observed at week 48 as compared to a 7% mean decrease in the placebo arm. In addition, in patients with hydrocephalus at baseline, a reduction in ventricular volume was also observed. Consistency of effect was demonstrated across all subgroups, irrespective of use of enzyme-inducers, age or gender.

6 patients in the placebo arm discontinued treatment due to disease progression. All 6 were offered open-label everolimus. Of these, 2 patients experienced a SEGA response, whilst 3 experienced stable disease. All presented with >40% reduction from baseline in SEGA volume. One patient only started everolimus one day prior to the data cut-off date and therefore data was not included.

A key secondary endpoint was change from baseline to week 24 in total seizure frequency. This analysis was not statistically significant between the two treatment groups (p=0.2004). However, as most patients did not have any seizures at baseline, the analysis is not particularly meaningful. A further sensitivity analysis restricted to patients with seizures at baseline was also inconclusive as there was an imbalance in the baseline seizure frequency with a higher frequency in the placebo arm versus everolimus (median 11 versus 5.5).

The other two key secondary endpoints were TTSP and worsening of skin lesions. Both demonstrated a statistically significant difference from placebo (p=0.0002 and p=0.0004, respectively), however, the data could not be formally declared as significant due to the pre-defined testing hierarchy and the failure of the seizure frequency endpoint.

Effects of everolimus as compared to placebo were also noted for the angiomyolipoma lesions (AML) in SEGA patients. The best overall response rate (for percentage reductions of >50%) was 53.3% as compared to 0 on placebo.

The updated 2–year as well as the available 3–year analysis from Study C2485, confirms that the SEGA response in patients is long-lasting in patients on treatment, with a durable response of >50% reduction from baseline observed in 34.6% at month 12, 50% at month 24 and 55.6% at month 36 as per independent radiology review. Whilst two patients met the criteria for progression, the investigator did not discontinue treatment as patients were obtaining ongoing symptomatic clinical benefit. Subsequent radiographic evaluations revealed stabilisation or shrinkage of the tumour in these two patients.

Study C2485 also described a durable improvement in facial angiofibroma lesions with 7 out of 9 patients showing improvement at month 18. This rose to 9 out of 9 patients at month 30.

There were 13 SEGA patients in the subgroup < 3 years treated with everolimus in the M2301 study. These patients were successfully treated and SEGA response in favour of everolimus was observed in patients < 3 years of age treated with everolimus compared to placebo (difference in response rate 23.08; 90% CI: -24.07 – 63.04). Thus, these results justify the elimination of the age limit “aged 3 years and older” from the current indication.

The analysis of reduction in seizure frequency at 24 weeks, which was a key secondary endpoint in study M2301, did not demonstrate a statistically significant difference between everolimus and placebo.

Additional expert consultation

The CHMP addressed the following questions to the PDCO:

1. Does the PDCO consider that there is a clear need for everolimus treatment in patients less than 3 years old who require therapeutic intervention, for whom neurosurgery is not an option?

2. What would be the clinical relevance of everolimus treatment in patients less than 3 years old if most patients in this age group do not require interventional treatment, or would be amenable to neurosurgery?

On February 08, 2013, the PDCO issued the following opinion:

1. The PDCO considers that there is a clear need for everolimus treatment in patients less than 3 years old who require therapeutic intervention, for whom neurosurgery is not an option.

2. Everolimus treatment in patients less than 3 years old could be of clinical relevance.

In addition to adopting the above answers, the PDCO noted the safety concerns with respect to a use in children younger than 3 years of age, according to the CHMP assessment of the results of the clinical and non-clinical studies.

The PDCO recently agreed on further paediatric trials with everolimus, targeting to treat paediatric patients with refractory partial-onset seizures (POS) associated with tuberous sclerosis (TSC) complex. For these, a separate PIP (EMEA-000019-PIP08-12) had to be agreed. Preliminary clinical data indicated that everolimus may reduce seizure frequency in TSC patients with refractory epilepsy (POS). This may allow concurrent AEDs to be reduced or discontinued, which the PDCO considers a relevant clinical benefit. This was the background for the proposal by the applicant and for the PDCO for studies of everolimus in children with infantile spasms as young as from 1 month of age onwards.

During the discussion of this development, the PDCO and its non-clinical expert group considered that non-clinical studies in various species did not suggest toxicity of concern for this age group so that juvenile toxicity studies were not requested.

The CHMP assessment considers that findings of delayed developmental landmarks in juvenile rats and the disruption of cortical lens fibers are of concern.

The PDCO shares the concern and there may be a need for further data.

2.5.2. Conclusions on the clinical efficacy

The updated 2 and 3–year results from study C2485 and the results from the double blind sequence of study M2301 confirm that treatment with everolimus reduces the volume of SEGA lesions to <50% from baseline and that this response is durable. In study M2301, the best overall response rate was 34.6% on everolimus as compared to 0% on placebo ($p<0.0001$). These results support the conclusions of the original analysis and demonstrate sustained benefit in SEGA patients. In addition, data on the patient subgroup < 3 years treated with everolimus showed a marked difference in SEGA response rate in favour of everolimus as compared to placebo. Thus, the elimination of the age limit "aged 3 years and older" from the current indication was accepted.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR refers to the EURD list which remains unchanged.

2.6. Clinical safety

Patient exposure

Overall, exposure to everolimus was considered appropriate to allow an assessment of safety in a population representative of patients with TSC who have SEGA. In Study M2301, the median duration of therapy with everolimus was 9.6 months (range: 5.5 to 18.1) with 50 patients (64.1%) exposed to everolimus for a period of ≥ 8.3 months; while the median study follow-up was 9.7 months. Total exposure amounted to 66.5 patient-years with everolimus versus 30.8 patient-years for those who received placebo. The median dose intensity for patients in the everolimus arm was 5.9 mg/m^2/day (range: 2.3 to 11.8).

In study C2485 the median duration of therapy with everolimus was 34.2 months (range: 4.7 to 47.1). Total exposure amounted to 75.6 patient-years. In total, 25 (89.3%) patients were exposed to everolimus for ≥ 2 years. The median dose intensity was 5.3 mg/m^2/day (range: 2.1 to 12.3).

Adverse events

Common AEs by system organ class in Study M2301

Overall, AEs were experienced by 96.2% of patients in the everolimus arm and 89.7% in the placebo arm. System organ classes (SOCs) where a higher proportion of everolimus-treated patients reported events (and where there was a ≥ 10% difference relative to placebo) included: Gastrointestinal disorders (+26.9%; primarily mouth ulceration and stomatitis), Skin and subcutaneous disorders (+23.1%; including rash and acne), Psychiatric disorders (+20.5%; including aggression, insomnia and agitation), Musculoskeletal and connective tissue disorders (+16.7%; including pain in extremity), General disorders and administration site conditions (+10.2%; including pyrexia and fatigue).

Table 25: Adverse events by system organ class (Safety Set) – Study M2301

System organ class	Everolimus N=78 n (%)	Placebo N=39 n (%)
Any primary system organ class	**75 (96.2)**	**35 (89.7)**
Gastrointestinal disorders	59 (75.6)	19 (48.7)
Infections and infestations	56 (71.8)	26 (66.7)
General disorders and administration site conditions	32 (41.0)	12 (30.8)
Skin and subcutaneous tissue disorders	30 (38.5)	6 (15.4)
Nervous system disorders	28 (35.9)	17 (43.6)
Psychiatric disorders	22 (28.2)	3 (7.7)
Respiratory, thoracic and mediastinal disorders	22 (28.2)	8 (20.5)
Investigations	18 (23.1)	6 (15.4)
Metabolism and nutrition disorders	15 (19.2)	5 (12.8)
Musculoskeletal and connective tissue disorders	13 (16.7)	0
Injury, poisoning and procedural complications	11 (14.1)	5 (12.8)
Blood and lymphatic system disorders	8 (10.3)	1 (2.6)
Reproductive system and breast disorders	8 (10.3)	1 (2.6)
Eye disorders	4 (5.1)	1 (2.6)
Vascular disorders	3 (3.8)	1 (2.6)
Immune system disorders	2 (2.6)	1 (2.6)
Renal and urinary disorders	2 (2.6)	0
Ear and labyrinth disorders	1 (1.3)	2 (5.1)
Endocrine disorders	0	1 (2.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	4 (10.3)

Table 26: Adverse events by system organ class (Safety Set) – Study C2485

System organ class	Everolimus N=28 n (%)
Any primary system organ class	**28 (100.0)**
Gastrointestinal disorders	27 (96.4)
Infections and infestations	27 (96.4)
Skin and subcutaneous tissue disorders	21 (75.0)
Investigations	19 (67.9)
Injury, poisoning and procedural complications	18 (64.3)
Respiratory, thoracic and mediastinal disorders	17 (60.7)
General disorders and administration site conditions	16 (57.1)
Psychiatric disorders	15 (53.6)
Nervous system disorders	13 (46.4)
Metabolism and nutrition disorders	8 (28.6)
Blood and lymphatic system disorders	7 (25.0)
Eye disorders	7 (25.0)
Musculoskeletal and connective tissue disorders	7 (25.0)
Renal and urinary disorders	6 (21.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (17.9)
Cardiac disorders	4 (14.3)
Vascular disorders	4 (14.3)
Immune system disorders	3 (10.7)
Reproductive system and breast disorders	2 (7.1)
Ear and labyrinth disorders	1 (3.6)
Endocrine disorders	1 (3.6)

Serious adverse event / deaths / other significant events

Clinically notable AE

Clinically notable adverse events are presented in Table 27 and 28 from study M2301 and C2485, respectively.

Table 27: Clinically notable adverse events irrespective of relationship to study drug by grouping (Safety Set) – Study M2301

Clinically notable category	Everolimus N=78 n (%)	Placebo N=39 n (%)
Any clinically notable adverse event	**73 (93.6)**	**29 (74.4)**
Infections and infestations	56 (71.8)	26 (66.7)
Stomatitis/ oral mucositis/ulcers	46 (59.0)	10 (25.6)
Rash and similar events	13 (16.7)	3 (7.7)
Cytopenia	12 (15.4)	1 (2.6)
Hemorrhages	7 (9.0)	2 (5.1)
Amenorrhoea	3 (3.8)	0
Hypersensitivity reactions (anaphylactic reaction)	2 (2.6)	0
Non-infectious pneumonitis	1 (1.3)	0
Renal events	1 (1.3)	0
Hyperglycemia/new onset of diabetes mellitus	0	1 (2.6)
Thromboembolism	0	0

Stomatitis/oral mucositis/ulcers= Stomatitis/related events

Table 28: Clinically notable adverse events irrespective of relationship to study drug by grouping (Safety Set) – Study C2485

Clinically notable category	Everolimus N=28 n (%)
Any clinically notable adverse event	**28 (100)**
Infections and infestations	27 (96.4)
Stomatitis/oral mucositis/ulcers	24 (85.7)
Hemorrhages	8 (28.6)
Rash and similar events	6 (21.4)
Cytopenia	5 (17.9)
Hypersensitivity reactions (anaphylactic reaction)	3 (10.7)
Renal events	2 (7.1)
Hyperglycemia/new onset of diabetes mellitus	2 (7.1)
Amenorrhoea	0
Non-infectious pneumonitis	0
Thromboembolism	0

Stomatitis/oral mucositis/ulcers= Stomatitis/related events

Detailed discussion of clinically notable events

1. Infections

The frequencies of infections were similar between the two treatment arms. Most of the infections observed were grade 1-2 in intensity and involved the upper respiratory tract. Pneumonia was seen in

a modest proportion of everolimus-treated patients (7.7%). There were no reported cases of opportunistic infections in the everolimus arm. Dose interruption or adjustment was required in a number of cases (Table 29).

Table 29: Clinical impact of infections – Safety Set (Study M2301)

Infections	Everolimus N=78 n (%)	Placebo N=39 n (%)
AE suspected to be drug related		
Grade 3	4 (5.1)	0
Grade 4	0	0

Infections	Everolimus N=78 n (%)	Placebo N=39 n (%)
AE leading to discontinuation	**0**	**0**
AE requiring dose adjustment/interruption		
Pneumonia	4 (5.1)	0
Bronchitis	2 (2.6)	0
Gastroenteritis	2 (2.6)	0
Gastroenteritis viral	2 (2.6)	0
Nasopharyngitis	2 (2.6)	0
Upper respiratory tract infection	2 (2.6)	0
Pharyngitis	1 (1.3)	1 (2.6)
Ear infection	1 (1.3)	0
Febrile infection	1 (1.3)	0
Influenza	1 (1.3)	0
Otitis media	1 (1.3)	0
Periorbital cellulitis	1 (1.3)	0
Respiratory tract infection	1 (1.3)	0
Respiratory tract infection viral	1 (1.3)	0
Sinusitis	1 (1.3)	0
Viral infection	1 (1.3)	0

Source: [Study M2301-Table 14.3.1-1.6], [Study M2301-Table 14.3.1-1.7] and [Study M2301-Table 14.3.1-1.14]

2. Stomatitis/rashes

In M2301, most cases of stomatitis were grade–1/2 in severity. Mouth ulcers were more common than in the placebo arm (59% versus 25.6%). Seven patients had grade–3 events versus one in the placebo arm. No patient discontinued due to stomatitis and no grade–4 events were experienced. Dose adjustment or interruption was required in 24.4% versus one patient in the placebo arm. In C2485 stomatitis was reported in 85.7% of patients. There were 2 grade–3 events of stomatitis in C2485. Dose reduction/interruption was implemented for 6 patients (21.4%). No patient discontinued due to stomatitis in C2485. Rashes were grade–1/2 in severity for both studies M2301 and C2485.

3. Cytopaenias

In study M2301, the majority of AEs in this grouping were related to neutropenia or decreased neutrophil count, with lymphopenia observed in only one everolimus-treated patient. Cytopenias were seen in 15.4% of everolimus-treated patients (including 5.1% of grade–3 severity), and were reported more frequently than in placebo-treated patients (2.6%). No grade–4 neutropenia or decreased neutrophil count was observed. Dose interruption or adjustment was required in 4 everolimus-treated patients (5.1%). No patients discontinued study drug as a result of cytopenias.

Table 30: Grading (severity) of cytopenias by preferred term irrespective of relationship to treatment (Safety Set) – Study M2301

MedDRA preferred term	Everolimus N=78		Placebo N=39	
	All grades n (%)	Grade 3 and 4 n (%)	All grades n (%)	Grade 3 and 4 n (%)
Any cytopenias	**12 (15.4)**	**4 (5.1)**	**1 (2.6)**	**1 (2.6)**
Neutrophil count decreased	6 (7.7)	1 (1.3)	0	0
Neutropenia	4 (5.1)	3 (3.8)	1 (2.6)	1 (2.6)
Lymphocyte count decreased	1 (1.3)	0	0	0
Monocyte count decreased	1 (1.3)	0	0	0
Platelet count decreased	1 (1.3)	0	0	0
White blood cell count decreased	1 (1.3)	0	0	0

In study C2485, cytopenias were seen in 5 patients (17.9%), with decreased neutrophil count reported in 4 patients (14.3%). Two patients (7.1%) had grade 3 decreased neutrophil count. No grade–4 cytopenia was reported. Dose interruption or adjustment was required in 3 patients (10.7%). No patients discontinued study drug as a result of cytopenias.

Table 31: Grading (severity) of cytopenias by preferred term irrespective of relationship to treatment (Safety Set) – Study C2485

MedDRA Preferred term	Everolimus N=28	
	All grades n (%)	Grade 3 and 4 n (%)
Any cytopenias	5 (17.9)	2 (7.1)
Neutrophil count decreased	4 (14.3)	2 (7.1)
Platelet count decreased	1 (3.6)	0
White blood cell count decreased	1 (3.6)	0

4. Haemorrhages

In study M2301, haemorrhage of grade 1-2 intensity was seen in 9.0% of everolimus-treated patients, mostly manifesting as epistaxis, but with single reports of blood urine, menorrhagia, metrorrhagia, and hematoma at the vessel puncture site. This incidence was slightly higher than that observed in the placebo arm (5.1%). Only one patient in each group had an event suspected to be drug related: epistaxis (grade-1) in the everolimus arm and gingival bleeding (grade-1) in the placebo arm. No patient required dose interruption/reduction as a result of haemorrhage.

Table 32: Grading (severity) of haemorrhages by preferred term irrespective of relationship to treatment (Safety Set) – Study M2301

MedDRA preferred term	Everolimus N=78		Placebo N=39	
	All grades n (%)	Grade 3-4 n (%)	All grades n (%)	Grade 3-4 n (%)
Any haemorrhage	**7 (9.0)**	**0**	**2 (5.1)**	**0**
Epistaxis	4 (5.1)	0	1 (2.6)	0
Blood urine	1 (1.3)	0	0	0
Menorrhagia	1 (1.3)	0	0	0
Metrorrhagia	1 (1.3)	0	0	0
Vessel puncture site haematoma	1 (1.3)	0	0	0
Gingival bleeding	0	0	1 (2.6)	0

In study C2485, haemorrhage of grade 1-2 intensity was observed in 28.6% of the patients, mostly manifesting as epistaxis, haematuria, and injection site hematoma, with single reports of haemoptysis, metrorrhagia, and petechiae. None of these events were suspected to be study drug related with the exception of one case of haematuria. One patient with petechiae required dose interruption/reduction. No patient discontinued study drug as a result of haemorrhage.

Table 33: Grading (severity) of haemorrhages by preferred term irrespective of relationship to treatment (Safety Set) – Study C2485

MedDRA preferred term	Everolimus N=28	
	All grades n (%)	Grade 3 and 4 n (%)
Any haemorrhage	**8 (28.6)**	**0**
Epistaxis	2 (7.1)	0
Haematuria	2 (7.1)	0
Injection site haematoma	2 (7.1)	0
Haemoptysis	1 (3.6)	0
Metrorrhagia	1 (3.6)	0
Petechiae	1 (3.6)	0

5. Amenorrhea

Table 34: Grading (severity) of amenorrhea by preferred term irrespective of relationship to treatment (Safety Set) – Study M2301

	Everolimus N=78		Placebo N=39	
	All grades n (%)	Grade 3 and 4 n (%)	All grades n (%)	Grade 3 and 4 n (%)
Amenorrhea and related events	**3 (3.8)**	**0**	**0**	**0**
Amenorrhea	3 (3.8)	0	0	0

All three cases were medically assessed as secondary amenorrhea, as patients had normal menses prior to study entry, and no prior reported medical history of amenorrhea. Post-database lock follow-up information indicates that all three of the above cases resolved subsequently. As of 19 December 2011, none of these cases of amenorrhea were ongoing, while treatment with everolimus was ongoing in all 3 patients. No events of amenorrhea and related events were reported during Study C2485.

6. Renal

In Study M2301, one AE of renal impairment was reported in the everolimus treatment arm. This event was of grade-1 severity and was not suspected to be related to everolimus. Three cases of grade 1-2 elevated serum creatinine were recorded as laboratory abnormalities however only one of these events was reported as an AE.

In study C2485, two patients developed proteinuria which was suspected to be drug related during the study. One event was grade-1 and the other was grade-2. Both events were ongoing at the time of data cut-off (31 December 2010).

No deaths were reported during the course of either trial.

Serious adverse events

In study M2301, SAEs were reported more frequently for everolimus (19.2%) as compared to placebo (7.7%).

Table 35: Serious adverse events, irrespective of relationship to study drug, by preferred term (Safety Set) – Study M2301

MedDRA preferred term	Everolimus N=78 n (%)	Placebo N=39 n (%)
Any serious adverse event	**15 (19.2)**	**3 (7.7)**
Convulsion	3 (3.8)	2 (5.1)
Pyrexia	3 (3.8)	0
Bronchitis	2 (2.6)	1 (2.6)
Gastroenteritis	2 (2.6)	0
Gastroenteritis viral	2 (2.6)	0
Pneumonia	2 (2.6)	0
Status epilepticus	2 (2.6)	0

MedDRA preferred term	Everolimus N=78 n (%)	Placebo N=39 n (%)
Upper respiratory tract infection	2 (2.6)	0
Abdominal pain	1 (1.3)	0
Adenovirus infection	1 (1.3)	0
Agitation	1 (1.3)	0
Bronchopneumonia	1 (1.3)	0
Dehydration	1 (1.3)	0
Febrile infection	1 (1.3)	0
Gastrointestinal infection	1 (1.3)	0
Grand mal convulsion	1 (1.3)	0
Hypersensitivity	1 (1.3)	0
Otitis media	1 (1.3)	0
Respiratory tract infection viral	1 (1.3)	0
Urinary tract infection	1 (1.3)	0

Source: [Study M2301-Table 14.3.1-1.5]

Laboratory findings

Haematology

In M2301 haematological abnormalities were more commonly reported in everolimus-treated patients than in those treated with placebo. Abnormalities where a higher proportion of everolimus-treated patients reported events (with a ≥10% difference relative to placebo) included: Increased partial thromboplastin time (+24.4%), Decreased haemoglobin (+23.1%). No grade–4 haematological laboratory abnormality was reported. All grade–3 cases resolved by the cut-off date of 02 March 2011.

Table 36: Grading (severity) of abnormal haematology values (Safety Set) – Study M2301

Laboratory parameters	Everolimus N=78			Placebo N=39		
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Partial thromboplastin time increased	51 (65.4)	2 (2.6)	0	16 (41.0)	2 (5.1)	0
Absolute neutrophils (seg. + bands) decreased	36 (46.2)	7 (9.0)	0	16 (41.0)	1 (2.6)	0
Haemoglobin decreased	32 (41.0)	0	0	7 (17.9)	0	0
WBC (total) decreased	29 (37.2)	0	0	14 (35.9)	0	0
Prothrombin time (INR) increased	22 (28.2)	5 (6.4)	0	14 (35.9)	2 (5.1)	0
Platelet count (direct) decreased	5 (6.4)	0	0	4 (10.3)	0	0
Absolute lymphocytes decreased	1 (1.3)	1 (1.3)	0	1 (2.6)	0	0

Table 37: Grading (severity) of abnormal haematology values (Safety Set) – Study C2485

Laboratory parameters	Everolimus N=28		
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
White blood cell count decreased	16 (57.1)	0	0
Absolute neutrophil decreased	12 (42.9)	5 (17.9)	2 (7.1)
Hemoglobin decreased	12 (42.9)	0	0
Platelet count decreased	6 (21.4)	0	0
Absolute lymphocyte decreased	3 (10.7)	0	1 (3.6)

Clinical chemistry

Biochemical abnormalities that were more frequent in the everolimus arm relative to the placebo arm by a difference of ≥ 10% in M2301 were the following (Table 38): Cholesterol increased (+42.3%), Serum glutamic oxaloacetic transaminase (SGOT) increased (+32.1%), Bicarbonate decreased (+23.1%), Serum glutamic pyruvic transaminase (SGPT) increased (+14.1%), Triglycerides increased (+11.6%).

Table 38: Grading (severity) of abnormal biochemistry values (Safety Set) – Study M2301

Laboratory parameters	Everolimus N = 78			Placebo N = 39		
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Cholesterol (total) increased	61 (78.2)	0	0	14 (35.9)	0	0
Bicarbonate decreased	66 (84.6)	1 (1.3)	0	24 (61.5)	0	0
Fibrinogen decreased	30 (38.5)	0	0	25 (64.1)	1 (2.6)	0
SGOT (AST) increased	25 (32.1)	0	0	0	0	0
Triglycerides increased	19 (24.4)	0	0	5 (12.8)	0	0
SGPT (ALT) increased	13 (16.7)	0	0	1 (2.6)	0	0
Alkaline phosphatase, serum increased	10 (12.8)	1 (1.3)	0	6 (15.4)	1 (2.6)	0
Glucose decreased	9 (11.5)	0	0	2 (5.1)	0	0
Calcium increased	7 (9.0)	0	0	8 (20.5)	0	0
Phosphate (Inorganic Phosphorus) decreased	7 (9.0)	1 (1.3)	0	1 (2.6)	0	0
Potassium decreased	7 (9.0)	0	0	1 (2.6)	0	0
Glucose increased	4 (5.1)	0	0	4 (10.3)	0	0
Creatinine increased	3 (3.8)	0	0	0	0	0
Magnesium increased	3 (3.8)	0	0	1 (2.6)	0	0
Calcium decreased	2 (2.6)	0	0	1 (2.6)	0	0
Sodium decreased	2 (2.6)	0	0	1 (2.6)	0	0
Sodium increased	2 (2.6)	0	1 (1.3)	0	0	0
Bilirubin (total) increased	1 (1.3)	0	0	1 (2.6)	0	0
Magnesium decreased	0	0	0	1 (2.6)	0	0
Potassium increased	0	0	0	1 (2.6)	0	0

Table 39: Grading (severity) of abnormal biochemistry values (Safety Set) – Study C2485

Laboratory parameters	Everolimus N=28		
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
SGOT (AST) increased	26 (92.9)	1 (3.6)	0
Cholesterol (total) increased	21 (75.0)	0	0
Alkaline phosphatase, serum increased	16 (57.1)	1 (3.6)	0
SGPT (ALT) increased	16 (57.1)	0	0
Triglycerides increased	15 (53.6)	0	0
Glucose decreased	12 (42.9)	0	0
Sodium increased	12 (42.9)	0	0
Potassium decreased	11 (39.3)	0	0
Potassium increased	8 (28.6)	0	0
Glucose increased	7 (25.0)	0	0
Calcium decreased	4 (14.3)	0	0
Calcium increased	4 (14.3)	0	0
Creatinine increased	4 (14.3)	0	0
Sodium decreased	4 (14.3)	0	0
Albumin decreased	2 (7.1)	1 (3.6)	0
Phosphate (inorganic phosphorus) decreased	2 (7.1)	0	0

Calcium, magnesium, and phosphate values were not captured systematically for all patients

Urinalysis

In study M2301, the majority of patients did not show any notable abnormalities in blood, glucose, ketones, leukocytes or protein levels in the urine. No urinalysis was conducted in study C2485.

Vital signs:

ECGs were not routinely performed in either study. For those that did have ECGs performed no clinically important changes from baseline in QTc were observed.

Safety in special populations

In study M2301, a difference in the incidence of events in the everolimus arm exceeding that of placebo was relatively higher in the youngest age group < 3 years than in patients aged between 3 and < 18 years for: pharyngitis, cough, viral infection, neutrophil count decreased, rhinitis, hypercholesterolemia, dermatitis allergic, laryngitis, urticaria, dyspepsia, vomiting, and stomatitis.

Discontinuation due to adverse events

In Study M2301, the rate of treatment discontinuation was approximately 10-fold higher in placebo-treated patients (everolimus: 2.6%; placebo: 20.5%). Disease progression was reported as the most common reason for discontinuation in the placebo treatment arm (15.4%); there were no cases of disease progression leading to study discontinuation in the everolimus treatment arm (Table 40).

Table 40: Patient disposition (Safety Set) – Study M2301

Disposition	Everolimus N=78 n (%)	Placebo N=39 n (%)
Ongoing in double-blind treatment	76 (97.4)	31 (79.5)
Discontinued from double-blind treatment	2 (2.6)	8 (20.5)
Reasons for discontinuation		
Subject withdrew consent	1 (1.3)	1 (2.6)
Lost to follow-up	1 (1.3)	0
Disease progression	0	6 (15.4)
Administrative problems	0	1[a] (2.6)

[a] This patient (0150-00002) was not compliant with study visits

Study C2485

Twenty-eight patients with TSC who have SEGA were screened and subsequently enrolled between 07 January 2007 and 18 December 2008. As of the 31 December 2010 data cut-off, 25 out of 28 patients are ongoing in this study; all these 25 patients have ≥ 2 years of exposure. 3 patients discontinued due to potential adverse events, including hyperkinesis and infection.

Post marketing experience

The estimated worldwide post-marketing exposure to Afinitor (everolimus) since 30 March 2009 is 8814 PTY. The post-marketing experience with everolimus has been reviewed on an ongoing basis. No new information has emerged based on post-marketing usage of Afinitor that would substantially alter the known safety profile of everolimus in the oncology setting. Although of interest from a safety perspective, these data are not of direct relevance to the TSC setting due to differences in types of disease, concomitant medications, and therapeutic drug concentrations.

2.6.1. Discussion on clinical safety

In both studies M2301 and C2485, the majority of adverse events occurring at a higher incidence in the everolimus arm were mouth ulceration, stomatitis, rash, acne, cytopaenias and infection. These are all recognised side effects of everolimus. Subgroup analysis revealed that infection was more common in children age < 3 years. The MAH has added appropriate warnings to section 4.8 of the SmPC to highlight this increased risk.

Neutropaenia appears to be the most commonly experienced cytopaenia, although some cases of lymphopaenia are also described. Grade 3 and 4 cytopaenic events were experienced in both studies. The longterm consequences of this immunosuppresion are unknown.

Secondary amenorrhea has recently been added to the RMP as an identified risk. The MAH has committed to further investigate all serious reports, and to present a formal analysis across all studies following study completion. Furthermore, there is a mandated evaluation of endocrine hormone levels every 24 weeks, until the study ends to attempt to understand the implications of these findings. An international disease registry has also been set up and will collect information on adverse events including amenorrhea. The long-term implications of this finding are unknown.

In addition, the effects of everolimus on neurodevelopment in children age < 3 will be included in the RMP as missing information. This is considered to be an adequate pharmacovigilance measure.

Both studies highlighted increased incidence of haemorrhagic events, whilst study M2301 also highlights abnormal bleeding times. The events were primarily epistaxis. The SmPC already includes a warning on haemorrhagic events.

Both studies M2301 and C2485 identify rises in triglycerides and cholesterol. This adverse reaction is already covered in the SmPC.

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

2.6.2. Conclusions on the clinical safety

There were no new adverse reactions reported in study M2301 and the 2–year analysis of C2485. The safety of everolimus treatment has been appropriately addressed.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

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

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 8 the PRAC considers by consensus that the risk management system for everolimus (Votubia) in

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

could be acceptable provided that the MAH updates the RMP to include ''Effects of everolimus on brain growth and development, particularly in patients under 3 years of age" should be included as missing information.

The following points should be taken into account in the next update:

- The MAH should include a discussion of the risk of severe infections and pre-existing infection (reactivation, aggravation, or exacerbation) in the next global RMP update, including information on the risks in the subpopulation of patients younger than three years of age
- The format of the RMP needs to be updated in accordance with the latest EU-RMP template
- The addition of the effects of everolimus on neurodevelopment in children age < 3 included in the RMP as missing information.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

The MAH identified the following safety concerns in the RMP.

Table 41: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Non-infectious pneumonitis Severe infections Hypersensitivity (anaphylactic reactions) Stomatitis Wound healing complications Increased creatinine/proteinuria/renal failure Hyperglycaemia/new onset diabetes mellitus Dyslipidaemia Hypophosphataemia Cardiac failure Cytopenia Hemorrhages Thrombotic and embolic events Female fertility (including secondary amenorrhea) Pre-existing infection (reactivation, aggravation, or exacerbation) Safety in patients with hepatic impairment
Important potential risks	Postnatal developmental toxicity Reproductive (teratogenicity) toxicity Intestinal obstruction/ileus Male infertility Pancreatitis Cholelithiasis Muscle-wasting/muscle loss
Important identified interactions	Strong CYP3A4 inhibitors and PgP inhibitors Moderate CYP3A4 inhibitors and PgP inhibitor Strong CYP3A4 inducers and PgP inducers CYP3A4 substrates and PgP substrates
Missing information	Pediatric patients less than 3 years old Off-label use in pediatric and adolescent patients Pregnant or breast-feeding women Hormonal contraceptive use Patients with renal impairment Patients with CNS metastases Patients with uncontrolled cardiac disease Patients with impairment of GI function Patients undergoing chronic treatment with steroids or another immunosuppressive agent Long-term safety Carcinogenicity Comparative safety of combination vs. monotherapy in BOLERO-6

The PRAC considered that ''Effects of everolimus on brain growth and development, particularly in patients under 3 years of age" should also be included as missing information.

Pharmacovigilance plans

Table 42: Ongoing and planned studies in the PhV development plan

Proposed pharmacovigilance and risk minimization activities	Milestones	Timelines
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 M2301 includes a trial extension phase.	Updated data to be submitted in the EU for purpose of yearly renewal in Jan/Feb-2013 and 2014	Extension phase: 2Q 2015
CRAD001C2485: Everolimus (RAD001) therapy of giant cell astrocytomas in patients with tuberous sclerosis complex	Updated data to be submitted in the EU for purpose of yearly renewal in Jan/Feb-2013, 2014, and 2015	Extension phase: 2Q 2015
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	Updated data to be submitted in the EU for purpose of yearly renewal in Jan/Feb 2013 and 2014	Extension phase: 3Q2015
Formal amenorrhea analysis across CRAD001C2485, CRAD001M2301, and CRAD001M2302 following study completions	Submission of final analysis	3Q2015
Disease registry CRAD001MIC03: An international disease registry collecting data on manifestations, interventions, and outcomes in patients with tuberous sclerosis complex – TOSCA	First patient, first visit event Submission of interim analysis	First patient, first visit: 10-Aug-2012 1st interim analysis to include 100 patients; thereafter, annual interim analyses
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	Submission of final data,	4Q2014
CRAD001W2301 A randomized, 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	Submission of final data, including long-term safety	3Q2015
CRAD001Y2301 A randomized, double-blind, placebo-controlled study of everolimus in combination with exemestane in the treatment of	Submission of final data	3Q-2017

Proposed pharmacovigilance and risk minimization activities	Milestones	Timelines
postmenopausal women with estrogen receptor positive locally advanced or metastatic breast cancer who are refractory to letrozole or anastrozole		

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Table 43: Summary table of Risk Minimisation Measures

Safety concern	Proposed risk minimization activities (routine and non-routine)
Important identified risks	
Non-infectious pneumonitis	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 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	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

Safety concern	Proposed risk minimization activities (routine and non-routine)
	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)	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, 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	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	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	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	Warning in SPC Section 4.4: "Hyperglycaemia, hyperlipidaemia and hypertrigylceridaemia have been reported in clinical trials (see section 4.8). Monitoring of fasting serum glucose is recommended prior to the start of Afinitor therapy and periodically thereafter. When possible optimal glycaemic control should be achieved before starting a patient on Afinitor." Glucose increased, triglycerides increased, and new-onset diabetes mellitus are included as ADRs in SPC Section 4.8.
Dyslipidaemia	Warning in SPC Section 4.4: "Hyperglycaemia, hyperlipidaemia and hypertrigylceridaemia

Safety concern	Proposed risk minimization activities (routine and non-routine)
	have been reported in clinical trials (see section 4.8)." Cholesterol increased and triglycerides increased are included as ADRs in SPC Section 4.8.
Hypophosphataemia	Phosphate decreased is included as ADR in SPC Section 4.8.
Cardiac failure	Congestive cardiac failure is included as ADR in SPC Section 4.8.
Cytopenia	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	Haemorrhage is included as ADR in SPC Section 4.8.
Thrombotic and embolic events	Pulmonary embolism is included as ADR in SPC Section 4.8.
Female fertility (including secondary amenorrhea)	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)	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. "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	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:

Safety concern	Proposed risk minimization activities (routine and non-routine)
	"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 is recommended for patients with hepatic impairment."
Important potential risks	
Postantal developmental toxicity	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	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 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	None.
Male infertility	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	None
Cholelithiasis	None
Muscle-wasting/muscle loss	None
Important identified interactions	

Safety concern	Proposed risk minimization activities (routine and non-routine)
Strong CYP3A4 inhibitors and PgP inhibitors	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 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	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 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	Relevant information in SPC Section 4.4:

Safety concern	Proposed risk minimization activities (routine and non-routine)
PgP inducers	"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 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	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."
Missing information	
Pediatric patients less than 3 years old	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	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)."
Pregnant or breast-feeding women	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."

Safety concern	Proposed risk minimization activities (routine and non-routine)
Hormonal contraceptive use	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	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	None
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	None
Comparative safety of everolimus combination vs. monotherapy in BOLERO-6	None

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice without changes.

2.9. Update of the Product information

As a consequence of this new indication and line extension, sections 2, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 5.1, 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly and a new section on instructions for use of an oral syringe for administration of the dispersible tablet as an oral suspension has been included.

The changes to the SmPC consist of the following:

- Section 4.1
  - Extension of the indication to patients below the age group 3 years

- Section 4.2
  - Recommendation on how to dose patients based on Body Surface Area (BSA), a new recommendation on the starting dose of 4.5 mg/m^2
  - New wording on dosing patients and monitoring of patients during the treatment
  - Recommendation not to dose patients below 18 years of Age with SEGA and hepatic impairment
  - Information on paediatric patients concerned and statement that efficacy and safety has not been studied in patients below 1 year of age
- Section 4.4
  - Recommendation for childhood vaccination for paediatric patients prior to the start of therapy
- Section 4.8
  - Information on the safety data for patients below 18 years of age
  - Information on how to report adverse reactions via the national reporting system
- Section 5.1
  - Update of information concerning VEGF levels
  - Update of efficacy from study M2301 and C2485
- Section 5.2
  - Introduction of new section on “relative bioavailability/bioequivalence” concerning administration of tablets as a suspension versus intact tablet. There is also some wording on dispensing tablets
  - Update of section “distribution” with data on the uptake of everolimus and the crossing of the blood-brain barrier
  - Update of section “paediatric patients” with values on C_{min} based on BSA

The Package Leaflet was updated in sections 1, 2, 3, 4, 5 and 6.

As per the request from the CHMP, additional changes related to sections 4.2 of the SmPC have been included with regard to dose adjustment due to adverse reactions, which was evaluated during a separate procedure for Afinitor.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative of Malta.

2.10. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

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

The pharmacology studies X2105 and X2106 assessed the pharmacokinetics of dispersible tablets of everolimus in healthy subjects. These studies were submitted to satisfy a measure in a PIP for age

appropriate formulation of Votubia 2 mg, 3 mg and 5 mg dispersible tablets for children or patients who cannot swallow whole tablets. The design of the studies was considered acceptable as relevant data was obtained on blood concentration-time profiles and C_{max}, AUC and other PK parameters. The clinical data was considered acceptable in order to grant a bio waver for the strength of 3 mg. The data showed good correlation with the standard non-dispersible tablet. However, it is of note that C_{max} was lower compared to the intact tablet suggesting that the dispersible tablet is not interchangeable with the non-dispersible tablet. This has been adequately addressed in the SmPC.

The CHMP considered that the data submitted in the PK modelling study was sufficiently relevant in order to change the starting dose which has been increased from 3 mg/m^2 to 4.5 mg/m^2 for patients with TSC who have SEGA.

The proposed reduction of the lower limit of the recommended therapeutic trough level from 5 to 3 ng/ml was withdrawn by the applicant.

The data from the PK study in rats using everolimus co-administered with cyclosporin as well as the toxicology review which showed no impact of everolimus on brain development were supportive of the extension of indication covering patients that are less than 3 years of age. The results from study M2301 showed a SEGA response in favour of everolimus treatment in patients that were less than 3 years of age. Thus, the data suggested that children less than 3 years could also benefit from treatment with everolimus. Given these data, the extension of indication for SEGA patients less than 3 years of age was considered appropriate.

The updated 2 and 3–year results from study C2485 and the results from the double blind sequence of study M2301 confirmed the SEGA response data provided for the initial marketing authorisation and also the durability of the response. The SmPC has been updated to reflect the updated data from the clinical trials. The safety and tolerability of everolimus in the SEGA patient population continues to be acceptable. Thus, the benefit risk balance in the new indication “for the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not amenable to surgery.” is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations consisting of an Extension and a Type II variation to add a paediatric indication acceptable and therefore recommends by consensus the variations to the terms of the Marketing Authorisation, concerning the following changes:

Extension of the Marketing Authorisation for the above mentioned medicinal product concerning:

- new strengths: 2, 3 and 5 mg dispersible tablets

and the following variation:

Variation requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication to include treatment of patients < 3 years of age with TSC who have SEGA. In addition, the SmPC was updated based on efficacy and safety data from the pivotal Study M2301 and longer-term follow-up from the Study C2485 for the SEGA paediatric population. A revised starting dose from 3 mg/m^2 to 4.5 mg/m^2 for patients with TSC who have SEGA has also been included. The

SmPC was modified in sections 2, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 5.1 and 5.2. The Package Leaflet and Labelling were updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

The requested group of variations proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.

Conditions or restrictions regarding supply and use

Medicinal product subject to special and restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Clinical study report comprising the extension phase of study M2302	31/08/2015

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
The applicant shall provide long-term follow-up on duration of response and time to progression for study C2485 and M2301.	31/03/2015

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan EMA/169079/2012 (EMEA C2-00019-PIP02-07-M02) and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.