EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/646111/2011

Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Votubia

everolimus

Procedure No.: EMEA/H/C/002311//0000

Note

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

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List of abbreviations

AED	anti-epileptic drug
AEs	adverse events
ALT	alanine aminotransferase/glutamic pyruvic transaminase/GPT
AML	angiomyolipomata
ANC	absolute neutrophil count
AST	aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	area under the curve
AUC_{0-24h}	Area under the blood concentration-time curve from time zero to time 24h
AUC_{0-t}	Area under the blood concentration-time curve from time zero to time t, using the log-linear trapezoidal rule. Concentrations below the LOQ are set to zero and therefore excluded from the calculation. Actual sample collection times are used. Where 0-t is shown as tlast this denotes the AUC from time zero to time of the last quantifiable concentration. Where 0-t is shown as τ this denotes the AUC under a dosing interval
$AUC_{0-\infty}$	Area under the blood concentration-time curve from time zero to infinity. For extrapolation to infinity Clast/λz is used, where Clast is the estimated concentration at the last sample time point above LOQ from linear regression of the terminal elimination phase
BE	Bioequivalence
BHT	butylhydroxytoluene
BSA	body surface area
BVD	blood vessel density
CCHMC	Cincinnati Children's Hospital Medical Center
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL/F	Apparent clearance in blood after oral administration, calculated as Dose/ AUC0-∞ after a single dose or Dose/AUC0-τ at steady-state after repeated administration
C_{max}	Maximum blood concentration after a single dose
C_{min}	Pre-dose trough blood concentration in a dosing interval
CMH	Cochran-Mantel-Haenszel
COMP	Committee for Orphan Medicinal Products
CsA	ciclosporin
CSF	cerebral spinal fluid
CTC	common terminology criteria
CTCAE	common terminology criteria for adverse events
DNA	deoxyribonucleic acid
EEG	electroencephalography
EIAED	enzyme inducing anti-epileptic drug
EMA	European Medicines Agency
ER	estrogen receptor
ErbB1/2	epidermal growth factor receptor 1 and 2
4E-BP1	eukaryotic initiation factor 4E binding protein
HR	hazard ratio
IC_{50}	Drug concentration necessary to inhibit 50% of a given in vitro response
i.v.	Intravenous
LAM	lymphangioleiomyomatosis
LC-MS	Liquid chromatography coupled to mass spectrometry
LOCF	last observation carried forward
MA	Marketing Authorization
MLR	mixed lymphocyte reaction
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
mTORC1	mammalian target of rapamycin complex 1
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamics
PIP	Paediatric Investigation Plan
PK	pharmacokinetics
pNET	pancreatic neuroendocrine tumor
p.o.	Oral
PTYs	patient-years
QoL	quality of life

R	Accumulation index, calculated as AUCτ steady-state/ AUCτ single dose
RAD001	everolimus
RCC	renal cell carcinoma
s.c.	subcutaneous
SD	standard deviation
SEGA	subependymal giant cell astrocytoma
SEN	Subependymal nodule
SmPC	summary of product characteristics
S6K1	p70 ribosomal S6 kinase 1
t1/2,λz	Apparent terminal elimination half-life (t½) or rate constant (λz), calculated from at least three consecutive data points and with an r2 value ≥ 0.9
tmax	Time to the maximum observed blood concentration
TS	tuberous sclerosis
TSC	tuberous sclerosis complex
TSC1	tumour suppressor gene (gene product hamartin)
TSC2	tumour suppressor gene (product tuberin)
ULN	Upper limit of normal range
VEGFr	vascular endothelial growth factor receptor
Vss	Volume of distribution at steady-state
Vd/F	apparent volume of distribution
Vd	volume of distribution

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Ltd. submitted on 23 July 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Votubia , through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 May 2010. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant therapeutic innovation.

Votubia was designated as an orphan medicinal product EU/3/10/764 on 4 August 2010. Everolimus was designated as an orphan medicinal product in the following indication: Treatment of tuberous sclerosis. The calculated prevalence of this condition was 1 per 10,000 EEA population.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Votubia as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find Medicine/Human medicines/Rare disease designations.

The applicant applied for the following indication:

Votubia is indicated for the treatment of patients aged 3 years and older with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS).

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants own tests and studies.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/105/2010 on the agreement of a paediatric investigation plan (PIP).

At the time of the submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market exclusivity

Not applicable.

Applicant's request for consideration

Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14(7) of the above mentioned Regulation based on the following claim(s):

- The risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive.

The applicant stated that the efficacy in terms of reduction of SEGA size/volume was demonstrated in study C2485.

The applicant stated that the safety of everolimus in the applied indication is manageable and the adverse events (AEs) recorded are consistent with previously identified risks associated with everolimus therapy in the advanced renal cell carcinoma (RCC) population.

Thus, the applicant claimed that the safety of everolimus is manageable and the risk is outweighed by a meaningful and clinically relevant effect on SEGA volume (and its clinical sequelae).

- It is likely that the applicant will be in a position to provide comprehensive clinical data.

M2301 study, a randomised, placebo controlled phase III trial, is actively enrolling (76 patients enrolled as of June 18, 2010, aiming to recruit 99 patients [approximately 66 on everolimus and 33 on placebo]), and the applicant claimed that it is likely to be in a position to provide the comprehensive clinical data from the phase III that will support the efficacy and safety of the phase II study C2485. The applicant stated that the final analysis of the core phase of this study is planned for Q3 2011.

- Unmet medical needs to be fulfilled.

The applicant claims that there is a lack of approved and effective pharmacological treatment other than surgical resection for patients with SEGA and that there is a need in the SEGA patient population that could be fulfilled with the proposed medicinal product.

- The benefits to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

The applicant claimed that the potential risks inherent in marketing everolimus for the specific indication, while additional, more comprehensive data will be available in the future, would be offset by the potential benefit to the mostly paediatric patients whose only treatment option currently available is surgery.

Scientific advice

The applicant received Scientific Advice from the CHMP on 18 October 2007. The Scientific Advice pertained to clinical aspects and in relation to paediatric development of the dossier.

Licensing status

Afinitor (everolimus) was given a Marketing Authorisation in EU/EEA on 3 August 2009 for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.

A new application for everolimus was filed for patients with SEGA associated with tuberous sclerosis complex in the following countries: USA.

1.2. Manufacturers

Manufacturers of the active substance

Sandoz GmbH
Biochemiestrasse 10
A-6250 Kundl
Tyrol
Austria

Novartis Pharma AG
Lichtstrasse 35
CH-4056 Basel
Switzerland

Novartis Pharma Schweizerhalle AG
Rothausweg
CH-4133 Pratteln
Switzerland

Novartis Pharma Stein AG
Schaffhauserstrasse
CH-4332 Stein
Switzerland

An inspection of these manufacturing sites was carried out by Swissmedic. The findings of the inspection are in compliance with the EU Good Manufacturing Practice requirements.

Manufacturers of the finished product

Novartis Pharma AG
Lichtstrasse 35
CH-4056 Basel
Switzerland

Novartis Pharma Stein AG
Schaffhauserstrasse
CH-4332 Stein
Switzerland

Pharmanalytica SA
Via Serafino Balestra 31
CH-6600 Locarno
Switzerland

Konapharma AG
Im Wannenboden 16
CH-4133 Pratteln
Switzerland

Allpack Group AG
Pfeffingerstrasse 45
CH-4153 Reinach
Switzerland

Ivers-Lee AG
Kirchbergstrasse 160
CH-3400 Burgdorf
Switzerland
Promlog AG
Lohagstrasse 15
CH-4133 Pratteln
Switzerland

Sanico N.V.
Veedijk 59 Industriezone IV
B-2300 Turnhout
Belgium

Novartis Pharma SAS
Site industriel de Huningue
26 rue de la Chapelle
FR-68330 Huningue
France

PB Beltracchini S.r.l.
Via S. Erasmo 6
I-20027 Rescaldina (MI)
Italy

PharmLog Pharma Logistik GmbH
Siemensstrasse 1
D-59199 Bönen
Germany

FAMAR S.A
7, Anthousa Avenue
GR-153 44 Anthousa, Attiki
Greece

Tjoapack B.V.
Columbusstraat 4
NL-7825 VR Emmen
The Netherlands

Novartis Farmacéutica S.A.
Ronda de Santa Maria 158
E-08210 Barberà del Vallés (Barcelona)
Spain

Novafarm Manipulaciones Generales S.A.
C/D, 52-54 Zona Franca
E-08040 Barcelona
Spain

Kronans Droghandel AB
Fibervägen P.O. Box 252
Solsten, S-43525 Mölnlycke
Sweden

Novartis Pharmaceutical UK Ltd.
Wimblehurst Road
Horsham
West Sussex
RH12 5AB
United Kingdom

An inspection of these manufacturing sites was carried out by Swissmedic, RHI, FAGG, afssaps, AIFA, Bezirksregierung Arnsberg, Public Health Supervisory Group, Direccio General de Recursos Sanitaris, Lakemedelsverket and MHRA. The findings of the inspection are in compliance with the EU Good Manufacturing Practice requirements.

Manufacturer responsible for batch release

Novartis Pharma GmbH
Roonstrasse 25
D-90429 Nürnberg
Germany

1.3. Steps taken for the assessment of the product

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

Rapporteur: **Harald Enzman** Co-Rapporteur: **Ian Hudson**

- The application was received by the EMA on 23 July 2010.
- The procedure started on 18 August 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 5 November 2010 . The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 November 2010.

- During the meeting on 16 December 2010, 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 17 December 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 11 February 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 25 March 2011.
- During the CHMP meeting on 14 April 2011, 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 consolidated List of Outstanding Issues on 24 May 2011.
- During the meeting on 20 -23 June 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a conditional Marketing Authorisation to Votubia on 23 June 2011.

2. Scientific discussion

2.1. Introduction

Tuberous sclerosis complex (TSC) is a potentially devastating multisystem disorder with a prevalence approaching 1 in 6000 live births[1]. Approximately 55,000 people in the EU and 1 million people worldwide are affected[2]. Disease expression is highly variable, with manifestations ranging from mild skin findings to seizures (which affect approximately 90% of patients), developmental delay (60%), mental retardation (50%), autism (25%), and fatal renal, cardiac, or pulmonary disease.[3] A decreased life expectancy can be associated with the disease, due to neurologic disorders (SEGAs and seizures), renal disease (angiomyolipomas and renal cell carcinoma), pulmonary disease (lymphangioleiomyomatosis and bronchopneumonia), and cardiovascular disease (rhabdomyoma and aneurysm).[4]

TSC is an autosomal dominant condition involving the *TSC1* and/or *TSC2* genes (encoding hamartin and tuberin, respectively). Mutations in either *TSC1* or *TSC2* are found in 80% to 85% of patients. [5] The TSC1/TSC2 protein complex is a negative regulator of the mTOR (mammalian target of rapamycin) pathway and loss or mutation of these gene products in preclinical models is associated with increased mTOR pathway activation and increased sensitivity to mTOR inhibitors. mTOR pathway up-regulation has been observed in lesions derived from TSC patients and TSC1/2 defective experimental animal models have been shown to be sensitive to mTOR inhibition.

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. Some centres advocate early surgery once clear evidence of serial growth is documented whilst others wait for the lesions to become symptomatic or for hydrocephalus to develop. 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-

[1] Krueger DA, Franz DN (2008) Current management of tuberous sclerosis complex. Pediatric Drugs; 10: 299-313.
[2] Anon (2010) What is TSC? How many people have TSC? Available from <http://www.tsalliance.org/pages.aspx?content=2> (Last accessed 14-Mar-2010).
[3] Curatolo P, Verdecchia M, Bombardieri R (2002) Tuberous sclerosis complex: a review of neurological aspects. Eur J Paediatr Neurol; 6: 15-23.
[4] Levine NB, Collins J, Franz DN, et al (2006) Gradual formation of an operative corridor by balloon dilation for resection of subependymal giant cell astrocytomas in children with tuberous sclerosis: specialized minimal access technique of balloon dilation. Minim Invasive Neurosurg; 49: 317-20.
[5] Crino PB, Nathanson KL, Henske EP (2006) The tuberous sclerosis complex. N Engl J Med; 355: 1345-56.

operative complications including meningitis, haematomas, hemiparesis, adhesions and incomplete resection.

To date, no effective alternative to surgical resection has been identified. Recently, rapamycin and related mTOR inhibitors have been tried in the setting of SEGA and the clinical literature contains a number of reports which identify response of the SEGA in terms of a decrease in size to rapamycin and related mTOR inhibitors. This is also the case for other TSC associated complications, including angiomyolipoma and lymphangioleiomyomatosis.

Everolimus, a rapamycin derivative, is currently licensed in Europe as Afinitor and as Certican. As Afinitor, everolimus is licensed for the treatment of patients with advanced renal cell carcinoma (RCC), whose disease has progressed on or after treatment with VEGF-targeted therapy. Afinitor was approved via the centralised route on 3/08/2009 (EMEA/H/C/001038). In addition, everolimus is also marketed in the EU as Certican. Certican was approved in 2003 for the prophylaxis of organ rejection in adult patients at low or moderate immunological risk of receiving an allogeneic renal or cardiac transplant of adults via a mutual recognition procedure.

Everolimus is a selective mTOR inhibitor that specifically targets the mTOR signal transduction complex (mTORC1). Rapamycin analogues are highly lipophilic and can cross the blood-brain barrier. The mTOR kinase is mainly activated via the phosphatidylinositol 3-kinase (PI3K) pathway.

The applicant is requesting a conditional approval in terms of Commission Regulation 507/2006 pointing out that according to article 2 (3) orphan medicinal products fall within the scope of the regulation.

The applicant applied for the following indication:
Votubia is indicated for the treatment of patients aged 3 years and older with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS).

The indication for Votubia is the following:

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.

2.2. Quality aspects

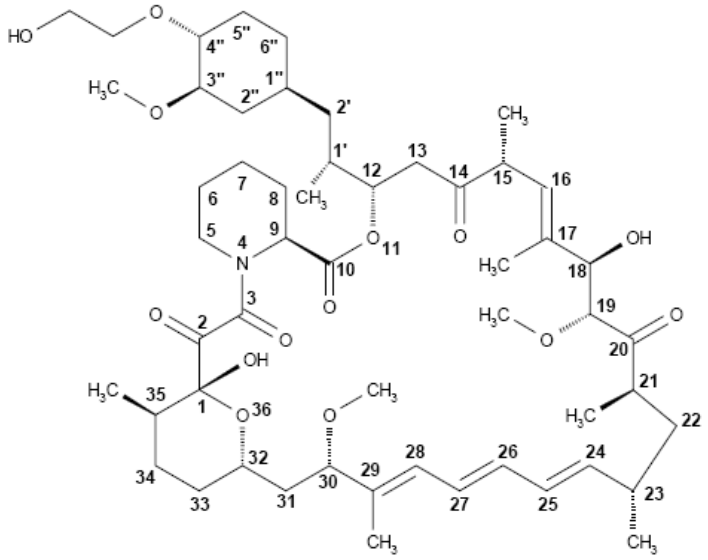
2.2.1. Introduction

Everolimus is approved since 2003 in Europe (trade name: Certican 0.25, 0.5, 0.75 and 1.0 mg tablets and 0.1 and 0.25 mg dispersible tablets) via the Mutual Recognition Procedure for the indication "Prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving an allogenic renal or cardiac transplant". Since August 2009, Everolimus is authorised via the centralised procedure for advanced RCC under the trade names Afinitor 5mg and 10mg tablets. The pharmaceutical development of Afinitor 5 mg and 10 mg tablets was based on the development of Certican tablets.

This marketing authorisation application refers to a new centralised procedure for Votubia 2.5mg, 5mg and 10mg tablets in the indication "treatment of subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS)."

2.2.2. Active substance

The active substance everolimus is a hydroxyethyl derivative of rapamycin, which is a macrolide, isolated from the micro-organism *Streptomyces hygroscopicus*. The chemical name of the active substance is 42-O-(2-hydroxyethyl)-rapamycin or $C_{53}H_{83}NO_{14}$ and its structure is shown below.



Everolimus is a white to faintly yellow amorphous powder and is stabilised with 0.2 % butylhydroxytoluene (BHT) as antioxidant. It is almost insoluble in water, is unstable at temperatures above 25 °C and is sensitive to light.
The structure of everolimus has been fully elucidated using spectroscopic techniques such as ultraviolet absorption spectroscopy (UV), Infra-red spectroscopy (FT-IR), proton and carbon nuclear magnetic resonance spectroscopy (^{1}H and ^{13}C NMR), mass spectroscopy, diffractometry (X-ray) and elemental analysis.
Everolimus contains 15 asymmetric carbon atoms and 4 substituted double bonds. The configuration of the asymmetric carbon atoms and the double bonds are guaranteed by the microbial origin of rapamycin. Everolimus- stabilized with BHT consists of different isomers, which are in equilibrium with each other. The configuration at carbon 40 is not changed by the chemical conversion of Rapamycin into 42-O-(2-hydroxyethyl)-rapamycin (everolimus).

Polymorphism has been comprehensively discussed and it was demonstrated that the active substance remains amorphous and there is no experimental evidence of spontaneous solid-state transitions.

Manufacture

Rapamycin is the key starting material for the synthesis of everolimus and is obtained through a fermentation process. The synthetic process of everolimus consists of four main steps, (1) fermentation, (2) extraction of rapamycin from the fermentation broth, (3) chemical modification of rapamycin starting material, (4) purification of crude everolimus and stabilisation with BHT. The choice of BHT as stabiliser has been sufficiently explained and justified by experimental results.
The synthetic process is well described. The reaction conditions (molar ratios, yields, temperatures) and the necessary in-process controls have been sufficiently depicted.

Adequate specifications for the starting materials and isolated intermediates (including rapamycin and crude everolimus) and descriptions of the test procedures have been provided.
Rapamycin is manufactured using a fermentation process which is in compliance with the requirements of the Ph. Eur. monograph on products of fermentation, where applicable.
Comprehensive information was provided on producer micro-organism, the master and working cell banks, the fermentation process, in-process controls, raw materials and the downstream process.

No starting material of animal or human origin is used in the fermentation. The quality of the solvents, reagents and auxiliary materials used in the synthesis has been adequately documented.

An extensive discussion has been presented on related substances. The complex structure of everolimus allows several possible degradation pathways to occur at various positions of the molecule. Due to the new and highly susceptible patient population of children above the age of three, the justification of the applicant to not further elucidate the safety of everolimus impurities, which was acceptable in the light of the usage only in adult patients so far, is no longer acceptable. The potential for degradation genotoxic impurities which may be present in everolimus should be further analysed as in the degradation scheme an "epoxide" product was observed. Furthermore, in the re-evaluation a consideration should be given to the indication, potential duration of treatment and life expectancy of the recipients.
Any impurities found to carry a potential genotoxic risk have to be restricted to acceptable limits.

Everolimus is extremely sensitive to oxidation. By the addition of the antioxidant BHT, the sensitivity to oxidation is significantly reduced. The stabilization of everolimus with BHT has improved considerably the quality of the active substance. Batch analysis data have shown a clear difference between batches stabilized or not stabilized with BHT, as expected.

The synthetic process involves the use of class II and class III solvents. The presence of residual solvents in the active substance is controlled on a skip lot testing, which is justified based on batch analysis results obtained during development and production scale manufacturing.

At the time of the CHMP opinion, it was recommended to update the active substance specification with details on the frequency of the skip lot testing, together with validation information on the analytical procedures that will be used to control certain residual solvents.

Specification

There is no monograph for everolimus – stabilized with BHT in either the Ph. Eur. or the USP at present. The in-house monograph includes the following tests: appearance (visual examination), identity (IR, X-ray, HPLC), related substances (HPLC), identity of antioxidant (GC), tautomer (HPLC), residual solvents (GC), sulphated ash, water content (Karl-Fischer), optical rotation, colour of the solution, active content (HPLC), antioxidant content (HPLC), microbial quality.
All routine tests either comply with the requirements of Ph. Eur. or have been described and validated in detail.

Analytical certificates for six batches of everolimus have been documented. The certificates were found in compliance with the in-house specification. The proposed specifications and analytical methods were considered appropriate for quality control of the active substance.

The everolimus stabilized with BHT is packaged in either in

- triple laminated aluminium foil bags (PE/Al/PET) or
- quadruple laminated aluminium foil bags (PE/PET/Al/PET)

The polyethylene layer is in contact with the active substance. A certificate of analysis for each primary packaging material was provided as well as the IR identification spectrum and the statements of compliance with the Ph. Eur corresponding monographs. The bags are sealed in an atmosphere of protective gas (Nitrogen or Argon), to protect the material from humidity, light and oxidation, placed in suitable containers during handling.

Stability

Long Term and Accelerated Stability Studies

Three pilot and one production-scale batches kept in triple laminated aluminium foil bags (PE/Al/PET) or amber glass bottles placed in aluminium bags have been placed under ICH stability studies: up to 60 months under long term conditions (-20°C and +5°C°) and up to 1 year under accelerated conditions (25°C/60% RH and 30°C/70 % RH). Nitrogen was used as protective gas for all packaging. The test methods and their validation have been described in a satisfactory manner.
The following parameters were tested: appearance, identity everolimus (HPLC, IR), identity BHT, X-ray diffraction pattern, specific optical rotation, water (Karl Fischer), appearance of the solution, related substances (HPLC), assay BHT and assay everolimus (HPLC).
No significant change in the quality of the active substance could be observed when stored in the deep freezer in a very tight packaging (aluminium bags) under protective gas. When increasing temperature, a clear correlation could be observed between the increase of degradation products and a decrease of the antioxidant BHT. The comparison of the stability of samples with BHT (0.2 %) or without BHT demonstrated the protective effect of the antioxidant.

Stability studies under stress conditions

Stress testing (such as light, high temperature, humidity and forced degradation conditions) was performed on one batch kept in glass ampoules. A significant decrease of BHT was observed only after storage at higher temperature or when the active substance was unpacked. The content of BHT was optimized in a way that no increase in degradation products could be observed.

The active substance was found sensitive to light, acid and base as well as hydrogen peroxide. Furthermore, the active substance is hygroscopic.

Stability of Production Batches

Long term stability results were presented on three production scale batches of everolimus (stabilized with BHT) kept in triple laminated aluminium foil bags (PE/Al/PET) or in quadruple laminated aluminium foil bags (PE/PET/Al/PET). Everolimus was stable for 60 months at - 20°C or 5°C. Storage of the same batches under accelerated conditions documented for 6 months at 25°C / 60 %RH.

Re-test period

Based on the above results, a re-test period of 60 months of Everolimus stabilized with BHT can be granted when kept at 2-8°C in a very tight packaging: triple laminated aluminium foil bags (PE/Al/PET)) or quadruple laminated aluminium foil bags (PE/PET/Al/PET) and under protective gas.

Comparability exercise for active substance

n/a

2.2.3. Finished medicinal product

Votubia is presented as white to slightly yellowish, elongated tablets with bevelled edge, containing 2.5 mg, 5 mg and 10 mg of everolimus as the active substance.
Other ingredients include lactose anhydrous, crospovidone, hypromellose, lactose monohydrate, magnesium stearate and butylhydroxytoluene.
The tablets are packaged in PA/Al/PVC blister packs.

Pharmaceutical development

The objective was to develop an oral dosage form for a hydrophobic, poorly soluble and chemically unstable active substance. The pharmaceutical development of everolimus 2.5 mg, 5 mg and 10 mg tablets is based on the experience gained during development and commercial manufacture of Certican 0.25 mg, 0.5 mg, 0.75 mg and 1 mg tablets.

The 5 mg and 10 mg everolimus containing tablets have been already marketed under the trade name Afinitor. Development and quality data of the 2.5 mg tablet were also included in module 3; however, at that time the 2.5mg tablet was not considered for registration.

Since all three strengths are dose proportional, the manufacturing process and controls are the same for the 2.5 mg, 5 mg and 10 mg tablets, with the exception that a part of pre-validation and validation of 2.5 mg tablet are performed separately, all other aspects of development, including registration stability, were carried out simultaneously.

Everolimus is almost insoluble in water and by itself, it would have a very low oral bioavailability. In order to increase solubility, and bioavailability, it is converted into a solid dispersion with a hydrophilic polymer (HPMC). This is standard way of increasing solubility. When added in water the polymer dissolves rapidly leaving a large surface area of the active substance, which is then more easily taken into solution.

During development, it was demonstrated that tablets manufactured from a solid dispersion containing BHT as antioxidant were shown to be the optimum dosage form to stabilise the sensitive active substance everolimus.

Compatibility with excipients

During the early stages of development, stress tests of binary mixtures of active substance with a number of excipients commonly used for oral formulations were stored and tested for compatibility. Based on those experiments, the following excipients were chosen: butylhydroxytoluene (antioxidant), lactose monohydrate (filing agent), hypromellose (carrier), magnesium stearate (lubricant), and lactose anhydrous (filling agent).
Everolimus 2.5 mg, 5 mg and 10 mg tablets contain the same excipients, but ratios may differ.

Particle size of solid dispersion

The influence of the particle size of the solid dispersion on content uniformity of the tabletting blend was investigated. For all strengths tested, content uniformity of the tabletting blend was slightly better

using a fine milled solid dispersion than with a coarse milled material. However, no significant differences in dissolution characteristics were found between tablets prepared with these two extreme batches indicating that particle size distribution of the dispersion is not critical.

Tabletting process

Since Everolimus tablets are manufactured by direct compression, it is important that the solid dispersion as one main component of the tablet mass and the other excipients have similar particle sizes and densities in order to prevent segregation and thus to obtain good compression properties as well as good content uniformity results. Therefore, the particle size and density of the solid dispersion are similar to lactose anhydrous which is used as the main filler.

In-vitro dissolution

The dissolution method for Everolimus 2.5 mg, 5 mg and 10 mg tablets was appropriate. The test method utilizes USP / Ph. Eur. apparatus 2 (Paddle method) at 50 rpm in 500 ml water with addition of 0.4 % sodium dodecyl sulfate (SDS). Dissolution is fast and complies with the specification of not less than 85 % (Q-value) of the declared content of active substance released in 30 minutes, therefore, everolimus 2.5 mg, 5 mg and 10 mg tablets are classified as 'Immediate Release Solid Oral Dosage Form'. The choice of the dissolution method has been adequately justified.

Clinical trial formulae

The composition of the tablets used in the clinical studies is identical to the composition of the tablets applied for.

Adventitious agents

The only excipients potentially related to BSE/TSE are lactose and magnesium stearate. The applicant has stated that the magnesium stearate is of vegetable origin and that the lactose is obtained from milk, fit for human consumption and is in accordance with the requirements stated in 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. 2-October 2003). There is no risk of TSE/BSE foreseen.

Manufacture of the product

The manufacture is a two step process: preparation of the solid dispersion and tabletting.

Manufacture of everolimus solid dispersion

The manufacture of everolimus solid dispersion consists of standard processes with appropriate in-process control testing. No process step during manufacture is considered to be critical.
The solid dispersion is packaged in tightly closed stainless steel drums or in sealed triple laminated aluminium foil bag, under with nitrogen and stored between 2 to 8°C. Prior to use in the manufacture of the tablets it has to be placed for 24 hours at room temperature for equilibration. The dispersion (pharmaceutical intermediate) is tested in accordance with an intermediate monograph. All testing procedures are described and validated.

The solid dispersion is tested for identity everolimus (XRPD, detection of crystalline everolimus in the solid dispersion), residual solvents, water (Karl Fischer), identification and assay of BHT (GC),

identification everolimus (HPLC), assay everolimus (HPLC), degradation products (HPLC) and microbial limit tests.
Batch results of seven production batches of everolimus solid dispersion are documented.
Despite the fact that in all cases the intermediate batches consistently met the specified acceptance criteria, different levels have been observed for a certain impurity, although they still lie within the set acceptance levels having no impact on the safety of the product. Nevertheless, it was recommended to further investigate the root causes of the observed variability and to tighten the limit of this impurity in the solid dispersion intermediate specification and the finished product specification if necessary.
In addition, at the time of the CHMP opinion it was recommended to update the intermediate specification for the solid dispersion in order to be in line with the tightened limits for various impurities agreed during the procedure.
Based on the stability data, a shelf life of 12 months can be assigned for the everolimus solid dispersion when stored at 5°C in triple laminated foil bags or stainless steel containers. The product has to be protected from water uptake by storing it in tightly closed containers.

Manufacture of everolimus 2.5 mg, 5 mg and 10 mg Tablets

The manufacture of Everolimus 2.5 mg, 5 mg and 10 mg tablets consists of standard process with appropriate in-process control testing. The solid dispersion is subsequently processed with the other excipients by direct compression to obtain the medicinal product. The equipment used consists of a diffusion mixer, a sieve and a powder assisted tablet press. The tabletting mixture is prepared with conventional mixing and sieving procedures and final direct compression. None of the process steps were considered as critical when applying parameters from within the established operational ranges. During tabletting in-process controls of average mass, hardness, friability and disintegration time were carried out. Everolimus tablets are packaged in double-sided aluminium blister packs. Blisters are assembled in a cardboard-based pack.

As a conclusion, 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 products.

Medicinal Product Process Validation

The two manufacturing steps (solid dispersion and tablets preparation) have been validated independently from each other.

Validation for the solid dispersion manufacturing process

The manufacturing method of Everolimus solid dispersion has been validated on three production-scale batches which have been processed in the same manufacturing facilities, using the same process and the same equipment as for the batches intended for marketing.
All three batches fully met the quality control specifications. Together with the in-process control data and the additional testing performed, it was demonstrated that the manufacturing process is robust and consistently yields a product capable of meeting the predefined quality characteristics.

Validation of Everolimus 2.5 mg, 5 mg and 10 mg tablets

The tablets are produced according to standard manufacturing processes such as mixing, sieving and compression. The manufacturing process was validated on three full-scale production batches of each strength processed in the same manufacturing facilities, using the same process and the same equipment as the batches intended for marketing.

All three batches fully met the quality control specifications including particle size, and microbial enumeration test. With the in-process control data and the additional testing it has been demonstrated that the manufacturing process is robust and consistently leads to a product capable of meeting the pre-defined quality characteristics.

Control of excipients

The excipients used in the composition and during the manufacture of Everolimus 2.5 mg, 5 mg and 10 mg tablets are common pharmaceutical excipients used for tablets such as BHT, Magnesium stearate, Lactose monohydrate, Hypromellose, Crospovidone, Lactose anhydrous, Nitrogen, Ethanol anhydrous and Acetone. A certificate of analysis was presented for each excipient and they all comply with their respective Ph. Eur monographs.

Product specification

Adequate specifications at release and at the end of shelf-life have been described for the 2.5 mg, 5 mg and 10 mg tablets including parameters such as: appearance (visual examination), identity everolimus (UV and HPLC), identity BHT (GC), mean mass, dissolution everolimus (UV), related substances (HPLC), water content (Karl-fischer), microbial quality, assay everolimus (HPLC), assay BHT (GC), uniformity of dosage unit (content uniformity Ph. Eur).

Analytical procedures for the quality control of the medicinal product have been described in detail and non-compendial methods validated in accordance with ICH requirements whereas no validation was deemed necessary for the pharmacopoeial methods.

Batch analyses for 3 pilot scale and 1 production-scale batches for the 5 mg and 10 mg strengths and for 3 pilot and 4 production-scale batches for the 2.5 mg strength have been provided. Those batches were used for pre-validation, registration stability, bioequivalence and in clinical studies. All batches consistently met the release specifications.

The tablets will be packed in double sided aluminium blister consisting of an aluminium covering (or lidding) foil with a heat seal lacquer (vinyl acryl resin) and of a PA/Al/PVC bottom (or forming) foil in which the cavities are formed. The suitability of the container closure system has been demonstrated during stability studies. A certificate of analysis for each primary packaging material was provided as well as the IR identification spectrum and the statements of compliance with the Ph. Eur corresponding monographs.

Stability of the product

Registration Stability Studies

Studies have been conducted on three batches of everolimus 2.5 mg tablets and three batches of everolimus 10 mg tablets. A bracketing approach was used for the 5 mg strength. Since all dosage strengths are manufactured from the same tabletting mixture of identical qualitative and quantitative composition the bracketing design was found acceptable. The tablets only differ in size and weight.

Batches were kept in the commercial packaging during 24 months under long term (25°C/60 %RH) and intermediate conditions (30°C/75 %RH) as well as for 6 months under accelerated conditions (40°C/75 %RH). Stability studies were also performed during 3 months (50°C / 75% RH) and 6

months (-20°C and 5°C). The analytical methods used for stability testing were the same as those used for the release testing.
All requirements of the Votubia test specifications are valid at release and throughout shelf-life. However, for shelf-life only the stability indicating parameters were tested, as they are colour, dissolution, impurities (water, degradation products), assay of BHT and assay of everolimus. Tablet form and surface, identity of everolimus and BHT, mean mass, uniformity of dosage and microbial purity are tested only at release.
No significant change could be observed for most of the parameters tested during long-term, intermediate and accelerated stability testing. Total amount of impurities shows a slight increase at intermediate and accelerated conditions but all values remained within the specification.

At the time of the CHMP opinion, it was recommended that the shelf-life total impurity limits be further reviewed based on the agreed tightened limits for all specified impurities. The applicant committed to tighten the finished product specification for impurities.

Photostability studies were conducted on one batch of each strength. The tablets were treated unpacked with 3,000 luxh, 50,000 luxh and 1.2 million luxh. Unexposed samples packed in the designated commercial packaging material were used for comparison. Results showed that everolimus was sensitive to light.
A complete analysis (chemical and physical testing) was performed on one batch of each strength stored for 4 complete freeze and thaw cycles of -20°C for 6 days followed by 1 day at 25°C. Samples were taken after 28 days and analyzed. No significant changes were observed.
The Microbial limit test was performed with one batch of each strength at the initial time point, after 12 months storage and will be performed at the end of the anticipated shelf life at 25°C/60% RH and 30°C/75% RH. Data after 12 months storage were presented. All values were within specified limits.

Stability Summary

Based on the results of the registration stability data, data support the proposed shelf life when the product is stored under the storage conditions as defined in the SmPC.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The quality of this medicinal product is considered satisfactory when used within the conditions defined in the SmPC. The documentation provided for the active substance everolimus is comprehensive and adequately detailed. The pharmaceutical development is adequate and took into consideration the properties and the stability of the active substance. The excipients used are common excipients for immediate release dosage forms. Similarly, the packaging material is well documented and no incompatibility has been noticed. The validation of the manufacturing process ensures consistency and reproducibility of the finished product. The finished product has been satisfactorily controlled and stability studies conducted under ICH conditions showed that the product is stable throughout the proposed shelf-life of 3 years.

Quality Development

Not applicable

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, apart from the need to re-evaluate the genotoxic potential of the impurities in the active substance, which is reflected as an obligation to conduct this post-authorisation measure in Annex II of the CHMP Opinion. However, this does not have a negative impact on the Benefit Risk balance of the product at this stage.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. Update of the intermediate specification for RAD001 9.09% solid dispersion in line with tightened limit for various impurities agreed during the procedure.

2. Investigation into the varying levels of impurity 008-96 in the manufacture of the solid dispersion. The limit for this impurity in the solid dispersion intermediate specification and the finished product specification should be tightened as necessary if the variation in levels of impurity 008-96 can be mitigated during the manufacture of the 9.09% solid dispersion.

3. Revision of the total impurity limit of NMT 4.0% at shelf-life based on limits finalised for all specified impurities. The finished product specification should be updated to introduce the tightened limit for impurities.

4. Revision, in accordance with ICH Q3C(R4), of the limit for pyridine and 1,2-dimethoxy-ethane in the final drug substance to NMT 200 ppm and NMT 100 ppm, respectively. Testing for these solvents should be performed on every tenth batch or one batch per year, whichever is more frequent. An appropriate method should be developed and validated.

5. Validation of an appropriate method for the determination of trifluoromethane sulfonic acid and N-ethyldiisopropylamine.

2.3. Non-clinical aspects

2.3.1. Introduction

The preclinical studies were performed between 1992 and 2010 by Novartis Pharma AG and in contract research laboratories. Relevant toxicity studies were performed in compliance with GLP. According to standards valid during the compound selection phase, pharmacology, general pharmacology, early toxicity studies and a limited number of investigational studies were, however, not performed in compliance with GLP. Some safety pharmacology studies, which were conducted prior to the implementation of ICH S7A/B, were conducted under non-GLP conditions.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Everolimus has been demonstrated to specifically bind the intracellular immunophilin FKBP-12 and inhibit downstream effectors of mTOR, including S6K and 4E-BP1. A dose-dependent effect has been demonstrated in human and rodent tumour cell lines, both *in vitro* and *in vivo*, in rat skin and circulating PBMCs both in rats and patients treated with everolimus. Endothelial (HUVEC) cells also showed a high sensitivity to everolimus *in vitro*, and consistent with this effect, everolimus showed anti-angiogenic activity on solid tumours including decreasing VEGF levels, reducing blood vessel density (BVD) and inhibiting mature blood vessel growth. Although S6K activity as a marker was not sufficient to identify sensitive cells, it did prove useful for a PK/PD model which helped identification of a suitable dose and schedule in phase-I clinical trials. Normal haematopoietic stem cells were not sensitive to everolimus, with an IC_{50} about 15-fold higher than the tumor lines. The effect of everolimus in tumour models is summarised in Table 1.

Furthermore, the efficacy attained was in most cases similar to standard cytotoxic agents such as cisplatin, doxorubicin, paclitaxel and 5FU.

Table 1 Effect of everolimus in experimental tumor models

Study ID	Tumor Cell line	IC50 (nM)	Compound	Regimen	Tumor Response T/C and Regressions i.e. – T/C (R)	Host Response % Body Weight Change
RD-2001-00848	A549 Lung	2.4	RAD001 Cisplatin Doxorubicin None	2.5 mg/kg, po., q24h 5 mg/kg, iv., q7d 9 mg/kg, iv., q7d	-0.1; R: persistent 0.79; R: transient 0.49 1.0	1 ± 1 -2 ± 3 -18 ± 1 6 ± 2
RD-2001-00860	NCI-H596 Lung	5	RAD001 Taxol Doxorubicin Cisplatin None	2.5 mg/kg, po., q24h 15 mg/kg, iv, 3x/wk 9 mg/kg, iv., q7d 5 mg/kg, iv., q7d	0.17 -0.33 0.31 0.65 1.0	9 ± 2 -3 ± 2 -22 ± 3 7 ± 2 9 ± 1
RD-2002-00002	NCI H-520 Lung	42.6	RAD001 Cisplatin None	2.5 mg/kg, po, q24h 5 mg/kg, iv., q7d	0.15 0.34 1.0	12 ± 4 -6 ± 2 6± 2
RD-2000-02548	AR42J Pancreatic	nd	RAD001 RAD001 Doxorubicin None	2.5 mg/kg, po., q24h 5 mg/kg 2x/wk, po. 9 mg/kg, iv., q7d	0.24 R: transient 0.44 0.14 1.0	11 ± 1 7 ± 2 -4 ± 2 10 ± 2

Study ID	Tumor Cell line	IC50 (nM)	Compound	Regimen	Tumor Response	Host Response
					T/C and Regressions i.e. – T/C (R)	% Body Weight Change
RD-2000-02548	MiaPaCa Pancreatic	nd	RAD001 None	5 mg/kg, po, q24h	0.45 1.0	6 ± 4 7 ± 5
RD-2000-02550	HCT-116 Colon	65	RAD001 5-FU None	5 mg/kg, po, q24h 75 mg/kg, iv., q7d	0.37 0.30 1.0	-6 ± 2 -8 ± 3 - 5 ± 3
	RIF-1 Fibrosarcoma (McSheehy et al2010a)	2.6	RAD001	10 mg/kg	0.05	3 ± 1
RD-2001-00854	B16/BL6 Melanoma Primary tumors B16/BL6 Melanoma Cranial metastases	0.7 0.7	RAD001 RAD001	5 mg/kg, po, q24h 1.0 5 mg/kg, po, q24h Nd	0.24 0.34	9 ± 1 9 ± 1
RD-2000-02549	KB-31 Epidermoid	1779	RAD001 Doxorubicin None	2.5 mg/kg, po., q24h 9 mg/kg, iv., q7d	0.26 0.30 1.0	6 ± 1 -8 ± 2 5 ± 2
RD-2002-03237	KB-8511 Epidermoid (MDR)	1489	RAD001 Taxol None	2.5 mg/kg, po., q24h 15 mg/kg, iv, 3x/wk	0.28 0.71 1.0	4 ± 1 -2 ± 5 6 ± 3

T/C: mean increase of tumor volumes of treated animals divided by the mean increase of tumor volumes of control animals. Regression is a negative T/C value.

Everolimus was tested in a broad range of human tumor cells *in vitro* for inhibition of proliferation. Most cell lines (80%) were considered sensitive with IC_{50} values of between 0.3 and 70 nM.

Everolimus also showed significant anti-tumor activity in a wide range of different human xenografts grown in athymic mice. At doses ranging from 0.1 to 10 mg/kg, p.o., once per day (well-below the maximally tolerated dose of > 60 mg/kg, p.o., once per day) [Report RD-2000-02547], everolimus reduced tumour growth rate and final tumor volume, and inhibited tumour lines considered sensitive *in vitro* (A549, NCI H-596, NCI H-520, B16/BL6) as well as those described as insensitive *in vitro* (HCT-116, KB-31 and the P-gp over-expressing (MDR) line KB-8511).

The penetration levels of everolimus into rat brain [Study DMPK(CH) R00-2214], were above the *in vitro* anti-proliferative IC_{50} for HUVEC cells as well as a panel of PTEN-/- glioblastoma cell lines for 168 hr post administration and also some PTEN+/+ lines for approximately 24 hr [Report RD-2001-00852]. In athymic mice, following administration of 5 mg/kg p.o. everolimus [Report RD-2002-02880] levels in the brain were within the *in vitro* anti-proliferative IC_{50} values for PTEN+/+ glioblastoma cells for approximately. 9 hr and above the IC_{50} values for PTEN-/- glioblastoma cells for approximately 24 hr.

The anti-angiogenic properties of everolimus were investigated in a growth factor-impregnated, s.c. implant mouse model [Report RD-2001-00853] and in an orthotopic murine melanoma model routinely used for analysis of anti-angiogenic agents [Report RD-2001-00854]. Everolimus, administered p.o. at 0.5 to 10 mg/kg/day, inhibited primary tumour growth in a dose-dependent manner. Cranial lymph node metastases were also inhibited, but not strictly in a dose-dependent. Everolimus activity in established lesions (treatment beginning 7 days post tumour cell injection when primary and metastatic tumours are detectable) compared with freshly injected tumour cells (treatment beginning one day post injection) showed comparable activity irrespective of a delay in treatment initiation with reduction in BVD, decreased VEGF production and reduced smooth muscle actin on the tumor vasculature *in vivo*.

Significant anti-tumour effects were also seen in xenograft models which were classed as insensitive e.g. in the HCT-116 colon and KB-31 cervical xenograph models in which everolimus had IC_{50} values of 4.1 and 1.8 µM respectively.

A knock-out mouse model for TSC1 has been developed[6]. The results showed that daily treatment of rapamycin or everolimus improved median survival from 33 days to more than 100 days. There was also an improvement in behaviour, phenotype, and weight gain. There was significant brain penetration by both drugs, with accumulation over time with repetitive treatment, and also effective reduction of levels of the S6K1 substrate pS6. Mice treated with rapamycin or everolimus for 23 days only (postnatal days 7-30) had a median survival of 78 days.

Secondary pharmacodynamic studies

Immunosuppressive activity

In a rat model, everolimus reduced IgG levels in response to a T-cell dependent antigen at a schedule of 2.5 mg/kg daily or 5 mg/kg weekly [Study RD-2002-01534]. Both schedules showed anti-tumour activity in a rat model (0.5 mg/kg, 6 days per week: T/C=0.3; 5 mg/kg, weekly: T/C=0.36) [Study RD-2002-03707]. Everolimus also blocked lymphocyte proliferation in response to a mitogenic stimulus [Study RD-2001-01010; Study RD-2001-01459; Study RD-2004-00475] in *in vitro* MLR assay. The six known everolimus metabolites were also active, but at least 100-fold less than that of everolimus.

Bone activity in vitro

Everolimus showed reduced mouse osteoclast and osteoblast differentiation and also osteoclast bone-resorbing activity *in vitro* at concentrations similar to that of sensitive human tumour cell lines (0.6 to 13.5 nM).

Safety pharmacology programme

Safety pharmacology studies are shown in Table 2.

[6] Meikle L, Pollizzi K, Egnor A, Kramvis I, Lane H, Sahin M, Kwiatkowski DJ. (2008) Response of a neuronal model of tuberous sclerosis to mammalian target of rapamycin (mTOR) inhibitors: effects on mTORC1 and Akt signaling lead to improved survival and function. J Neurosci. May 21;28(21):5422-32.

Table 2 Safety pharmacology studies with everolimus

Organ systems evaluated	Species/ strain	Method of Admin.	Doses (mg/kg)[a]	Significant findings	Report number/GLP
Nervous and gastro-intestinal systems, and renal function	Mice	Oral	1.5, 5, 15 or 50	No effects on nervous system and intestinal transit	[RAD 02-c]
	Guinea pigs	Ex vivo Isolated ileum	10^{-7} to 10^{-5} M	Isolated ileum contraction induced by barium chloride and serotonin were inhibited by RAD at concentration of 10^{-5}M No noticeable effects on histamine or acetylcholine-induced contraction of isolated ileum strips	[RAD 02-c]
	Rats	Oral	1.5, 5, 15 or 50	No effects on renal function	[RAD 02-c]
	Sprague-Dawley rats	Oral	2, 20 or 50	No notable effects on primary observation test (POT) parameters of the nervous system	[PKF-93-02177]
Cardiovascular system	In vitro	hERG transfected HEK293 cells	100 ng/ml	No inhibition of hERG channel	[0120037_DITU 1014][b]
	In vitro	hERG transfected HEK293 cells	10 and 16 μM	At target concentrations of 10 and 16 μM, inhibition of hERG channel activity by 2.6 and 17.5%, respectively	[0770800][b]
	In vitro	Sheep Purkinje fibers	0.1-10 μg/ml for 0.5h	No potential for QT interval prolongation	[982042][b]
	Anesthetized pigs	Intravenous	0.01, 0.1, 1 or 10	No relevant ECG changes	[RD-2000-01460]
Lung function	Anesthetized Dunkin-Hartley guinea pigs	Intravenous	0.3, 3.0 or 30	No effects on basal airway resistance and dynamic compliance No biologically relevant acute effects on lung function	[RD-2000-01492]

a: single dose unless specified otherwise

b: GLP study

The studies in safety pharmacology showed that everolimus did not have any relevant effects on vital functions including the cardiovascular function, respiratory function and nervous systems. Everolimus had no influence on QT interval prolongation as shown with isolated sheep cardiac Purkinje fibers, in stable transfected HEK293 cells (hERG currents) and with conventional ECG monitoring in minipigs and

monkeys [Study SAZ494/951127]]; [Study 95/SPM049/1008]; [Study 96/SPM078/1067]; [Study 1534-1463-045]; [Study 1396-1463-019].

There were no relevant changes in the behaviour of rodents, even after single oral doses up to 2000 mg/kg [Study RCC 393131]; [Study RCC 393118].

Pharmacodynamic drug interactions

The combination of everolimus with other cytotoxic drugs was tested using both *in vitro* and *in vivo* models. Investigations included a) established drugs involving the more traditional targets of microtubules (paclitaxel, patupilone), anti-metabolites (gemcitabine and 5-fluorouracil) and DNA (cisplatinum, doxorubicin and temozolomide) and b) more targeted compounds/drugs for the ER (letrozole), ErbB1/2 (gefitinib, erlotinib, NVP-AEE788) and VEGF-R (NVP-AEE788, PTK/ZK, bevacizumab) signal transduction pathways. There was no case of *in vitro* anti-tumour antagonism observed, but *in vivo* there was antagonism with paclitaxel when it was administered 24h before or after everolimus, but not when administered concomitantly.

2.3.3. Pharmacokinetics

ADME and toxicokinetic studies were performed with 3H- or 14C-radiolabeled and non-radiolabeled everolimus in the mouse, rat and monkey after oral and intravenous administration. The blood/plasma distribution and plasma protein binding of 3H-radiolabeled everolimus in the mouse, rat, monkey and human was studied *in vitro*. The ability to cross the blood-brain barrier was investigated *in vivo* in the rat. The metabolism of everolimus was investigated *in vivo* in the mouse, rat and monkey as well *as in vitro* using animal and human liver microsomal fractions and liver slices. The absorption and intestinal metabolism of everolimus was studied *in vitro* and *in vivo*.

Absorption

The oral absorption of everolimus was low in mice (12%), monkey (18%) and medium in rats (~ 40%). The bioavailability of unchanged everolimus was 14-26% in the rat and 6% in the monkey. Everolimus is a substrate for the transmembrane efflux transporter system P-glycoprotein (P-gp; MDR1;ABCB1)[7]. The absolute bioavailability of everolimus was 5% in the mouse, 26% in the rat and 6% in the monkey.

Multiple daily oral doses (0.5 mg/kg/day) of $^{[3H]}$everolimus given to rats increased the $AUC_{0\text{-}24h}$ exposure of everolimus radioactivity moderately 2.4-fold on Day 21 compared to Day 1.

Distribution

In plasma, the free fraction of everolimus was independent of concentration and averaged 7.6% in the rat, 16% in the monkey, and 25% in human, but only 0.1% in the mouse. The *in vitro* distribution of

[7] Crowe A and Lemaire M (1998). In vitro and in situ absorption of SDZ-RAD using a human intestinal cell line (Caco-2) and a single pass perfusion model in rats: comparison with rapamycin. Pharm Res; 15(11):1666-72.

[3H]everolimus between blood cells and plasma was concentration-dependent over the range of 5 to 5000 ng/mL in the rat (24 to 90%) monkey (21 to 82%) and human (17 to 73%). In contrast, in the mouse the blood/plasma partitioning was concentration-independent with ≥ 93% of [3H]everolimus confined to plasma. Everolimus was highly bound to plasma proteins in the mouse (99.9%) and rat (92%) and moderately bound in the monkey (84%) and human (75%). The volume of distribution at steady-state (Vss) based on blood concentrations, was high in rats (44-52 L/kg), moderate in monkeys (4.3 L/kg) and very low in the mouse (0.42 L/kg). Multiple oral dosing at 0.5mg/kg/day over 21 days led to increased 24 hour trough radioactivity levels by a factor of 4.4 fold and up to 3-fold in rat blood and tissues respectively. Everolimus showed dose dependent blood distribution. At therapeutic concentrations most of the drug was blood cell bound. Protein binding was 75-92% in rats, monkeys and humans and 99.9% in the mouse.

In rats, tissue distribution of radioactivity was essentially extravascular with highest levels found in heart, lung, liver, kidney, spleen, thyroid and adrenal gland. Unchanged everolimus was the major component of tissue radioactivity at all sampling times after oral and intravenous administration[8].

Following single and multiple oral administration for 21 days (0.5 mg/kg/day), metabolite patterns in tissues, such as liver and kidney were comparable to those in blood. Tissue levels of radioactivity were in general higher than those measured at the corresponding time point in blood. In particular, everolimus and/or its metabolites displayed no special affinity to melanin-containing tissue of the pigmented rat. In the rat, the blood-brain passage of everolimus and/or its metabolites was found to be dose-dependent. At intravenous doses between 0.1 and 1 mg/kg, the brain/blood concentration ratio was from 0.3 to up to 3 at an i.v. dose of 30 mg/kg. The blood and brain concentrations of [3H]everolimus showed a rapid uptake in the brain followed by a slow efflux (t½ = 10 days). At 168 h post-dose, there were still significant levels observed in the brain, whereas no significant blood levels were detected in the periphery. In contrast, the radioactive metabolites of [3H]everolimus did not significantly cross the blood-brain barrier in the rat and no significant metabolism was apparent in brain.

[3H]Everolimus-related radioactivity passed the placenta of pregnant rats to a limited degree and was readily transferred into milk of lactating rats.

Metabolism

The metabolism of everolimus was investigated *in vivo* in mice, normal and bile duct-cannulated rats, lactating rats, monkeys and human using ^{3}H- and/or ^{14}C-radiolabeled compound. The animals were dosed intravenously and/or orally. The metabolite pattern was essentially similar in all species.

Everolimus is mainly eliminated by metabolism in the mouse, rat, monkey and human. Everolimus was the main circulating drug-related component in blood of all species. The metabolite patterns in the blood were comparable in all species. In the rat, everolimus formed a large number of metabolites. The metabolites were excreted almost exclusively via the bile into faeces [Study 303-013] and only trace amounts of parent drug could be detected. In bile and in faeces, the chromatographic metabolite profile consisted of one broad peak reflecting a complex biotransformation pattern for everolimus

[8] Laplanche R, Meno-Tetang GM, and Kawai R (2007). Physiologically based pharmacokinetic (PBPK) modeling of everolimus (RAD001) in rats involving non-linear tissue uptake. J Pharmacokinet Pharmacodyn; 34(3):373-400.

[Study 303-013]. Everolimus inhibited competitively the metabolism of the CYP3A4 substrate cyclosporine (Ki = 2.3 µmol/L) and was also a mixed inhibitor of the metabolism of the CYP2D6 substrate (Ki = 1.7 µmol/L) *in vitro*.

In human blood, five major metabolite peaks (P36, P40, P42, P50, P57) containing six metabolites were present. These metabolite peaks were also detected in blood of the mouse, rat and monkey. Peak P57 (ATG181) was identified as a direct phosphatidylcholine conjugate of everolimus. The main metabolites P40, P36, P42, P50 and the phosphatidylcholine conjugate P57 were tested for biological activity in a mixed lymphocyte reaction (MLR) assay. They were found to be about two orders of magnitudes less active than everolimus. P57 affinity for FKBP-12 was 2 to 3 times higher than everolimus. Despite this high affinity for FKBP-12, ATG181 was at least 100-fold less active than everolimus in the MLR assay.

In vitro incubations of everolimus with liver microsomal fractions from mouse, rat, monkey and human resulted in metabolite patterns comparable to those observed in blood of the corresponding investigated species[9, 10, 11, 12], except peak P57 (ATG181) which was not formed.

Excretion

Essentially no unchanged everolimus was present in faeces and in urine of all species. Faeces, representing the predominant excretory route, contained a large number of metabolites. With exception of metabolite peak P147 (see below), characterization of faecal metabolites was not feasible due to the complexity of the pattern and the difficulties separating the peaks. In urine, only one very polar peak was observed. Structures of metabolites in that peak could not be elucidated.

In the mouse, more than 95% of either an oral or intravenous dose of $^{[3H]}$everolimus was recovered in the faeces. Excretion was almost complete within 48 hours. The half-life of everolimus in mouse was about 9 hours, and total blood clearance was 0.79 mL/min/kg corresponding to about 0.9% of the hepatic blood flow.

In the rat, 3H radioactivity was recovered predominantly in the faeces (69 to 82% of dose). Excretion was almost complete. In bile duct cannulated rats, biliary excretion amounted to 71% after the i.v. dose. The excretion of parent drug was almost negligible in urine (< 0.05% of dose) and in bile (0.5% of dose). The terminal half-life of everolimus ranged from 47 to 61 hours after i.v. and oral doses.

In the monkey the radioactivity was excreted mainly in faeces (ca. 67% of dose, i.v.; 76%, p.o.). Balance of excretion was not complete after 7 days, due to slow and continuing faecal excretion (77%, i.v.; 85%, p.o.). The terminal half-life of the parent drug in blood was 27 and 18 hours after i.v. and p.o. administration, and the systemic clearance was low (3.1 mL/min/kg) corresponding to about 7% of the hepatic blood flow (44 mL/min/kg).

[9] Strom T, Haschke M, Zhang YL, et al (2007). Identification of everolimus metabolite patterns in trough blood samples of kidney transplant patients. Ther Drug Monit; 29(5):592-9.
[10] Kuhn B, Jacobsen W, Christians U, et al (2001). Metabolism of sirolimus and its derivative everolimus by cytochrome P450 3A4: Insights from docking, molecular dynamics, and quantum chemical calculations. J Med Chem; 44(12);2027-34.
[11] Jacobsen W, Serkova N, Hausen B, et al (2001). Comparison of the in vitro metabolism of the macrolide immunosuppressants Sirolimus and RAD. Transplant Proc; 33:514-5.
[12] Vidal C, Kirchner GI, Sewing K-F (1998). Structural elucidation by electrospray mass spectrometry: an approach to the in vitro metabolism of the macrolide immunosuppressant SDZ RAD. J Am Soc Mass Spectrom; 9: 1267-74.

The transfer/excretion of ^{3}H-radiolabeled everolimus and its metabolites into milk was investigated after a single oral administration of 0.9 mg/kg to lactating rats at Day 9 after parturition [Study DMPK(CH) R98-708]. The transfer of radioactivity from blood into milk was detected at 30 minutes post-dose. Maximum radioactivity concentrations in milk were reached at 2 h post-dose. The terminal elimination half-life of total radioactivity was roughly similar to that in blood over the time interval 48 to 96 h. The milk-to-blood (M/B) radioactivity concentration-ratio was >1 over the entire investigation period except at 30 min post-dose (factor 0.5-fold).

Potential of everolimus to interact with cytochrome P450 isoenzymes

The identification of enzymes responsible for the metabolism of everolimus was carried out *in vitro* in human liver microsomes (HLM) and in microsomes from cells expressing single human cytochrome P450 isoenzymes (CYPs). CYP3A4 was the major enzyme involved in the microsomal biotransformation of everolimus [Study DMPK (US) 1998/005]. Other CYP isoenzymes, such as CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A5 did not metabolize everolimus. Metabolism of everolimus by CYP3A4 was consistent with its selective inhibition in HLM by a series of CYP3A inhibitors [Study DMPK (US) 1998/005].

The effect of a series of compounds on the metabolism of everolimus (1 µM) was investigated in human liver microsomes [Study DMPK (US) 1998/005]; [Study DMPK(CH) R99-2448]. IC_{50} values determined for inhibition of everolimus microsomal metabolism by cyclosporine (CsA) (2.2 µmol/L), rapamycin (0.8 µmol/L), ketoconazole (0.03 µmol/L and 0.35 µmol/L) and itraconazole (0.18 µmol/L) showed that comedications with strong inhibitors of CYP3A4 have the potential to reduce everolimus metabolism *in vivo*.

Potential of everolimus as an inhibitor of co-administered drugs

Everolimus was shown to be a competitive inhibitor of the CYP3A4 probe substrate CsA *in vitro* (Ki = 2.3 µmol/L) and was also a mixed inhibitor of the CYP2D6 probe substrate dextromethorphan (Ki = 1.7 µmol/L) [Study DMPK (US) 1998/005]. Everolimus had no effect on CYP1A2 and CYP2E1 as indicated by the lack of effect on phenacetin and chloroxanone metabolism, respectively. Using paclitaxel, tolbutamide and s-mephenytoin, everolimus had little or no effect on CYP2C8, CYP2C9 and CYP2C19, respectively.

No interaction between everolimus and oral anticoagulants such as warfarin (a CYP2C9 substrate; IC_{50} ~ 33 µmol/L) is expected as confirmed *in vitro* in human liver microsomes [Study DMPK R0700186]. The generation of 7-hydroxywarfarin, a marker for CYP2C9 activity, was inhibited with an IC_{50} value of 106 µmol/L.

Potential of everolimus to interact with P-glycoprotein (P-gp)

Everolimus was shown to be a substrate of the P-glycoprotein (P-gp; MDR1)[13] and to be a moderate inhibitor of P-gp *in vitro* using a cell line over-expressing P-gp. The IC_{50} value of the inhibition was 9.4

[13] Kovarik JM, Beyer D, Bizot MN, et al (2005). Blood concentrations of everolimus are markedly increased by ketoconazole. J Clin Pharmacol; 45(5):514-8.

µmol/L, 9-fold higher than that of the positive control CsA [Study DMPK R0700777]. This IC_{50} value is more than 50-fold and 150-fold higher than the maximal steady-state blood concentrations following a 70 mg/week and 10 mg/day everolimus dose, respectively, in patients [Study C2102].

Potential of everolimus to induce the liver drug-metabolizing enzymes

A 26-week oral toxicity study in rats at doses of 0.15, 0.5 and 1.5 mg/kg/day, minor changes were noted for rat CYP2B1/2 level (20% reduction compared to control) and for the rate of total metabolite formation (38%-50% increase). There were no significant alterations in the total liver cytochrome P450 content and in the CYP1A1, CYP3A and CYP4A levels [Study DMPK(CH) 1997/526]; [Study DMPK(CH) 1997/526-01].

Potential of co-administrated drugs to induce the metabolism of everolimus

In toxicology studies, co-administration of CsA, a known CYP3A4 inhibitor/substrate and P-gp inhibitor in human, to rat (5 and 10 mg/kg/day) or monkey (50 and 100 mg/kg/day) for four weeks significantly increased the blood AUC of everolimus by 1- to 5-fold in the rat [Study 96/SPM096/0570], and by 3- to 7-fold in the monkey [Study SAZ529/962269]. Conversely, everolimus did not increase significantly the AUC of CsA. For comparison, co-administration of single-dose cyclosporine microemulsion with single-dose everolimus in human increased everolimus C_{max} by 82% and AUC by 168% [CP Study A2304].

The combination of everolimus with tacrolimus in the rat had no relevant effect on the toxicokinetic profile of tacrolimus, whereas the exposure to everolimus was markedly increased after a 4-week treatment by a factor of approximately 2 and 5 at a daily dose of 0.75 and 3 mg/kg tacrolimus, respectively [Study 48EXR].

2.3.4. Toxicology

Single dose toxicity

Single dose toxicity studies were conducted in rats and mice. The study design and key results are summarized in Table 3.

Table 3 Single dose toxicity studies

Study ID / GLP	Species/ Sex/Number/ Group	Dose (mg/kg)/ Route	Approx. lethal dose / observed max non-lethal dose (mg/kg)	Major findings
[RCC 393131] GLP	Mouse, HanIbm: NMRI (SPF) 5m, 5f	2000/ Oral gavage	> 2000 > 2000	No mortality. ↓ Body weight (1F); Slight dyspnea and moderate ruffled fur (2F);
[RCC 393142] GLP	Mouse, HanIbm: NMRI (SPF)	0, 0, 40, 60, 96 intravenou	> 96 > 96	Mortality (placebo groups); Sedation, dyspnea, ruffled fur,

Study ID / GLP	Species/ Sex/Number/ Group	Dose (mg/kg)/ Route	Approx. lethal dose / observed max non-lethal dose (mg/kg)	Major findings
	5m, 5f	s		ventral recumbency and hunched posture (all groups)
[RCC 393118] GLP	Rat, HanIbm: WIST (SPF) 5m, 5f	2000 Oral gavage	> 2000 > 2000	slight ↓ body weight (1M)
[RCC 393120] GLP	Rat, HanIbm: WIST (SPF) 5m, 5f	2.5, 10, 40 intravenous	10 2.5	≥ 10 mg/kg: Mortality (100%); Sedation, dyspnea, ventral or lateral recumbency and convulsion; 10 mg/kg: dark red discoloration of the lungs; LD_{50} = 6.3 mg/kg (calculated by the LOGIT-Model)

No lethality or severe toxicity was observed after single oral doses of 2000 mg/kg (limit test) in either mice or rats.

Intravenous administration to mice [Study RCC 393142] at doses up to 96 mg/kg caused no lethality, whereas 6/20 control animals died from the same amount of the vehicle. In rats [Study RCC 393120], intravenous administrations at 10 and 40 mg/kg were lethal, but at 2.5 mg/kg all animals survived.

Repeat dose toxicity

Repeat-dose oral toxicity studies were performed in mice over 13 weeks, in rats up to 26 weeks, in monkeys up to 52 weeks and in minipigs up to 4 weeks. Study design and major findings of these toxicity studies are summarized in Tables 4, 5, 6 and 7.

Table 4 Repeat dose toxicity studies in mice

Study ID/ GLP	Species/Sex/ Number/ Group	Dose/ Route (m/kg)	Duration	NTEL (mg/kg/day)	Major findings
96/SPM107/1177 GLP	CD-1 Mouse/ 10/sex/group	0, 0.15, 0.5, 1.5, 5 and 15/ oral	13 w	NTEL=0.15 (m), and 0.5 (f) m: AUC(0-24h)=803 ng.hr/mL f: AUC(0-24h)=1258 ng.hr/mL	≥ 0.15 mg/kg: higher incidence of swollen spleen. ≥ 0.5 mg/kg: ↓ testis and epididymide weight; depletion of germ cells and vacuolation of the germinal epithelium of testis; ↓ sperm content and germ cells in tubular lumina of epididymides (m), skin lesions (f); ↑ microvesiculation of zona glomerulosa and/or zona fasciculate of the adrenals (m); thymic atrophy. ≥ 1.5 mg/kg: ↑ liver weight (m); ↑ cholesterol, slight (m); skin lesions (+m); foamy alveolar macrophages (f); ↓ ovarian follicular development and atrophy of uterus (f). ≥ 5 mg/kg: ↓ body weight gain (m); higher incidence of skin abrasions (m); ↑ cholesterol (+f); ↓ uterus weight (f); renal tubular

Study ID/ GLP	Species/Sex/ Number/ Group	Dose/ Route (m/kg)	Duration	NTEL (mg/kg/day)	Major findings
					degeneration with karyomegaly and interstitial inflammation (m); foamy alveolar macrophages (+m). 15 mg/kg: high incidence of skin abrasions (+f); ↑ creatinine concentrations (m); ↓ albumin and A/G ratio (m); ↓ thymus weight; ↑ spleen weight (m); ↑ liver weight (+f), renal tubular degeneration with karyomegaly and interstitial inflammation (+f).

Table 5 Repeat dose toxicity studies in rats

Study ID	Species/Sex/ Number/ Group	Dose/Route (mg/kg)	Duration	NTEL (mg/kg/day)	Major findings
196DFR (non-pivotal) non-GLP	Rat, HanIbm: WIST (SPF)/ 4/sex/group	0, 2.5, 10, 40 Rapamycin for comparison: 40 oral	2 w	NTEL < 2.5 mg/kg.	≥ 2.5 mg/kg: ↓ body weight gain, food intake (m); ↓ lymphocytes, platelets and albumin; thymic atrophy; lymphoid depletion of spleen and lymph nodes; atrophy/decreased secretion of prostate and seminal vesicles; ↑ focal myocardiac degeneration; ↓ extramedullary splenic hemopoiesis; ↑ alveolar macrophages in lungs. ≥ 10 mg/kg: ↓ body weight gain, food intake (+f); ↑ cholesterol (m); skin lesions; bone marrow depletion (m). 40 mg/kg: ↑ WBC/neutrophils; degenerative changes in testes; ↑ incidence of diestrus stage. No major differences in toxicity profile compared to rapamycin.
RCC 617951 GLP	Rat, HanIbm: WIST (SPF)/ 10/sex/group	0, 1.5, 15/ oral	2 w	not applicable	Comparison of microemulsion and solid dispersion formulations: No relevant differences in toxicity profile and exposure between microemulsion and solid dispersion.
95/SPM052/0888 GLP	Rat, HanIbm: WIST (SPF)/ 10/sex/group	0, 0.5, 1.5, 5, 15 oral	4 w + 2 w recovery	NTEL approx. 0.5 mg/kg. Cmax: 8.5 ng/mL (m + f combined)	≥ 0.5 mg/kg: ↓ body weight gain, food intake (m); hemo-concentration; ↓ platelets; ↑ cholesterol (m); chronic myocarditis (m). ≥ 1.5 mg/kg: ↓ body weight gain, food intake (+f); ↑ triglycerides (f); chronic myocarditis (+f); medullary atrophy of thymus; foamy alveolar macrophages; loss of germ cells in testes; atrophy/reduced secretion of seminal vesicles; interstitial cell hypertrophy of ovaries; depletion of secretory granules in salivary glands. ≥ 5 mg/kg: ↑ neutrophils; ↑ cholesterol (+f); low albumin; anterior suture line

Study ID	Species/Sex/ Number/ Group	Dose/Route (mg/kg)	Duration	NTEL (mg/kg/day)	Major findings
					opacities in lens; swelling/disruption of anterior cortical lens fibers; atrophy/reduced secretion of prostate; uterus atrophy; thinning of cortical bone. 15 mg/kg: ↓ sperm counts in testes; reduced contents in epididymides. Recovery of changes except for lungs, heart, eyes and testes.
96/SPM0 90/0404 GLP	Rat, HanIbm: WIST (SPF)/ 10/sex/group	0, 0.1, 0.25, 0.5, 1.5	4 weeks + 2 weeks recovery	NTEL = 0.5 mg/kg. m: Cmax: 10 ng/mL; AUC(0-24h): 102 ng·h/mL f: Cmax: 6 ng/mL; AUC(0-24h): 56 ng·h/mL	≥ 0.5 mg/kg: Medullary atrophy of thymus. 1.5 mg/kg: ↓ body weight gain, food intake; anterior suture line opacities in lens; hemo-concentration; ↓ platelets; ↑ cholesterol (m); chronic myocarditis; ↑ alveolar macrophages; interstitial cell hyperplasia of ovaries; uterus atrophy; depletion of secretory granules in salivary glands. Recovery of changes except for heart. EM: Alveolar macrophages in lungs with vacuoles and multi-lamellar bodies.
96/SPM0 83/1130 and 0770978 GLP	Rat, HanIbm: WIST (SPF)/ 20/sex/group	0, 0.05, 0.1, 0.15, 0.5, 1.5/ oral	26 w + 4 w recovery	NTEL = 0.15 mg/kg. m: Cmax: 1.5 ng/mL; AUC(0-24h): 7.1 ng·h/mL f: Cmax: 1.1 ng/mL; AUC(0-24h): 8.1 ng·h/mL	≥ 0.15 mg/kg: ↓ body weight gain (f); medullary atrophy of thymus (f) ≥ 0.5 mg/kg: Hemo-concentration (m); ↓ platelets (m); ↑ amylase (m); medullary atrophy of thymus (+m); lymphoid atrophy of LN; pigment (lipofuscin) in renal tubular epithelial cells; ↑ hydronephrosis (m); ↑ alveolar macrophages and perivascular lymph. infiltration; mucus cell hypertrophy/plasia of stomach; follicular cell hypertrophy/vacuolation of thyroids (m). 1.5 mg/kg: ↓ body weight gain (+m), food intake; hemo-concentration (+f); ↓ platelets (+f); ↑ neutrophils; ↑ cholesterol (m) and amylase (+f), ↓ albumin (m) and iron; interstitial pneumonitis (m); splenic hemosiderosis; depletion of germ cells, tubular vacuolation and spermatid giant cells in testes. Recovery of changes except for lungs or testes. Special investigations on the liver drug metabolizing enzyme levels and on the overall metabolism: ↑ total metabolite formation, ↓ P450 2B1/2.

Table 6 Repeat dose toxicity studies in monkeys

Study ID	Species/Sex/ Number/ Group	Dose/Route (mg/kg)	Duration	NTEL/ NOAEL (mg/kg/day)	Major findings
SAZ471/	Cynomolgus	1/2/4/10/2	4/3/4/3/4/	Not	≥ 2 mg/kg: Quietness (f).

Study ID	Species/Sex/ Number/ Group	Dose/Route (mg/kg)	Duration	NTEL/ NOAEL (mg/kg/day)	Major findings
943030 non-GLP	Monkey/ 1/sex/group	0/ 40/60 rising-dose study/ oral	3/3 days	achieved	≥ 20 mg/kg: ↑ WBC. ≥ 40 mg/kg: Quietness (m), piloerection and huddled posture (f). 60 mg/kg: Piloerection and huddled posture (+m); ↓ lymphoid activity in thymus, spleen, LN.
SAZ494/ 951127 GLP	Cynomolgus Monkey/ 1/sex/group	0, 5, 15, 45/ oral	2 weeks	NTEL < 5 mg/kg. m: AUC(0-24h): 2460 ng·h/mL f: AUC(0-24h): 2156 ng·h/mL	≥ 5 mg/kg: Piloerection, rash on chest; ↑ fibrinogen (m), activated partial thromboplastin time; ↓ lymphoid activity in thymus, spleen and LN; sub-endocardial/interstitial hemorrhage in heart; ↓ cellularity of bone marrow (f). ≥ 15 mg/kg: Quietness; ↑ fibrinogen (+f); subendocardial/interstitial hemorrhage in heart (m). 45 mg/kg: Rough coat, huddled posture (f); body weight loss and ↓ food intake; ↑ glucose and cholesterol (m); ↓ phosphorus (m); ↑ globulins; sub-endocardial/ interstitial hemorrhage in heart (f); ↓ cellularity of bone marrow (f).
95/SPM 049/1008 GLP	Cynomolgus Monkey/ 5/sex/group	0, 1.5, 5, 15/ oral	4 weeks + 2 weeks recovery	NTEL = 1.5 mg/kg. m: Cmax: 95 ng/mL; AUC(0-24h): 975 ng·h/mL f: Cmax: 131 ng/mL; AUC(0-24h): 1196 ng·h/mL	≥ 1.5 mg/kg: ↓ food intake (f); ↑ fibrinogen; ↓ phosphorus; splenic lymphoid atrophy. ≥ 5 mg/kg: ↑ skin lesions; ↓ food intake (+m); ↓ RBC parameters; ↑ α2/β globulins, ↓ albumin, Alb/Glob ratio (m); thymic medullary atrophy; ↑ histiocytosis in small intestine (f). 15 mg/kg: Pilo-erection, reddening of abdomen (m); ↑ WBC, neutrophils, monocytes; ↑ alanine and aspartate aminotransferases; ↑ α2/β globulins; ↓ albumin, Alb/Glob ratio (+f); ↓ urine sodium; ↑ histiocytosis in small intestine (+m).
96/SPM 078/1067 GLP	Cynomolgus Monkey/ 4/sex/group	0, 0.1, 0.5, 1.5, 5/ oral	26 weeks	NTEL = 0.5 mg/kg. m: Cmax: 68 ng/mL; AUC(0-24h): 358 ng·h/mL f: Cmax: 59 ng/mL; AUC(0-24h): 466 ng·h/mL	≥ 0.5 mg/kg: ↑ skin lesions (m); ↓ body weight gain; splenic lymphoid atrophy; lymphoid depletion in LN; macrophage aggregation in small intestine. ≥ 1.5 mg/kg: Early sacrifice (2m) in weeks 14/25 due to poor health condit.; ↑ skin lesions (+f); ↓ food intake; ↓ RBC parameters; ↑ neutrophils/monocytes, fibrinogen; ↓ phosphorus; ↑ cholesterol; thymic cortical and medullary atrophy; myocardial degeneration/necrosis (1m); degranulation of pancreatic exocrine cells (m); ↓ follicular development and atresia of ovaries. 5 mg/kg: Early termination in weeks 9/10 due to skin lesions, poor health, body weight loss; ↑ α2/β globulins; ↓ albumin, Alb/Glob ratio; ↑ triglycerides, ↑ mucosal inflammation of large intestine; myocardial degeneration/necrosis (m);

Study ID	Species/Sex/ Number/ Group	Dose/Route (mg/kg)	Duration	NTEL/ NOAEL (mg/kg/day)	Major findings
					degranulation of pancreatic exocrine cells; ↑ islet cell degeneration; vacuolation of adrenals. Virology: Coxsackievirus in plasma (including pretest) and heart tissue.
1534-1463-045 GLP	Cynomolgus Monkey/ 4/sex/group	0, 0.1, 0.3, 0.9/ oral	39/52 weeks	NOAEL = 0.1 mg/kg. m: Cmax: 8.5 ng/mL; AUC(0-24h): 98.0 ng·h/mL f: Cmax: 10.1 ng/mL; AUC(0-24h): 59.6 ng·h/mL	≥ 0.3 mg/kg: Diarrhea/soft feces (m); ↓ body weight/food intake (2m); ↑ neutrophils (f); inflammatory changes in GI tract; atrophy of testes. 0.9 mg/kg: Termination after 39 weeks; 1m and 2f sacrificed early due to poor health condition consequent to diarrhea/soft feces and inflammation/ ulceration of large intestine; ↓ body weight and food intake; ↑ fibrinogen (f).

Table 7 Repeat dose toxicity studies in minipigs

Study ID	Species/Sex/ Number/ Group	Dose/Route	Duration	NTEL/ NOAEL (mg/kg/day)	Major findings
212DFP non-GLP	Göttingen Minipig SPF/ 1/sex/group	0, 0.5, 1.5, 5	2 weeks	NOAEL 5 mg/kg	≥ 0.5 mg/kg: ↓ platelets and lymphocytes; ↑ creatinine (f); ↑ seminiferous tubular atrophy in testes; thymic cortical lymphocytolysis; ↓ germinal centre activity in LN. ≥ 1.5 mg/kg: ↓ albumin, γ-globulins, Alb/Glob ratio; ↑ ß1 globulins. 5 mg/kg: Early sacrifice (f) due to pneumonitis; ↑ creatinine (m).
971033 GLP	Göttingen Minipig SPF/ 3/sex/group	0, 1.5, 5, 15/ oral	4 weeks+ 4 weeks recovery	NTEL < 1.5 mg/kg. m: Cmax: 145 ng/mL; AUC(1-24h): 2937 ng·h/mL f: Cmax: 153 ng/mL; AUC(1-24h): 2403 ng·h/mL	≥ 1.5 mg/kg: Diarrhea related to increased coccidial infestation of intestine (m); ↓ body weight gain, food intake (m); ↑ fibrinogen and neutrophils (m); ↓ albumin, alb/glob ratio (m); ↓ phosphorus, alkaline phosphatase, γ-globulins; ↑ α2 and β1 globulins; ↑ percent. of β-lipoproteins; ↓ percent. of chylomicrons (m); thymic atrophy; atrophy/decreased lymphoid activity in LN; myelitis and focal encephalitis (m); ↑ dermatitis; ↑ testicular tubular atrophy and oligospermia in epididymides. ≥ 5 mg/kg: Lymphoid depletion of spleen (1f); necrotic follicles in uterus; microvacuolation of adrenals. 15 mg/kg: Diarrhea (+f) with one death (m)/early sacrifices (3m/1f) due to intestinal erosion with coccidial infestation; ↓ body weight gain and food intake (+f); ↓ platelets (m); ↑ urea, creatinine (2f); ↓ cholinesterase; ↑ LDL (LDL-3 to LDL-6) and ↓ HDL-2a;

Study ID	Species/Sex/ Number/ Group	Dose/Route	Duration	NTEL/ NOAEL (mg/kg/day)	Major findings
					lymphoid depletion of spleen (m); vacuolation of exocrine pancreatic cells with necrosis (m); atrophy of vagina and uterus. Recovery of all changes except for the testes.

The major target organs in all animal species were male and female reproductive organs (testicular tubular degeneration, reduced sperm content in epididymides and uterine atrophy). Males were generally more affected than females. Histopathological findings consisted mainly of depletion of germ cells and tubular vacuolation in testes, reduced sperm content in epididymides, reduced ovarian follicular development and uterine atrophy. Reversibility of changes in male reproductive organs was demonstrated in a 13-week rat study at 0.5 mg/kg after 13 weeks of recovery, whereas at 5.0 mg/kg full recovery was achieved in only half of the animals. Lesions were most probably attributed to an endocrine imbalance. This was evidenced in rats by a decrease in plasma testosterone levels as a consequence of an inhibition of key regulators of steroid hormone synthesis. A slight depletion of cortical bone mass in the rat in the 4-week rat studies at ≥ 5.0 mg/kg at higher doses might also be related to hormonal imbalance but might possibly be a result of bone activity of everolimus as found *in vitro.*

Findings in the lungs related to an increased number of alveolar macrophages were detected at ≥ 1.5 mg/kg in the mouse and at ≥ 0.5 mg/kg in the rat. Eye lesions (swelling/disruption of cortical lens fibers) occurred at ≥ 5 mg/kg which was further investigated in a specific study with two different strains and ages of animals [Study 96/SPM098/0796] and found that lenticular anterior suture lines (at ophthalmic examination), and of swelling/disruption of cortical lens fibers (at histopathological evaluation), were present in both strains of rats. Renal tubular degeneration in CD-1 mice after 13 weeks of treatment at ≥ 5 mg/kg was considered related to the exacerbation of pre-existing interstitial inflammation, possibly as a consequence of immunosuppression and/or an impaired regeneration of renal lesions as reported for rapamycin[14] . There was no indication of kidney toxicity in mice after life-long treatment up to 0.9 mg/kg. Findings in the pancreas were evident in the 4-week minipig and in the 26-week monkey study. In the exocrine pancreas, degranulation (monkeys) and vacuolation (minipigs) of cells have been related to the affected general health condition of the animals. Cholesterol was increased in most species at ≥ 0.5 mg/kg. In the 4-week minipig study, effects on lipid metabolism consisted of a slight increase in low-density lipoproteins and a slight decrease in high-density lipoproteins. In renal transplant patients treated with sirolimus (rapamycin), hyperlipidemia was suggested to be the result of a reduced catabolism of apoB100-containing lipoproteins [15].

Genotoxicity

[14] Lieberthal W, Fuhro R, Andry CC, et al (2001) Rapamycin impairs recovery from acute renal failure: role of cell-cycle arrest and apoptosis of tubular cells. Am J Physiol Renal Physiol; 281(4):F693-F706.
[15] Hoogeveen RC, Ballantyne CM, Pownall HJ, et al (2001) Effect of sirolimus on the lipid metabolism of ApoB 100-containing lipoproteins in renal transplant patients. Transplantation; 72(7):1244-50.

Everolimus was tested in standard test battery for evaluating its genotoxic potential. The study design and key results are presented in Table 8.

Table 8: Overview on genotoxicity test conducted with everolimus.

Type of test/Study ID/ReportID/GLP	Test substance batch	Test system	Concentrations Metabolising system	Results Positive/negative/equivocal
In vitro				
Gene mutations in bacteria / Mut.Bakt. 27/95 / yes	94902	Salmonella strains : TA 1535, TA 97a, TA, TA 98, TA 100, TA 102	+/- S9 0 - 5000 µg/plate	Negative
Gene mutations in mammalian cells / 1463/4-1052 / yes	95905	TK+/- Mouse lymphoma L5178Y cells	-S9 3h treatment: 0-90 µg/ml +S9 3h treatment: 0-120µg/ml	cytotoxic effects: - S9: 3.9 % RS at 60 µg/ml +S9 15.1 % RS at 65 µg/ml genotoxicity: negative
Chromosomal aberrations in vitro./ Z59 / yes	94902	Chinese hamster fibroblast cells (V79)	- S9 3h treatment 0 - 440 µg/ml - S9 20h treatment: 0 - 200 µg/ml + S9 3h treatment: 0- 300 µg/ml	cytotoxic effects: - S9: 30 % RMI at 3h 440 µg/ml, 4.6 % RMI at 20h 36 µg/ml +S9: 30 % RMI at 300 µg/ml genotoxicity: negative
In vivo				
Cytogenetic in vivo / MK 36 / yes	Y182 0895	CD-1 mice, micronuclei in bone marrow 5/sex/group/	two doses oral gavage. 24h apart: 50, 160, 500 mg/kg sampling time point 24 h after last treatment	Negative slight clinical signs of toxicity at 500 mg/kg, 500 mg/kg max feasible dose due to solubility

Carcinogenicity

Long term studies on the effect of everolimus on carcinogenicity in mouse and rat were negative. In the mouse and rat carcinogenicity studies, there was no indication of a tumourigenic potential up to the high dose of 0.9 mg/kg. Exposure levels were above the corresponding systemic exposure in humans only for the mouse study.

Reproduction Toxicity

Reproductive toxicity studies were conducted in rats and rabbits, and embryofoetal development studies in rats, embryofoetal development study in rabbits, peri- and post-natal development study in rats, neonatal and juvenile study in rats and juvenile study in monkeys. The study designs and key results are summarized in Tables 9, 10, 11 and 12.

Table 9 Male fertility studies

Study type/ Study ID / GLP	Species; Number Female/ group	Route & dose	Dosing period	Major findings	NTEL/NOEL (mg/kg &AUC)
Fertility dose-range finding 7061R GLP	Rat	0, 0.15, 0.5, 1.5/ Oral (gavage)	4 weeks prior to mating through day 16 post coitum	1.5 mg/kg: ↓ Body weight gain and food intake; testicular germ cell degeneration and depletion. No male-mediated effects on progeny.	NTEL (paternal): 0.5 mg/kg AUC(0-6h): 38 ng·h/mL
7073R 13-week investigative fertility study with 13 weeks recovery GLP	Rat	0, 0.1, 0.5, 5/ Oral (gavage)	10 weeks prior to mating through day 92 (part 1) 13 weeks recovery and necropsy on day 183 (part 2)	≥ 0.5 mg/kg: ↓ body weight gain. 0.5 mg/kg: Slight and reversible effects on testicular morphology. 5 mg/kg: Marked effects on male fertility with complete recovery in only half of the animals.	NOEL (paternal): 0.1 mg/kg AUC(0-24h): 9.9 ng·h/mL.

Table 10 Female fertility/Embryo-fetal development toxicity studies

Study type/ Study ID / GLP	Species; Number Female/ group	Route & dose	Dosing period	Major findings	NTEL (mg/kg &AUC)
Study 1060R Reproductive toxicity dose-range finding study with toxicokinetics and placental transfer GLP	Rat	0, 0.15, 0.5, 1.5/ Oral (gavage)	2 weeks prior to mating through day 16 post coitum	≥ 0.5 mg/kg: ↓ Body weight gain; ↑ post-implantation loss. 1.5 mg/kg: ↓ food intake; resorption of all implants.	NTEL (maternal/ embryotoxicity): 0.15 mg/kg AUC(0-6h): 10 ng·h/mL Embryonic tissue: 42 ng/g.
3074R Fertility and embryo-fetal development study GLP	Rat	0, 0.1, 0.3, 0.9 Oral (gavage)	Males: not dosed Females: 2 weeks prior to mating through day 16 post coitum	≥ 0.1 mg/kg: ↑ Pre- and postimplantation losses; delay in skeletal development. ≥ 0.3 mg/kg: ↓ Body weight development; ↓ fetal weight; ↑ incidence of unspecific malformations (e.g. thoracic vertebrae, ribs, sternebrae) 0.9 mg/kg: ↓ Food intake; ↑ incidence of 14 ribs. Two fetuses	NTEL (intrauterine development): < 0.1 mg/kg; AUC(0-6/24h): 7.9/20.0 ng·h/mL Embryonic tissue: Below LOQ NTEL (maternal): 0.3 mg/kg; AUC(0-6/24h): 11.4/37.5 ng·h/mL

Study type/ Study ID / GLP	Species; Number Female/ group	Route & dose	Dosing period	Major findings	NTEL (mg/kg &AUC)
				with sternal cleft.	Embryonic tissue: 0.8 ng/g (6 h) Concentration ratio embryonic tissue/maternal blood: 0.8; Accumulat. factor placenta: 26.2.
2059K Embryo-fetal development dose-range finding study GLP	Rabbit	0, 0.5, 1, 1.5, 5 Oral (gavage)	GD 6-18	≥ 0.5 mg/kg: ↓ Body weight, food and water intake. ≥ 1.5 mg/kg: ↑ Post-implantation loss.	NTEL (intrauterine development): 1.0 mg/kg; AUC(0-6h): 178 ng·h/mL. NTEL (maternal): < 0.5 mg/kg.
4070K Embryo-fetal development study GLP	Rabbit	0, 0.05, 0.2, 0.8 Oral (gavage)	GD 6-18	≥ 0.2 mg/kg: One dam died. ↓ body weight gain. 0.8 mg/kg: One dam died. ↓ Body weight; ↓ food intake; ↑ percentage of late resorptions.	NTEL (intrauterine development): 0.2 mg/kg; AUC(0-6/24h): 16.4/61.2 ng·h/mL; Embryonic tissue: below LOQ (1 ng/g); Accumulation factor placenta: 5.3. NTEL (maternal): 0.05 mg/kg; AUC(0-6/24h): 5.2/18.4 ng·h/mL.

Table 11 Pre/Postnatal developmental studies

Study type/ Study ID / GLP	Species; Number Female/ group	Route & dose	Dosing period	Major findings	NTEL/NOEL (mg/kg &AUC)
987105 Pre- and post natal development study GLP	Rat	0, 0.03, 0.1, 0.3 Oral (gavage)	GD 6 – LD 20	≥ 0.1 mg/kg: Slightly reduced body weights and survival in F1 generation.	NOEL (F0): 0.3 mg/kg NOEL (F1): 0.03 mg/kg.

Table 12 Juvenile animal studies

Study type/ Study ID / GLP	Species; Number Female/ group	Route & dose	Dosing period	Major findings	NTEL (mg/kg)
0170129 non-GLP	Rat	RAD001: 0, 1.5, 3 and 5 Rapamycin: 3 Oral (gavage)	Post partum days 7 to 27	Decreased body weight, delay in testes decent in all treated groups. At 3 mg/kg, effects were similar for RAD001 and rapamycin.	NTEL<1.5 mg/kg
0270015 GLP	Rat	RAD001: 0, 0.15, 0.5 and 1.5 Rapamycin: 1.5 Oral (gavage)	Post partum days 7 to 70 with 13- and 26-week recovery	In all treated groups: decreased body weight gain, food consumption, delayed attainment of major developmental landmarks, with full or partial recovery. Target organ for RAD001 and rapamycin included: lens, hematolymphopoietic compartment, prostate, testes, epididymides, seminal vesicles, ovaries, uterus and kidneys. With the exception of lens findings, it appears that there was no significant difference in the sensitivity of the juvenile animals to the adverse effect of RAD001 compared to the adult animals.	NTEL<0.15 mg/kg
1396-1463-019 GLP	Monkey	0, 0.1, 0.25, 0.5 Oral (gavage)	4 weeks + 2 weeks recovery	No findings indicating toxicity up to 0.5 mg/kg.	NTEL = 0.5 mg/kg. m: AUC(0-24h): 604 ng·h/mL f: AUC(0-24h): 624 ng·h/mL

Local Tolerance

The sensitization potential of everolimus was investigated in the guinea pig and the skin irritation potential in the rabbit. Furthermore, the intravenous tolerability of a microemulsion formulation of everolimus was evaluated in the rabbit.

All solutions were locally well tolerated [Study 80LTRB]. Everolimus was not irritant to the rabbit skin after semi-occlusive exposure for 4 hours [Study 246781]. Everolimus did not show a potential to cause contact hypersensitivity when applied onto the skin of guinea pigs in the Maximization test [Study 246792].

Other toxicity studies

Antigenicity

The antigenicity potential for everolimus was tested by active systemic anaphylaxis (ASA) reaction in guinea pigs, the passive cutaneous anaphylaxis (PCA) reaction in guinea pigs (with serum from sensitized guinea pigs) and rats (with serum from sensitized mice). Everolimus caused no anaphylactic reactions in guinea pigs in the ASA test, and did not induce cutaneous reactions in guinea pigs or rats.

Immunotoxicity

No specific immunotoxicity study was conducted with everolimus. However, everolimus is expected to modulate immune function due to the mechanism of action (immunosuppressant).

Impurities

Repeat dose toxicity studies in rats did not show any toxic effects that could be attributed to any impurity or degradant.

2.3.5. Ecotoxicity/environmental risk assessment

Patients with subependymal giant cell astrocytoma (SEGA) represent a subpopulation of patients with tuberous sclerosis.

Based on the prevalence of tuberous sclerosis, the applicant calculated a market penetration factor for everolimus of 0.0104 % for the EU market. Using this market penetration factor and a maximum daily dose of 10 mg per patient the predicted environmental concentration (PEC) of everolimus in surface water resulted in a value of 0.00052 µg/L. This value is below the trigger value for a Phase II - Tier A assessment of 0.01 µg/L. According to the result of the Ready Biogradability Test (OECD 301F). Everolimus is not readily biodegradable. A summary of the main studies are found in Table 13.

Table 13: 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 at 22.0 – 22.5 °C	No Potential PBT
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined (prevalence, literature)	0.00052	µg/L	> 0.01 threshold No
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Ready Biodegradability Test	OECD 301	2% within 28d	Not readily

					degradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	3h-NOEC > 1000	mg/L	No toxic to micro-organisms

2.3.6. Discussion on non-clinical aspects

Everolimus is a selective mTOR inhibitor. mTOR is a key serine-threonine kinase, the activity of which is known to be upregulated in a number of human cancers.
Everolimus belongs to the pharmacotherapeutic group: anti- neoplastic agents, other anti-neoplastic agents, protein kinase inhibitors, ATC code: L01XE10

Everolimus binds to the intracellular protein FKBP-12, forming a complex that inhibits mTORC1 activity. Inhibition of the mTORC1 signalling pathway interferes with the translation and synthesis of proteins by reducing the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4EBP-1) that regulate proteins involved in the cell cycle, angiogenesis and glycolysis. Everolimus reduces levels of vascular endothelial growth factor (VEGF), which potentiates tumour angiogenic processes. Everolimus is a potent inhibitor of the growth and proliferation of tumour cells, endothelial cells, fibroblasts and blood-vessel-associated smooth muscle cells and has been shown to reduce glycolysis in solid tumours *in vitro* and *in vivo*.

Two primary regulators of mTORC1 signalling are the oncogene suppressors tuberin-sclerosis complexes 1 & 2 (*TSC1*, *TSC2*). Loss of either *TSC1* or *TSC2* leads to elevated rheb-GTP levels, a ras family GTPase, which interacts with the mTORC1 complex to cause its activation. mTORC1 activation leads to a downstream kinase signalling cascade, including activation of the S6 kinases. In tuberous sclerosis complex syndrome, inactivating mutations in either the *TSC1* or the *TSC2* gene lead to hamartoma formation throughout the body. *TSC1* mutations account for 20–25% of all mutations identified, and *TSC2* mutations account for the remainder.

Everolimus demonstrated significant activity in reversing many of the symptoms of TSC in one mouse model of the disease. In a mouse neuronal model of TSC in which *TSC1* is ablated in most neurons during cortical development, everolimus improved median survival from 33 days to more than 100 days, and behaviour, phenotype, and weight gain all also markedly improved. There was brain penetration, with accumulation over time with repetitive treatment, and effective reduction of levels of phospho-S6, a downstream marker of mTORC1. Neurofilament abnormalities, myelination and cell enlargement were all improved by the treatment, although dysplastic neuronal features persisted, and there were only modest changes in dendritic spine density and length. Strikingly, mice treated with everolimus for 23 days only (postnatal days 7–30) displayed a persistent improvement in phenotype, with median survival of 78 days. In summary, everolimus is a highly effective therapy for this neuronal model of TSC, with benefit apparently attributable to effects on mTORC1 and Akt signalling and, consequently, cell size and myelination. Although caution is appropriate, the results suggest the possibility that everolimus may have benefit in the treatment of TSC brain disease, including infantile spasms.

Everolimus is mainly eliminated by metabolism in the mouse, rat, monkey and human. Everolimus is metabolized mainly through oxidation by cytochrome P450 3A4 in the liver and partially in the gut wall. Therefore, co-medications that are strong CYP3A4 have the potential to reduce everolimus metabolism in vivo. This is highlighted in the SmPC in section 4.4 and 4.5.

Safety pharmacology studies were performed to investigate effects of everolimus on cardiovascular, respiratory, central nervous system, gastrointestinal and renal function. Under the condition tested no relevant effects on vital function were observed.

The non-clinical safety profile of everolimus was assessed in mice, rats, minipigs, monkeys and rabbits. The major target organs were male and female reproductive systems (testicular tubular degeneration, reduced sperm content in epididymides and uterine atrophy) in several species; lungs (increased alveolar macrophages) in rats and mice; pancreas (degranulation and vacuolation of exocrine cells in monkeys and minipigs, respectively, and degeneration of islet cells in monkeys), and eyes (lenticular anterior suture line opacities) in rats only. Minor kidney changes were seen in the rat (exacerbation of age-related lipofuscin in tubular epithelium, increases in hydronephrosis) and mouse (exacerbation of background lesions). There was no indication of kidney toxicity in monkeys or minipigs.

Hyperglycemia without pancreas findings also occurred in monkeys treated with sirolimus.

Hyperglycaemia and hyperlipidemia have also been reported in clinical trials and recommendation for monitoring the serum glucose level has been uptaken in the SmPC section 4.4. Several findings observed in toxicity studies are due to pharmacological effects of the compound such as atrophic changes in lymphatic organs and a variety of skin alterations in mouse and monkey. Everolimus appeared to spontaneously exacerbate background diseases (chronic myocarditis in rats, coxsackie virus infection of plasma and heart in monkeys, coccidian infestation of the gastrointestinal tract in minipigs, skin lesions in mice and monkeys). These findings were generally observed at systemic exposure levels within the range of therapeutic exposure or above, with the exception of the findings in rats, which occurred below therapeutic exposure due to a high tissue distribution (see section 4.4 of the SmPC).

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. 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.

In juvenile rat toxicity studies, systemic toxicity included decreased body weight gain, food consumption, and delayed attainment of some developmental landmarks, with full or partial recovery after cessation of dosing. With the possible exception of the rat-specific lens finding (where young animals appeared to be more susceptible), it appears that there is no significant difference in the sensitivity of juvenile animals to the adverse reactions of everolimus as compared to adult animals. Toxicity study with juvenile monkeys did not show any relevant toxicity. The potential for growth/developmental delays with long-term treatment in SEGA patients is unknown.

Genotoxicity studies covering relevant genotoxicity endpoints showed no evidence of clastogenic or mutagenic activity. Administration of everolimus for up to 2 years did not indicate any oncogenic

potential in mice and rats up to the highest doses, corresponding respectively to 4.3 and 0.2 times the estimated clinical exposure. Everolimus was considered to have no antigenicity potential.

The CHMP considered that there was no need for further environmental risk assessment beyond phase I.

2.3.7. Conclusion on the non-clinical aspects

The adverse treatment-related effects on the reproduction system in the non-clinical studies are of concern in view of the fact that these patients are likely to be of reproductive age and are likely to require long-term treatment. In addition, the clinical relevance of the developmental delay observed in the juvenile rat studies with both rapamycin and everolimus need further clarification. The applicant should evaluate the clinical relevance of these findings. This is of importance as patients with SEGA are likely to be children and will require long-term treatment.

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of PgP. Therefore, absorption and subsequent elimination of everolimus may be influenced by products that affect CYP3A4 and/or PgP. *In vitro*, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

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.

There are no adequate data from the use of everolimus in pregnant women. Studies in animals have shown reproductive toxicity effects including embryotoxicity and foetotoxicity (see section 5.3 of the SmPC). The potential risk for humans is unknown.

2.4. Clinical aspects

2.4.1. Introduction

The demonstration of clinical efficacy was based on a prospective, open-label, single-arm phase II study conducted to evaluate the safety and efficacy of Votubia in patients with SEGA (C2485). Preliminary results from a randomized, double-blind, placebo-controlled Phase III study (Study M2301) have also been submitted.

The applicant applied for the following indication:

Votubia is indicated for the treatment of patients aged 3 years and older with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS).

Following CHMP assessment, the indication for Votubia is the following:

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.

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

Table 14 Summary of key pharmacokinetic studies

Study No.	Study objectives, population	No. of subjects	Treatment duration	Medication dose
Healthy subjects				
[A2302]	Drug interaction study (rifampin)	12	2 x single doses	4 mg
[A2303]	Impaired hepatic function	16	Single dose	1 mg
[A2304]	Drug interaction study (cyclosporine)	24	2 x single doses	2 mg
[A2408]	Drug interaction study (erythromycin)	16	2 x single doses	2 mg
[A2409]	Drug interaction study (ketoconazole)	12	2 x single doses	1 or 2 mg
[A2410]	Drug interaction study (verapamil)	16	2 x single doses	1 mg
[W302]	Food interaction study	24	2 x single doses	1 mg
[W303]	Drug interaction study (atorvastatin, pravastatin)	24	3 x single doses	2 mg
Patients				
[B157]	Impaired renal function in renal transplant patients	94	Multiple doses (1 year)	1, 2, 4 mg/day
[C2101]	Basic pharmacokinetics in patients with advanced solid tumours	92	Multiple doses (4 weeks)	5, 10 mg/day 5, 10, 20, 30, 50, 70 mg/week
[C2102]	Basic pharmacokinetics in patients with advanced solid tumours		Multiple doses (4 weeks)	5, 10 mg/day 5, 10, 20, 30, 50, 70 mg/week
[C2107]	Exposure-response relationships in patients with advanced solid tumours	55	Multiple doses (4 weeks)	5, 10 mg/day 20, 50, 70 mg/week
[W107]	Mass-balance study in renal transplant patients	4	Single ^{14}C-radio-labelled dose	1 mg
[C2120]	light-fat meal vs. high-fat meal vs. fasting	24	three-period, six-sequence crossover study of single dose	10 mg
[B351]	Phase III pediatric renal transplant study	Cohort I: 19 Cohort II: 18	oral dose of 0.8 mg/m2 body surface area (BSA) of bid, 12 hours apart, in combination with ciclosporin and corticosteroids.	(0.1 - and 0.25-mg pediatric dispersible tablets)

Table 15: Controlled and uncontrolled studies for everolimus in the proposed indication

Protocol No. & Study Dates Investigator & Country	**Development phase, Study Design & Purpose** Population Studied	**Total No.& Race (w,b,a,o) Age Range (mean) Group No. & Sex (m,f)**	**Treatment, Route, Regimen, Duration of Therapy, Dosage**	**Study Status**
protocol: [CRAD001C2485] **invest.:** Franz DN **countries:** USA **start:** 07-Jan-2007 **cut-off:** 09-Dec-2009 (corresponding to the date that the last patient had his 12-month assessment visit)	**design, goal & population**: Prospective, nonrandomized, open-label, investigator-initiated, single center study to evaluate safety and efficacy in patients, aged ≥ 3 years, with a confirmed diagnosis of TS and radiological evidence of serial SEGA growth	**total**: 28 (24 w, 2 b, 2 o) **age**: 3-34 years (mean 12.5) **groups**: 17 m, 11 f	**form(s)**: oral everolimus tablets 2.5 mg and 5 mg **duration**: 6-mo core treatment phase after which patients were able to transition into a long-term extension. Treatment continues for as long as therapeutic benefit is evident without significant adverse effect or risk to the patient **doses**: starting dose of 3.0 mg/m^2 BSA daily or every other day and titrated to achieve trough concentrations of 5-15ng/mL	**status:** ongoing
protocol: [CRAD001M2301] **phase:** III **countries:** **start:** 10-Aug-2009 **end:** 24-Apr-2014 **publ.:** none	**design, goal & population:** 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).	**total:** 99 (m/w) (planned) **age:** any age (inclusion criteria) **groups:** 2 Everolimus vs. placebo, 2:1 randomisation	**form**: Everolimus 1-mg tablet **duration**: until SEGA progression, unacceptable toxicity or discontinuation for any other reason. **doses**: starting dose: 4.5 mg/m^2/day. Dose adjustments permitted based on safety findings and blood trough measurements.	**status:** ongoing

2.4.2. Pharmacokinetics

Absorption

Everolimus concentrations in whole blood were determined by a liquid chromatography-mass spectroscopy (LC-MS) method following liquid extraction.

Absorption characterised in patients with advanced solid tumours, showed that peak everolimus concentrations (C_{max}) were reached at a median time of 1 hour after daily administration of 5 and 10 mg everolimus under fasting conditions or with a light fat-free snack. C_{max} was dose-proportional between 5 and 10 mg.

- *Bioavailability*

Study C2121 compared the bioavailability of everolimus tablets taken whole versus suspension. This was a single-center, open-label, randomized, two-way cross-over study with two treatment periods and two treatment sequences, conducted in 40 healthy individuals (male and female), 18 to 55 years of age. A single oral 5 mg dose of everolimus was administered as either 5 x 1-mg everolimus intact tablets (reference) or 5 x 1-mg everolimus tablets suspended in 30 mL of water (test).

The treatment periods were separated by a washout interval of 14 days. The test product was administered to subjects 30 minutes after a light, fat-free breakfast. Forty (40) healthy subjects, all male except 3 females of non-childbearing potential with an age range of 21 up to 55 years, were recruited into the clinical study. Everolimus concentrations in whole blood were determined by a LC-MS method following liquid extraction. The method had a LLOQ of 0.300 ng/mL.

A total of 40 subjects were enrolled, of whom 37 completed both treatment periods. Two subjects were discontinued due to abnormal laboratory values, which were considered to be of CTC grade 1. One patient had raised liver enzymes and one patient had raised neutrophils. Both events normalised and no treatment was necessary. One subject was lost to follow up.

The pharmacokinetic analysis set included the 39 subjects who had completed at least one period with evaluable pharmacokinetic samples. Due to the intake of prohibited medication (clotrimazole a CYP3A4 substrate) one subject was excluded from the pharmacokinetic set.

Elimination kinetics were similar after the intake of 5 x 1-mg intact everolimus tablets and the 5 x 1-mg everolimus tablets in suspension; mean $T_{1/2}$ were 36.0 and 35.9 hours, mean CL/F were 14.1 and 16.0 L/h/m^2 and mean Vd/F were 1395.4 and 1607.9 L respectively (Table 16).

There were no subjects with non-zero plasma concentrations at the start of period 2. There were 9 observations where AUC_{0-t} did not cover 80% of AUC_{0-inf}. This was less than 20% of the total number of observation periods.

Peak and total exposure to everolimus were slightly decreased in the suspension form compared to the intact tablet form. Mean C_{max} and mean AUC_{0-inf} were 20.77 ng/mL and 184.33 ng.h/mL for the 5 mg tablets in suspension and 28.79 ng/mL and 205.82 ng.h/mL for the 5 mg intact tablets, respectively.

Table 16: Summary statistics of pharmacokinetic parameters of everolimus whole blood in healthy subjects following a single oral 5 mg dose of everolimus administered as 5X 1-mg intact tablets or as 5X 1-mg water suspended tablets – Study C2121

PK Parameter	(unit)	5 x 1-mg intact tablets (N=39)	5 x 1-mg tablets in suspension (N=36)
$AUC_{(0-t)}$	(ng.h/mL)	185.01 (75.56)	162.53 (73.44)
$AUC_{(0-inf)}$	(ng.h/mL)	205.82 (77.97)	184.33 (75.72)
C_{max}	(ng/mL)	28.79 (11.62)	20.77 (8.73)
T_{max}	(h)	1.00 (0.50- 1.50)	1.00 (0.50- 2.00)
$T_{1/2}$	(h)	36.04 (8.67)	35.92 (7.99)
λ_z	(1/h)	0.02 (0.004)	0.02 (0.004)
Vd/F	(L)	1395.4 (484.09)	1607.9 (628.87)
CL/F*	(L/h/m^2)	14.08 (6.20)	16.02 (7.45)

*CL/F was BSA (in square meter) normalised

Values are median (range) for Tmax and arithmetic mean (SD) for all other parameters
N=number of subjects

Relative bioavailability of the suspension was on average 86% relative to the intact tablets. The maximum systemic concentration, C_{max}, was on average 28% lower in suspension compared with the intact tablets. The inter-individual variability of C_{max}, AUC_{0-inf} and AUC_{0-t} from 5 x 1-mg everolimus tablets in suspension was similar to that from 5 x 1-mg intact everolimus tablets.

Distribution

The blood-to-plasma ratio of everolimus, which was concentration-dependent over the range of 5 to 5,000 ng/ml, was 17% to 73%. Approximately 20% of the everolimus concentration in whole blood was confined to plasma of cancer patients given 10 mg/day. Plasma protein binding was approximately 74% both in healthy subjects and in patients with moderate hepatic impairment. In patients with advanced solid tumours, Vd was 191 L for the apparent central compartment and 517 L for the apparent peripheral compartment.

Elimination

In humans, excretion of radioactivity occurred primarily through the faecal route (80%), and only a minor amount was excreted in urine (5%). The parent substance was not detected in urine or faeces. The mean CL/F of everolimus after 10 mg daily dose in patients with advanced solid tumours was 24.5 l/h. The mean elimination half-life of everolimus was approximately 30 hours.

Dose proportionality and time dependencies

Dose proportionality has been investigated in healthy volunteers at single doses of 0.5-4 mg (trials W105 and A1101, the latter in Japanese volunteers). Both trials showed linear pharmacokinetics in the single dose range investigated. It has been concluded that PK in the range investigated is linear with the exception of a less than dose proportionally increase of C_{max} at the dose of 20 mg or higher per week.

From trials C2101 and C2107 (solid tumour patients) steady state is reached by week 2, after daily administration of either 5 or 10 mg. After week 2 there is no apparent time dependency but no comparison to Day 1 has been made, thus a time –dependency in pharmacokinetic at the 10 mg daily dose could not be evaluated. With a half-life of approximately 30 h, steady state is expected to be reached after 1 week.

Special populations

PK data in children were available from the paediatric transplant trial B351 and from the SEGA study C2485. Intra-patient steady-state trough concentrations were dose-proportional at daily doses of 1.5 to 14.6 mg/m^2 in study C2485 (see SmPC section 5.2).

Pharmacokinetic interaction studies

Everolimus is a substrate of CYP3A4 and PgP. Therefore, absorption and subsequent elimination of everolimus may be influenced by products that affect CYP3A4 and/or PgP.

In vitro, everolimus was a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6. *In vitro*, everolimus competitively inhibited the metabolism of the CYP3A4 substrate ciclosporin and was a mixed inhibitor of the CYP2D6 substrate dextromethorphan. The mean steady-state of everolimus C_{max} with an oral dose of 10 mg daily or 70 mg weekly was more than 12- to 36-fold below the Ki-values of the *in vitro* inhibition. An effect of everolimus on the metabolism of CYP3A4 and CYP2D6 substrates is therefore unlikely.

There was a significant increase in exposure to everolimus (C_{max} and AUC increased by 3.9-and 15.0-fold, respectively) in healthy subjects when everolimus was coadministered with ketoconazole (a strong CYP3A4 inhibitor and PgP inhibitor). There was an increase in exposure to everolimus in healthy subjects when everolimus was coadministered with the following 3 drugs: erythromycin (a moderate CYP3A4 inhibitor and a PgP inhibitor; C_{max} and AUC increased by 2.0- and 4.4-fold, respectively). verapamil (a moderate CYP3A4 inhibitor and a PgP inhibitor; C_{max} and AUC increased by 2.3-and 3.5-fold, respectively) and ciclosporin (a CYP3A4 substrate and a PgP inhibitor; C_{max} and AUC increased by 1.8- and 2.7-fold, respectively).

Pre-treatment of healthy subjects with multiple doses of rifampicin (a CYP3A4 and PgP inducer) 600 mg daily for 8 days followed by a single dose of everolimus, increased everolimus oral-dose clearance nearly 3-fold and decreased C_{max} by 58% and AUC by 63%.

Known and theoretical interactions with selected inhibitors and inducers of CYP3A4 and PgP are listed in Table 17 below.

CYP3A4 and PgP inhibitors increasing everolimus concentrations
Substances that are inhibitors of CYP3A4 or PgP may increase everolimus blood concentrations by decreasing metabolism or the efflux of everolimus from intestinal cells.

CYP3A4 and PgP inducers decreasing everolimus concentrations
Substances that are inducers of CYP3A4 or PgP may decrease everolimus blood concentrations by increasing metabolism or the efflux of everolimus from intestinal cells.

Table 17 Effects of other active substances on everolimus

Active substance by interaction	**Interaction – Change in Everolimus AUC/C_{max} Geometric mean ratio (observed range)**	**Recommendations concerning co-administration**
***Potent* CYP3A4/PgP inhibitors**		
Ketoconazole	AUC ↑15.3-fold (range 11.2-22.5) Cmax ↑4.1-fold (range 2.6-7.0)	Concomitant treatment of Votubia and potent inhibitors is not recommended.
Itraconazole, posaconazole, voriconazole	Not studied. Large increase in everolimus concentration is expected.	
Telithromycin, clarithromycin		
Nefazodone		
Ritonavir, atazanavir, saquinavir, darunavir, indinavir, nelfinavir		
Moderate CYP3A4/PgP inhibitors		

Erythromycin	AUC ↑4.4-fold (range 2.0-12.6) Cmax ↑2.0-fold (range 0.9-3.5)	Use caution when co-administration of moderate CYP3A4 inhibitors or PgP inhibitors cannot be avoided. If patients require co-administration of a moderate CYP3A4 or PgP inhibitor, reduce the daily dose by approximately 50%. Further dose reduction may be required to manage adverse reactions (see sections 4.2 and 4.4). Everolimus trough concentrations should be assessed approximately 2 weeks after the addition of a moderate CYP3A4 or PgP inhibitor. If the moderate inhibitor is discontinued the Votubia dose should be returned to the dose used prior to initiation of the moderate CYP3A4 or PgP inhibitor and the everolimus trough concentration should be re-assessed approximately 2 weeks later (see sections 4.2 and 4.4)
Verapamil	AUC ↑3.5-fold (range 2.2-6.3) Cmax ↑2.3-fold (range1.3-3.8)	
Ciclosporin oral	AUC ↑2.7-fold (range 1.5-4.7) Cmax ↑1.8-fold (range 1.3-2.6)	
Fluconazole	Not studied. Increased exposure expected.	
Diltiazem		
Amprenavir, fosamprenavir	Not studied. Increased exposure expected.	
Grapefruit juice or other food affecting CYP3A4/PgP	Not studied. Increased exposure expected (the effect varies widely).	Combination should be avoided.
Potent CYP3A4 inducers		
Rifampicin	AUC ↓63% (range 0-80%) Cmax ↓58% (range 10-70%)	Avoid the use of concomitant potent CYP3A4 inducers. Patients receiving concomitant potent CYP3A4 inducers may require an increased Votubia dose to achieve the same exposure as patients not taking potent inducers. Dosing should be titrated to attain trough concentrations of 5 to 15 ng/ml. If concentrations are below 5 ng/ml, the daily dose may be increased by 2.5 mg every 2 weeks, checking the trough level and assessing tolerability before increasing the dose. If the potent inducer is discontinued the Votubia dose should be returned to the dose used prior to initiation of the potent CYP3A4 inducer and the everolimus trough concentrations should be assessed approximately 2 weeks later (see sections 4.2 and 4.4)
Corticosteroids (e.g. dexamethasone, prednisone, prednisolone)	Not studied. Decreased exposure expected.	
Antiepileptic agents (e.g. carbamazepine, phenobarbital, phenytoin)	Not studied. Decreased exposure expected.	
Efavirenz, nevirapine	Not studied. Decreased exposure expected.	
St John's Wort (Hypericum perforatum)	Not studied. Large decrease in exposure expected.	Preparations containing St John's Wort should not be used during treatment with everolimus

Pharmacokinetics using human biomaterials

The applicant did not submit study reports for pharmacokinetics using human biomaterials.

2.4.3. Pharmacodynamics

Clinical pharmacodynamics have not been specifically investigated in SEGA (TSC) other than the explorative attempt to correlate C_{min} with SEGA volume reduction in the pivotal trial of this application (C2485, see Primary and secondary pharmacology).

Mechanism of action

The applicant has not submitted clinical study reports on mechanism of action.

Primary and secondary pharmacology

At the time study C2485 was initiated, data available from a limited number of patients with TSC-associated SEGA or angiomyolipoma suggested that responses to rapamycin therapy were evident at trough concentrations of 10-15 ng/ml [16,17]. Following a similar strategy, everolimus trough concentrations of 10-15 ng/mL were initially also targeted in Study C2485. Initial doses of rapamycin of 1.5 mg/m^2/day with subsequent titration to 7 mg/m^2/day (maximum) had effected tumour regression in all 4 treated patients and appeared to be associated with acceptable tolerability. As a result, the everolimus starting dose of 3.0 mg/m^2/day (administered as a once-daily or alternate-day regimen) was considered to be safe. This conservative approach was confirmed when the maximum tolerated dose for paediatric patients with refractory or recurrent solid tumors was found to be 5.0 mg/m^2 in the phase I study [18].

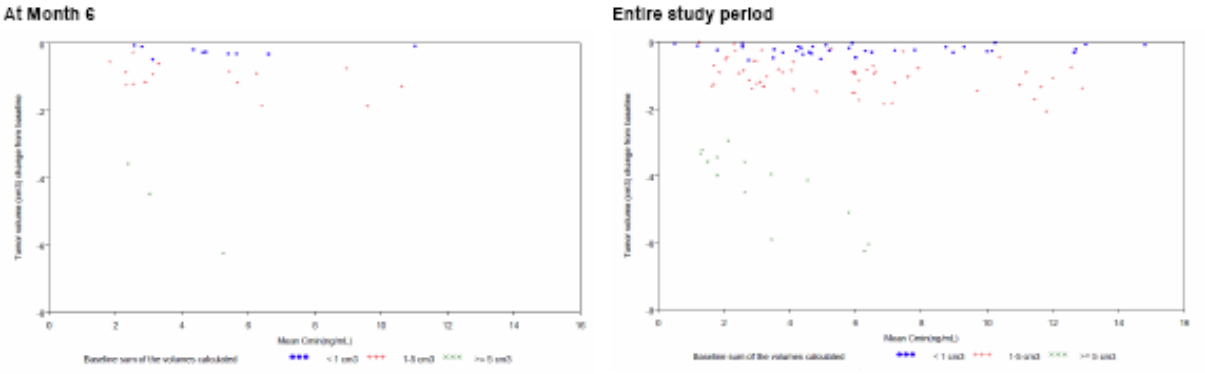
In attempts to attain the target everolimus trough concentrations, the majority of patients required multiple dose increases (most likely as a result of the concurrent use of strong CYP3A4 enzyme-inducing antiepileptic drugs [EIAEDS]). Despite these adjustments, many patients failed to achieve the minimum target trough level but still experienced significant clinical and radiological response. This led to a revised target trough concentration recommendation of 5-15 ng/mL.

Relationship between plasma concentration and effect

In the Phase II trial (C2485) higher C_{min} values appeared to be associated with larger reductions in SEGA volume, which were attenuated in the presence of a CYP3A4 inducer at all time points tested. This relationship was more evident in patients with SEGA volumes between 1-5 cm^3. However, responses were observed at trough concentrations as low as 2 ng/mL (Figure 1).

Figure 1: Relationship between reduction in SEGA volume and Cmin – PK sample set 3 (Safety Polupation) – Study 2485

[16] Franz DN, Leonard J, Tudor C, et al (2006). Rapamycin causes regression of astrocytomas in tuberous sclerosis complex. Ann Neurol; 59: 490-8.
[17] Bissler JJ, McCormack FX, Young LR (2008). Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. N Engl J Med; 358: 140-51.
[18] Fouladi M, Laningham F, Wu J, et al (2007). Phase I study of everolimus in pediatric patients with refractory solid tumors. J Clin Oncol; 25: 4806-12.



C_{min} at Month 6 = average of all C_{min} readings during the initial 6 months

2.4.4. Discussion on clinical pharmacology

The general PK parameters are considered to be well documented.

As part of the agreed PIP, the applicant conducted a bioavailability study (C2121) in 40 healthy individuals (male and female), to compare the relative bioavailability of everolimus (5x) 1 mg tablets taken whole versus their suspension in water. The relative bioavailability was statistically significantly lower when the tablets are taken as a suspension. Despite the difference, the lower C_{max} did not raise a safety concern as patients on everolimus will undergo therapeutic drug monitoring and dose will be adjusted accordingly in all patients. The slightly lower bioavailability of the suspension was acceptable and the suspension in water can be administered in patients unable to swallow tablets as a whole. Votubia must be administered orally once daily at the same time every day, consistently either with or without food (see SmPC section 5.2). Votubia tablets are to be swallowed whole with a glass of water. The tablets must not be chewed or crushed. For patients unable to swallow tablets, Votubia tablet(s) can be dispersed completely in a glass with approximately 30 ml of water by gently stirring, immediately prior to drinking. After the dispersion has been swallowed, any residue must be re-dispersed in the same volume of water and swallowed (see SmPC section 4.2 and 5.2).

The dose response information is based on data derived from 3 academic studies and supplemented by findings from study C2485. These studies were of limited value in terms of extrapolating the findings to everolimus treatment in SEGA, as they either used rapamycin or treated tumors where anatomical lesions are different than the SEGA patients (eg. no blood-brain barrier crossing).

In patients with advanced solid tumours, peak everolimus concentrations (C_{max}) are reached at a median time of 1 hour after daily administration of 5 and 10 mg everolimus under fasting conditions or with a light fat-free snack. C_{max} is dose-proportional between 5 and 10 mg. Everolimus is a substrate and moderate inhibitor of PgP.

In healthy subjects, high fat meals reduced systemic exposure to Votubia 10 mg (as measured by AUC) by 22% and the peak plasma concentration C_{max} by 54%. Light fat meals reduced AUC by 32% and C_{max} by 42%. Food, however, had no apparent effect on the post absorption phase concentration-time profile.

The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 to 5,000 ng/ml, is 17% to 73%. Approximately 20% of the everolimus concentration in whole blood is

confined to plasma of cancer patients given Votubia 10 mg/day. Plasma protein binding is approximately 74% both in healthy subjects and in patients with moderate hepatic impairment. In patients with advanced solid tumours, V_d was 191 L for the apparent central compartment and 517 L for the apparent peripheral compartment.

Everolimus is a substrate of CYP3A4 and PgP. Following oral administration, everolimus is the main circulating component in human blood. Six main metabolites of everolimus have been detected in human blood, including three monohydroxylated metabolites, two hydrolytic ring-opened products, and a phosphatidylcholine conjugate of everolimus. These metabolites were also identified in animal species used in toxicity studies, and showed approximately 100 times less activity than everolimus itself. Hence, everolimus is considered to contribute the majority of the overall pharmacological activity.

In order to support the dosing of everolimus in patients taking medications that interact with CYP 3A4 and PgP, the applicant should explore the expansion of the current population PK model to include the everolimus blood concentration data collected in the phase II study in SEGA patients (C2485) and the Phase I study in paediatric patients with refractory solid tumours. This would potentially allow (1) differentiation of the impact of inducers/inhibitors on everolimus pharmacokinetics, (2) a single pharmacokinetic model for adult and paediatric patients (answering the question of similarity of PK between these two populations) and (3) more precise recommendations for the starting dose of everolimus, allowing more efficient achievement of desired therapeutic concentrations. If necessary. a study should be conducted to support dosing recommendations in this population (see RMP).

Mean CL/F of everolimus after 10 mg daily dose in patients with advanced solid tumours was 24.5 l/h. The mean elimination half-life of everolimus is approximately 30 hours.

No specific excretion studies have been undertaken in cancer patients; however, data are available from the studies in transplant patients. Following the administration of a single dose of radiolabelled everolimus in conjunction with ciclosporin, 80% of the radioactivity was recovered from the faeces, while 5% was excreted in the urine. The parent substance was not detected in urine or faeces.

After administration of everolimus in patients with advanced solid tumours, steady-state AUC0-τ was dose-proportional over the range of 5 to 10 mg daily dose. Steady-state was achieved within two weeks. C_{max} is dose-proportional between 5 and 10 mg. Tmax occurs at 1 to 2 hours post-dose. There was a significant correlation between AUC0-τ and pre-dose trough concentration at steady-state.
The average AUC of everolimus in 8 subjects with moderate hepatic impairment (Child-Pugh class B) was twice that found in 8 subjects with normal hepatic function. AUC was positively correlated with serum bilirubin concentration and with prolongation of prothrombin time and negatively correlated with serum albumin concentration. The impact of severe hepatic impairment (Child-Pugh class C) on the pharmacokinetics of everolimus has not been assessed (see SmPC sections 4.2 and 4.4).

In renal impaired patients, in a population pharmacokinetic analysis of 170 patients with advanced solid tumours, 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.

In the paediatric population, intra-patient steady-state trough concentrations were dose-proportional at daily doses of 1.5 to 14.6 mg/m^2.
Oral clearance (CL/F) is similar in Japanese and Caucasian cancer patients with similar liver functions. Based on analysis of population pharmacokinetics, oral clearance (CL/F) is on average 20% higher in black transplant patients.

2.4.5. Conclusions on clinical pharmacology

Different aspects of clinical pharmacology (correlation of both efficacy and safety with C_{min}, interactions, starting dose, dose titration etc.) were extensively assessed and discussed during the procedure. The current SmPC, in particular in section 4.2 reflects these discussion appropriately. The CHMP concluded that although the recommended target C_{min} range 5-15 ng/ml may not be considered as fully optimal, the currently dosing recommendations as reflected in the SmPC are acceptable.

The CHMP considered the following measures necessary to address the missing clinical data:

- The applicant should commit to adequately document the population pharmacokinetics of everolimus in children (CL/F, apparent volumes, C_{max}, C_{min}, AUC, etc), including (but not limited to) the impact of age, weight, BSA, co-administration of enzyme inducers to complement the current sparse understanding of the disposition of everolimus in this patient group. This condition is part of the obligations in Annex II.
- Submit the result of trial X2103 (formal interaction trial for midazolam) once they will be available. This commitment is covered in the RMP.

2.5. Clinical efficacy

The clinical efficacy of everolimus in patients with SEGA associated with TSC is based on a single pivotal phase II trial (C2485). Preliminary results from a randomized, double-blind, placebo-controlled Phase III study (Study M2301) have also been submitted.

2.5.1. Dose response study(ies)

The rationale for the starting dose and the proposed up-titrating with PK monitoring as investigated in phase II trial C2485 and the currently ongoing phase III trial M2301 are derived from different sources (see primary and secondary pharmacology).

2.5.2. Main study

Title: Everolimus (RAD001) therapy of giant cell astrocytomas in patients with tuberous sclerosis complex

The applicant submitted the study report for trial C2485 as the main study for the application. This was a phase II, open-label, single-center investigator-initiated trial conducted at the Cincinnati Children's Hospital Medical Centre (CCHMC) in patients older than 3 years of age suffering from SEGA associated with TSC.

Methods

Study participants

Twenty-eight patients of the age 3 years or older with confirmed diagnosis of TSC and radiological evidence of serial SEGA growth were enrolled between January 07, 2007 and December 09, 2008 (note: December 09, 2009 is the date of data cut-off corresponding to the date that the last patient enrolled had his 12-month assessment visit). The main inclusion and exclusion criteria in the study protocol included:

Inclusion criteria:

- Age ≥ 3 years
- If female and of child-bearing potential, documentation of negative pregnancy test prior to enrolment
- Presence of giant cell astrocytoma as defined by imaging characteristics and serial increase in size of lesion on ≥ 2 MRI scans
- Adequate renal function (creatinine < 1.5 mg/dL)
- Clinically definite diagnosis of TS (per modified Gomez criteria[19] [see table 18] or positive genetic test)

Table 18: Gomez criteria

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

Exclusion criteria:

- Serious intercurrent medical illness or other uncontrolled medical disease which could compromise participation in the study (i.e., uncontrolled diabetes, uncontrolled hypertension, severe malnutrition, significant cardiac disease, chronic liver or renal disease, gastrointestinal disease that could significantly alter the absorption of everolimus, human immunodeficiency virus [HIV] positivity, or chronic treatment with systemic steroids or another immunosuppressive agent). Patients with uncontrolled epilepsy were not excluded.
- Significant hematologic or hepatic abnormality:
  - transaminase levels > 3 x upper limit of normal (ULN)
  - serum albumin < 3 g/dL
  - hematocrit (HCT) < 30%
  - platelets < 80,000 /mm^3
  - absolute neutrophil count (ANC) < 1,000 /mm^3
  - total white blood cell (WBC) count < 3,000 /mm^3
- Continuous requirement for supplemental oxygen
- Intercurrent infection at initiation of everolimus
- Embolization of angiomyolipoma within 1 month of initiation of everolimus; any other recent surgery within 2 months

[19] Roach ES, Gomez MR, Northrup H (1998). Tuberous Sclerosis Consensus Conference: revised clinical diagnostic criteria. J Child Neurol; 13: 624-8.

- Pregnant or lactating women
- Inadequate contraception. Patients who were fertile had to maintain adequate contraception throughout the trial and for 3 months after stopping study drug. Acceptable contraceptive measures included non estrogen-containing birth control regimen, prior hysterectomy, tubal ligation, complete abstinence, barrier methods that included both a cervical diaphragm and spermicidal jelly, intrauterine devices, progesterone-based contraceptives, or vasectomy in partner.
- Use of an investigational drug within the past 30 days
- Not adequately recovered from the acute toxicities of any prior therapy
- Clinical evidence of impending herniation or focal neurologic deficit related to the patient's astrocytoma

Treatments

The initial starting dose was to be 3.0 mg/m^2/day taken either daily or every other day. The protocol provided dose up- and down-titrations in relation to a targeted C_{min} range. The targeted C_{min} range was originally 10 to 15 mg/m^2 which was widened by protocol amendment 4 (as of June 17, 2008) to 5 to 15 mg/m^2.

Dose modifications had to be performed in terms of steps of 25% of the dose, either downwards in case patients were unable to tolerate the dose resulting in the targeted C_{min} range of 5 (10) to 15 mg/ml or upwards in case target range was not achieved (subject to tolerability).

The trial had a so called core treatment phase comprising 6 months. Upon completion of the core treatment phase, eligible patients entered an extension phase in which study drug treatment continued for as long as therapeutic benefit was evident without significant adverse effects.

Objectives

The primary objective of the trial was to evaluate the safety and potential side effects of everolimus therapy in patients with TSC. The primary *efficacy* objective was to evaluate the clinical effectiveness of everolimus to reduce the size of giant cell astrocytoma burden in patients with TSC, in order to:

(1) Test the hypothesis that everolimus therapy in TSC patients with SEGA tumors results in decreased SEGA tumor size.

(2) Test the hypothesis that everolimus may have beneficial activity separate from effects on SEGA tumors in patients with TSC.

(3) Test the hypothesis the mTOR inhibition by everolimus *in vivo* correlates with clinical outcome in TSC patients with SEGAs.

Outcomes/endpoints

The primary efficacy endpoint was the change from baseline in volume of the primary SEGA lesion at 6 months after the start of treatment (or at the last available assessment if a patient ended treatment prior to this timepoint) as determined by central radiology review.

In order to summarize the SEGA volume measurements over time, assessments were timeslotted using time windows. Brain MRIs were to be performed once during screening, and then at month 3, month 6 and then every 6 months. Time windows were defined as follows: The baseline time window was defined as being any time on or before the first day of treatment. The first on-study time window was from study day 2 (i.e., the day after the first day of treatment) until study day 137, which was 4.5

months after starting study treatment. The second on-study time window was from study day 138 (month 4.5) until study day 274 (month 9). Thereafter, all time windows are of 6 months duration and centered around the planned assessment date.

Volumetric assessment was performed using a Vitrea 2 workstation based on 1-mm coronal reformatted images from volume acquisitions either post-contrast sagittal 3-D SPGR (1.5- tesla GE MRI [GE Medical Systems, Milwaukee, WI] and 1.5-tesla Siemens MRI [Siemens Medical Systems, South Iselin, NJ]), or T-1 MPRAGE (3.0-tesla Siemens MRI). All measurements and volume determinations were performed by the same neuroradiologist.

The secondary efficacy endpoints included:

Seizure frequency: To ascertain whether seizure frequency or EEG was affected in patients with uncontrolled epilepsy (defined as > 1 seizure per month in the 6 months prior to enrollment), continuous 24-hour digital EEG/video monitoring was performed utilizing the 10/20 international system of electrode placement at baseline and Month 6. Bipolar and referential montages were reviewed. Interictal EEG segments and all ictal EEG and video segments were analyzed by an experienced epileptologist. Seizure diaries were also kept by all patients or their caregivers.

Quality of Life: The QOLCE questionnaire[20] (Sabaz, et al 2003) was to be completed by all patients or their caregivers at baseline and again at Month 3 and Month 6.

Response of facial angiofibromas: Response of facial angiofibromas was to be as assessed by the same clinician at each visit and compared to the appearance at baseline.

Neuropsychological assessments: Neuropsychological and cognitive effects were assessed using an age-appropriate battery of tests administered by a trained neuropsychologist at baseline and Month 6. No assessments were to be performed during the long-term extension phase of the study. The batteries consisted of the following measures, modified for patient chronological and cognitive age, as appropriate: WPPSI-III (core subtests), Bracken Preschool Screening, Beery VMI, NEPSY Phonological Processing, NEPSY Arrows, Purdue Pegboard Test, Grooved Pegboard Test, BASC Parent, BRIEF Parent, WISC-IV, WRAT-III, JLO, Conners CPT, WCST, WAISIII, SCL-90, and the Frontal Systems Behavior Scale. Total testing time for these batteries was estimated to be 2-2.5 hours for patients 3-5 years of age, and 3-3.5 hours for patients ages ≥ 6 years. This was consistent with the typical clinical assessments for such age groups.

Safety evaluations consisted of collecting all AEs and SAEs with their severity and relationship to study drug, and periodic monitoring of haematology, serum chemistry, urine, and physical condition. Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 3.0.

Sample size

The initial sample size was set to 20 and later amended (protocol amendments 4 and 6) to 27 evaluable patients. The applicant justified the choice as a sample size of 28, assuming a standard deviation of 1.33, would have ≥ 90% power to detect a mean reduction in SEGA volume of ≥ 1 cm^3 from baseline based on a one-sided t-test with α=0.025. The non-parametric Wilcoxon signed rank test would also have approximately 90% power to detect a median reduction of 1 cm^3.

Randomisation

[20] Sabaz M, Lawson JA, Cairns DR, et al (2003). Validation of the quality of life in childhood epilepsy questionnaire in American epilepsy patients. Epilespy Behav; 4: 680-91.

The trial C2485 was non-randomised.

Blinding (masking)

The trial C2485 was an open label trial.

Statistical methods

The primary analysis was based on a Wilcoxon signed rank test (normal approximation method) at the one-sided 2.5% level in the Full Analysis Set.

Results

Participant flow

The disposition of the enrolled 28 patients, as of the 09-Dec-2009 data cut-off, is summarized in Table 19.

Table 19: Patient disposition (Full Analysis Set) - Study C2485

Disposition	Everolimus N=28 n (%)	
Ongoing	25	(89.3)
Discontinued (from study)	3	(10.7)
Reason for discontinuation		
Subject withdrew consent	3 [a]	(10.7)

Recruitment

Twenty-eight patients with SEGA associated with TSC were screened and subsequently enrolled between January 07, 2007 and December 18, 2008.

Conduct of the study

As of the 09-Dec-2009 data cut-off, 27 of the 28 patients (96.4%) had completed ≥ 12 months of treatment with 1 patient (3.6%) having voluntarily discontinued after 4.7 months of everolimus therapy (Patient 0001/00002 withdrew consent due to non compliance with AED medication and worsening hyperkinesis prior to completion of the core 6-month treatment phase).

Among 3 patients withdrawing consent, 2 did so during the extension phase and 1 during the core treatment phase (first six months) so that 27 patients were treated for the full core treatment phase.

Overall, deviations from the protocol were evident for approximately three-fifths of patients (Table 20); however, only 1 patient (3.6%) was excluded from the Per-protocol Population as a result of insufficient treatment exposure.

Overall 6 amendments of the protocol were reported in-between January 19, 2007 and November 19, 2008.

Table 20: Protocol deviations (Full Analysis Set) - Study C2485

Protocol deviation	Everolimus N=28 n (%)	
Number of patients with at least 1 deviation	**17**	**(60.7)**
Nature of protocol deviation [a]		
Prohibited medication deviations	14	(50.0)
Coadministration of medication affecting CYP3A	14	(50.0)
Eligibility criteria deviations	7	(25.0)
Written informed consent partially incomplete [b]	6	(21.4)
Inadequate renal function (Cr ≥ 1.5 mg/dL)	1	(3.6)
Study medication deviations	2	(7.1)
Incorrect dosing	2	(7.1)
Other deviations	1	(3.6)
Lesion assessment performed with CT-scan	1	(3.6)

Cr Serum creatinine
[a] Not mutually exclusive
[b] Applies only to informed consent for protocol amendments effective after initial study entry

Baseline data

The major baseline demographic characteristics are provided in the Table 21 below:

Table 21: Demographic characteristics (Full Analysis Set) - Study C2485

Demographic characteristic	Everolimus N=28 n (%)	
Age (years)		
n	28	
Mean (standard deviation)	12.5	(7.53)
Median	11.0	
Range	3 to 34	
Age group (years) (n [%])		
3 to < 12	16	(57.1)
> 12 to < 18	6	(21.4)
≥ 18	6	(21.4)
Sex (n [%])		
Male	17	(60.7)
Female	11	(39.3)
Race (n [%])		
Caucasian/White	24	(85.7)
Black	2	(7.1)
Other [a]	2	(7.1)
Weight (kg)		
N	28	
Mean (standard deviation)	52.0	(30.60)
Median	48.2	
Range	13.1 to 132.6	
Height (cm)		
n	28	
Mean (standard deviation)	145.7	(27.09)
Median	141.0	
Range	91.5 to 187.0	
Body mass index (kg/m^2)		
n	28	
Mean (standard deviation)	22.3	(6.79)
Median	20.3	
Range	13.9 to 39.4	
Body surface area (m^2) [b]		
n	28	
Mean (standard deviation)	1.42	(0.54)
Median	1.38	
Range	0.6 to 2.6	

[a] 2 patients were of mixed race (0001/00002 - ¼ black / ¾ white and 0001/00019 - black/white)
[b] Body surface area = √([height (cm) x weight (kg)]/3600)

Twenty-seven patients were non-Hispanic/Latino (0001/00002 was of unknown mixed ethnicity)

As shown in Table 22, all patients qualified for the diagnosis TSC by having at least 2 major features according to the modified Gomez criteria.

Table 22: Patients and disease characteristics (Full Analysis Set) - Study C2485

Patient or disease characteristic	Everolimus N=28 n (%)	
Diagnosis of TS – modified Gomez criteria		
At least 2 major features	28	(100.0)
Number of SEGA lesions [a]		
1	15	(53.6)
2	13	(46.4)
≥ 3	0	
Bilateral SEGA [a]		
Yes	12	(42.9)
No	16	(57.1)
Inferior growth [a, b]		
Yes	0	
No	28	(100.0)
Parenchymal invasion [a, b]		
Superficial	25	(89.3)
Deep	2	(7.1)
None	1	(3.6)
Hydrocephalus [a, b]		
Yes	6	(21.4)
No	22	(78.6)
Facial angiofibroma [c]		
Yes	25	(89.3)
No	3	(10.7)

[a] As per independent central review
[b] Prognostic factors
[c] As per modified Gomez criteria

The vast majority of patients (23 of 28) were on antiepileptic treatment at baseline while only a minority had prior anti-SEGA treatment (Table 23). Of note, 2 patients already received prior systemic sirolimus (rapamycin).

Table 23: Previous disease-related treatments (Full Analysis Set) - Study C2485

Previous treatments	Everolimus N=28 n (%)	
Any prior anti-SEGA therapy/surgery	**5**	**(17.9)**
SEGA surgery [a]	4	(14.3)
Systemic therapy [b]	2	(7.1)
Any prior antiepileptic drug at baseline [c]	**23**	**(82.1)**
1 antiepileptic drug	10	(35.7)
2 antiepileptic drugs	10	(35.7)
≥ 3 antiepileptic drugs	3	(10.7)
Any prior enzyme-inducing antiepileptic drug at baseline [c]	**15**	**(53.6)**
1 enzyme-inducing antiepileptic drug	12	(42.9)
2 enzyme-inducing antiepileptic drugs	3	(10.7)

[a] As recorded on the medical history page of the case report form
[b] Use of rapamycin as recorded on the anti-tuberous sclerosis therapy case report form
[c] As recorded on the antiepileptic medication case report form

Numbers analysed

The analysis sets and the numbers of patients in each analysis set are summarized in Table 24. Efficacy analyses were performed on the intent-to-treat population (Full Analysis Set). The primary efficacy analyses were repeated using a 'Per protocol Population', Patient 0001/00014 was excluded from this population as he received everolimus on < 50% of days over the initial 12 weeks of planned therapy. Two treatment interruptions were required due to AEs – one lasting for 14 days and the second for 73 days.

Table 24: Analysis populations - Study C2485

Analysis population	Everolimus N=28 n (%)	
Screened	28	(100.0)
Full Analysis Set	28	(100.0)
Per-protocol Population	27	(96.4)
Safety Population	28	(100.0)

Outcomes and estimation

Primary efficacy endpoint(s)

Everolimus was associated with a statistically significant ($p<0.001$) reduction in SEGA volume. Primary SEGA volume was reduced by a median 0.80 cm^3 (range: 0.06-6.25) at Month 6 relative to baseline on independent central review (see Table26). Median reduction in primary SEGA volume as per local investigator assessment was 0.92 cm^3, with 75.0% and 39.3% of patients experiencing reductions of ≥ 30% and ≥ 50%, respectively. Tumour shrinkage was most rapid during the initial 3 months of treatment (corresponding to the time of the first assessment), with evidence of sustained responses at subsequent time points. After 6 months no further decreases in volume was noted.

All patients experienced relative reduction in tumour volume. Twenty-one patients (75.0%) experienced reductions in primary SEGA volume of ≥ 30% during the core 6-month treatment phase by independent central review, including 9 patients (32.1%) who experienced ≥ 50% reductions (Table 25).

One patient met the pre-specified criteria for treatment success, a 75% reduction in SEGA volume, and was temporarily taken off trial therapy.

In addition to the result concerning the primary efficacy endpoint it is reported that, as a consequence of the reduction in SEGA volume, no patient developed worsening hydrocephalus or signs of increased intracranial pressure, and none required surgical resection or other therapy for SEGA. Furthermore, no patient developed a new lesion.

Table 25: Response of primary SEGA lesion to everolimus therapy (Full Analysis Set) - Study C2485

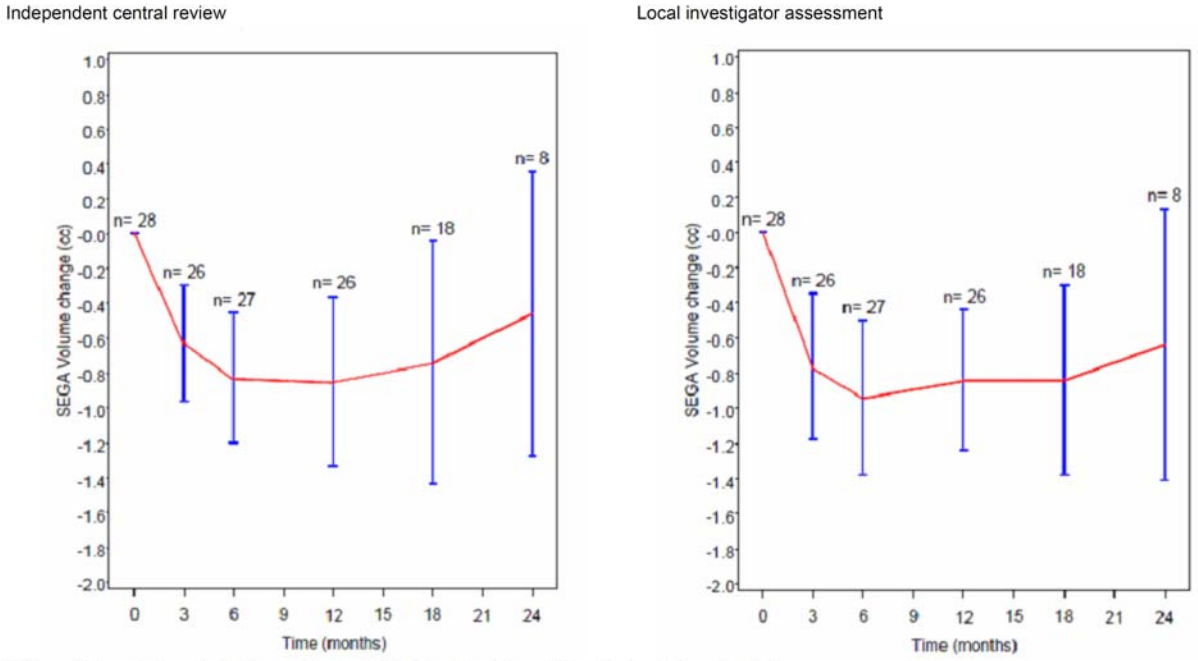
SEGA volume (cm^3)	Independent central review		Local investigator assessment	
	Baseline N=28	Month 6 N=28	Baseline N=28	Month 6 N=28
Mean (standard deviation)	2.45 (2.813)	1.30 (1.476)	2.25 (1.660)	1.24 (0.897)
Median	1.74	0.93	2.00	0.96
Range	0.49 to 14.23	0.31 to 7.98	0.35 to 7.10	0.19 to 3.40
Reduction from baseline				
Mean (standard deviation)	1.15 (1.421)		1.01 (1.044)	
Median	0.80		0.92	
Range	0.06 to 6.25		0.02 to 4.80	
Primary analysis				
p-value [a]	<0.001		<0.001	
95% CI for median [b]	0.4 to 1.2		0.5 to 1.4	
Percentage reduction from baseline, n (%)				
≥ 50%	9	(32.1)	11	(39.3)
≥ 30%	21	(75.0)	21	(75.0)
> 0%	28	(100.0)	28	(100.0)
No change	0		0	
% increase	0		0	

Month 6 time point corresponds to time window from 4.5 to 9.0 months from start of treatment or last assessment if patient discontinued early
[a] p-value is obtained from a one-sided Wilcoxon signed rank test
[b] 95% confidence interval obtained by bootstrap simulation

The median reduction from baseline to month 6 in total SEGA volume was 0.90 cm^3 by independent central review and 0.92 cm^3 by local investigator assessment.

The median value of the primary SEGA volume reduction from baseline is summarized in (Figure 2) for both the independent central review and local investigator assessment.

Figure 2: Median profile of primary SEGA volume shrinkage from baseline (Full Analysis Set) - Study C2485



The response of the primary SEGA lesion to everolimus therapy at different time points is presented in Table 26.

Table 26: Response of SEGA volume to everolimus therapy by time point (Full Analysis Set) - Study C2485

SEGA volume (cm^3)	Independent central review						Local investigator assessment					
	Baseline N=28	Month 3 N=26	Month 6 N=27	Month 12 N=26	Month 18 N=18	Month 24 N=8	Baseline N=28	Month 3 N=26	Month 6 N=27	Month 12 N=26	Month 18 N=18	Month 24 N=8
Primary tumor volume												
Mean (standard deviation)	2.45 (2.813)	1.47 (1.646)	1.33 (1.497)	1.26 (1.526)	1.45 (1.279)	1.05 (1.117)	2.25 (1.660)	1.42 (1.016)	1.27 (0.899)	1.15 (0.778)	1.37 (1.014)	1.34 (1.315)
Median	1.74	0.84	0.93	0.84	0.90	0.57	2.00	1.15	1.00	1.00	1.03	0.92
Range	0.49-14.23	0.25-8.32	0.31-7.98	0.29-8.18	0.33-5.20	0.33-3.66	0.35-7.10	0.18-4.00	0.19-3.40	0.25-3.60	0.32-3.90	0.53-4.50
Reduction from baseline												
Mean (standard deviation)		1.08 (1.338)	1.19 (1.433)	1.07 (1.276)	1.46 (2.220)	1.01 (1.259)		0.88 (0.896)	1.04 (1.052)	0.99 (0.762)	1.11 (1.111)	0.87 (0.833)
Median		0.63	0.83	0.85	0.74	0.46		0.77	0.94	0.84	0.84	0.64
Range		-0.12-5.91	0.06-6.25	0.02-6.05	-0.24-9.03	0.12-3.79		0.00-4.10	0.02-4.80	0.03-3.50	0.00-4.50	-0.18-2.10
Percentage reduction from baseline, n (%)												
≥ 50%		10 (38.5)	9 (33.3)	9 (34.6)	8 (44.4)	3 (37.5)		9 (34.6)	11 (40.7)	9 (34.6)	6 (33.3)	2 (25.0)
≥ 30%		17 (65.4)	21 (77.8)	20 (76.9)	12 (66.7)	6 (75.0)		16 (61.5)	20 (74.1)	21 (80.8)	13 (72.2)	6 (75.0)
> 0%		25 (96.2)	27 (100)	26 (100)	16 (88.9)	8 (100)		25 (96.2)	27 (100)	26 (100)	17 (94.4)	7 (87.5)
No change		0	0	0	1 (5.6)	0		1 (3.8)	0	0	1 (5.6)	0
Increase		1 (3.8)	0	0	1 (5.6)	0		0	0	0	0	1 (12.5)
Total tumor volume												
Mean (standard deviation)	2.72 (2.815)	1.61 (1.649)	1.48 (1.506)	1.40 (1.530)	1.50 (1.281)	1.07 (1.114)	2.44 (1.869)	1.54 (1.140)	1.38 (1.016)	1.24 (0.868)	1.38 (1.021)	1.37 (1.318)
Median	1.77	1.02	1.04	0.93	0.94	0.60	2.00	1.15	1.00	1.00	1.03	0.92
Range	0.49-14.23	0.27-8.32	0.34-7.98	0.29-8.18	0.33-5.20	0.33-3.66	0.35-7.10	0.18-4.00	0.19-3.40	0.25-3.60	0.32-3.90	0.53-4.50
Reduction from baseline												
Mean (standard deviation)		1.16 (1.335)	1.31 (1.431)	1.22 (1.315)	1.49 (2.213)	1.03 (1.283)		0.97 (0.985)	1.13 (1.128)	1.11 (0.934)	1.14 (1.127)	0.92 (0.928)
Median		0.72	0.91	0.91	0.86	0.46		0.77	0.94	0.84	0.84	0.64
Range		-0.12-5.91	0.07-6.25	0.02-6.05	-0.24-9.03	0.12-3.79		0.00-4.10	0.02-4.80	0.03-3.50	0.00-4.50	-0.18-2.44
Percentage reduction from baseline, n (%)												
≥ 50%		9 (34.6)	9 (33.3)	10 (38.5)	8 (44.4)	3 (37.5)		8 (30.8)	11 (40.7)	9 (34.6)	7 (38.9)	2 (25.0)

SEGA volume (cm^3)	Independent central review						Local investigator assessment					
	Baseline N=28	Month 3 N=26	Month 6 N=27	Month 12 N=26	Month 18 N=18	Month 24 N=8	Baseline N=28	Month 3 N=26	Month 6 N=27	Month 12 N=26	Month 18 N=18	Month 24 N=8
≥ 30%		18(69.2)	24(88.9)	19(73.1)	12(66.7)	6(75.0)		16(61.5)	20(74.1)	21(80.8)	13(72.2)	6(75.0)
> 0%		25(96.2)	27(100)	26(100)	16(88.9)	8(100)		25(96.2)	27(100)	26(100)	17(94.4)	7(87.5)
No change		0	0	0	0	0		1 (3.8)	0	0	1 (5.6)	0
Increase		1 (3.8)	0	0	2(11.1)	0		0	0	0	0	1(12.5)

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
95% confidence interval obtained by bootstrap simulation

Secondary efficacy endpoints

- **Seizure frequency**

Of the 16 patients with seizures at the start of the study (> 1 seizure in the 6 months prior to enrolment) and for whom video-EEG data were available, 9 experienced decreases in seizure frequency, 6 reported no change (5 of whom were event-free at both time points), and 1 patient experienced an increase (median change in overall seizure frequency -1.0, p=0.022).

A trend toward improvement in 'sleep' epileptiform abnormalities was also evident.

Further evaluation of the 9 patients for whom a reduction in seizure frequency was evident revealed that increases in AED doses (or additional AED therapy) were apparent for 5 of these patients. This prompted further discussion with the Principal Investigator who confirmed that evaluation of AED blood concentrations was more relevant and that these patients all had minimal variations in AED levels pre- and post-treatment despite adjustments in dosage.

- **Patient-reported seizure frequency**

Based on caregiver observation, the proportion of patients experiencing seizures on a daily basis was reduced from 26.9% (7 of 26 patients) at baseline to 8.0% (2 of 25) at Month 6 and subsequently to 4.0% (1 of 25 patients) at Month 12.

- **Quality of life**

There was no evidence that specific domains changed differently over time (Table 27), with the exception of 'stigma item' for which an improvement was evident (median change +25%).

Table 27: Quality of life in children with epilepsy questionnaire: overall quality of life score (Full Analysis Set) - Study C2485

	Baseline N=26	Month 3 N=25	Month 6 N=26
Overall quality-of-life score			
n	26	24	26
Mean (standard deviation)	57.82(13.956)	63.43(12.384)	62.08(14.184)
Median	52.14	63.20	59.72
Range	33.0 to 90.1	44.6 to 86.5	25.5 to 88.9
Change from baseline in quality-of-life score			
n		23	25
Mean (standard deviation)		3.14 (7.489)	3.29 (8.421)
Median		0.87	0.78
Range		-6.3 to 22.7	-13.7 to 24.1
Model-based analysis of change from baseline in quality-of-life score			
Least-square mean (standard error)		3.52 (1.507)	3.47 (1.582)
95% CI of least-square mean		0.39 to 6.65	0.19 to 6.74

An increase in score (i.e., a positive change) corresponds to an improvement in quality of life
Summaries are based on predefined time windows around scheduled assessment days
Least-square means and confidence intervals were calculated using a mixed model

- **Neuropsychometric functioning**

Of the 24 patients for whom neuropsychological data were available, essentially no deleterious changes were seen on neuropsychological, intelligence measures, academic achievement and visual spatial/motor integration. Four patients (14.3%) were cognitively and behaviourally impaired to such an extent that standardized assessment was not possible. As a result, no definitive conclusions can be drawn.

- **Response of facial angiofibromas**

Improvement in angiofibroma appearance (as per the clinical impression of the investigator) was evident after 1 month of therapy. At the end of the core 6-month treatment phase, 86.7% of patients were considered to have an improvement (Table 28). Two patients experienced worsening at the 12-month time point.

Table 28: Response of facial angiofibromas (Full Analysis Set) - Study C2485

	Month 1 N=9 n (%)	Month 3 N=12 n (%)	Month 6 N=15 n (%)	Month 12 N=14 n (%)
Improved compared to baseline	4 (44.4)	7 (58.3)	13 (86.7)	8 (57.1)
No change compared to baseline	5 (55.6)	5 (41.7)	2 (13.3)	4 (28.6)
Worsened compared to baseline	0	0	0	2 (14.3)

Ancillary analyses

- **Changes in ventricular volume**

Mean reduction in left ventricular volume was 3.22 cm^3 (range: -7.67 to 31.6) from 15.5 cm^3 at baseline to 12.3 cm^3 at Month 6. Mean reduction in right ventricular volume was 3.15 cm^3 (range: -4.76 to 26.1) from 17.3 cm^3 at baseline to 14.4 cm^3 at Month 6.

- **Changes in tuber and SEN volume**

Mean reduction in tuber volume was 3.39 cm^3 (range: - 4.84 to 18.00) from baseline to Month 6. No change was evident in SEN volume; mean reduction was 0.08 cm^3 (range: -0.46 to 0.73).

- **Annual rate of change in primary SEGA volume**

Prior to treatment with everolimus, the mean annual rate of change in primary SEGA volume was +0.57 cm^3/year (range: -0.10 to 2.20). The mean annual rate of change following treatment was -0.57 cm^3/year (range: -4.27 to 0.23).

- **Duration of response**

For study C2485, none of the 24 patients with a ≥ 30% reduction in primary SEGA volume at some time point met the definition for progression (i.e., an increase from nadir of ≥ 25% to a value greater than baseline). Median time from first response to censoring was 15.1 months (range: 5.7 to 31.1).

Summary of main study

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

Table 29: Summary of efficacy for Study C2485

<table>
<tr><td colspan="4"><u>Title: Everolimus (RAD001) therapy of giant cell astrocytomas in patients with tuberous sclerosis complex</u></td></tr>
<tr><td>Study identifier</td><td colspan="3">Protocol identification CRAD001C2485
ClinicalTrials.gov identifier NCT00411619</td></tr>
<tr><td rowspan="2">Design</td><td colspan="3">Phase II, prospective, non-randomized, open-label, single-arm, single-center, investigator-initiated study of everolimus in patients with SEGA associated with TS</td></tr>
<tr><td colspan="3">Duration of main phase: 6 months
Duration of Run-in phase: not applicable
Duration of Extension phase: Treatment continues for as long as therapeutic benefit is evident without significant adverse effect or risk to the patient</td></tr>
<tr><td>Hypothesis</td><td colspan="3">Exploratory: Median change from baseline in primary SEGA volume ≥ 0</td></tr>
<tr><td>Treatments groups</td><td colspan="2">Everolimus (RAD001)</td><td>Starting dose of 3.0 mg/m^2/day taken either daily or every other day with titration to achieve target concentrations of 5-15 ng/mL</td></tr>
<tr><td rowspan="2">Endpoints and definitions</td><td>Primary efficacy endpoint</td><td>Change in SEGA volume (cm^3)</td><td>Change from baseline in volume (cm^3) of Primary SEGA lesions at Month 3 and Month 6 as determined by local investigator assessment on MRI</td></tr>
<tr><td>Secondary efficacy endpoint</td><td>Seizure frequency</td><td>Change from baseline in seizure frequency at Month 6. Seizure frequency (total numbers of seizure) was assessed by 24-hr video-EEG monitoring.</td></tr>
</table>

	Secondary efficacy endpoint	QoL	Change from baseline in overall QoL score at Month 6. Quality of Life (QoL) was assessed by a standardized QoL in children with epilepsy (QOLCE) questionnaire.
	Secondary efficacy endpoints	Response of facial angiofibromas	Change from baseline in response of facial angiofibromas, as assessed by digital photography, at Month 6
Data cut-off	9 December 2009		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent-to-treat population		
Treatment group		RAD001	
Descriptive statistics and estimate variability	**Change in SEGA volume (cm^3)** Mean (standard deviation)	**N=28** **At Month 6*** 1.15 (1.421)	
	Median (range)	0.80 (0.06 to 6.25)	
	Primary analysis p-value 95% CI for median	<0.001 0.4 to 1.42	
	* Month 6 time point corresponds to time window from 4.5 to 9.0 months from start of treatment or last assessment if patient discontinued early		
	Change in SEGA volume (cm^3) Mean (standard deviation)	**N=26** **At Month 3** 1.08 (1.338)	**N=27** **At Month 6** 1.19 (1.433)
	Median (range)	0.63 (0.12-5.91)	0.83 (0.06 to 6.25)
	Change in Seizure frequency Mean (standard deviation)	**N=16** **At Month 6** -2.65 (6.089)	
	Median (range)	-0.99 (-17.0 to 10.8)	
	p-value	0.022	
	Change in QoL Mean (SD)	**N=25** **At Month 6** 3.29 (8.421)	
	Median (range)	0.78 (-13.7 to 24.1)	
	Least-square mean (standard error) 95% CI of least-square mean	3.47 (1.582) 0.19 to 6.74	
	Response of facial angiofibromas Improved compared to baseline No change compared to baseline Worsened compared to baseline	**N=15** **At Month 6** 13 (86.7%) 2 (13.3%) 0	
Notes	Neuropsychometric functioning as assessed by a battery of age-appropriate tests (see text).		

Analysis performed across trials (pooled analyses and meta-analysis)

No clinical study report was submitted for analysis performed across trials.

Clinical studies in special populations

No clinical study report was submitted for special populations. Subgroup evaluation by gender and by age of the response of the primary SEGA lesion showed statistically significant volume reductions in the subgroups investigated. No subgroup analysis by race was performed because of the small number of non-Caucasian patients recruited.

Supportive study

M2301: Randomized, double-blind, placebo-controlled, multi-center phase 3 trial evaluating treatment with Afinitor (everolimus) versus placebo in patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS).

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 the SEGA response rate as defined as the proportion of patients with a best overall SEGA response as per Independent Central Radiological Review. SEGA response was defined as:

- Reduction in SEGA volume of at least 50% relative to baseline, where SEGA volume is the sum of the volumes of all target SEGA lesions identified at baseline,
- Absence of unequivocal worsening of non-target SEGA lesions,
- Absence of new SEGA lesion ≥ 1.0 cm in longest diameter,
- Absence of new or worsening hydrocephalus, defined by independent central radiological assessment of ventricular configuration changes, ventricular cap signs (periventricular oedema) and qualitative assessment of cerebrospinal fluid (CSF) flow dynamics confirmed with a second scan performed approximately 12 weeks later (and no sooner than 8 weeks later).

All patients were to have a magnetic resonance image (MRI) of the brain at screening/baseline, 12, 24, and 48 weeks after the start of study treatment and annually thereafter until SEGA progression. All MRIs were sent to a central radiologist for an independent centralized radiology review.

24-hour video electroencephalography (EEG) was to be performed at screening/baseline and Week 24, and sent to an Independent Central Reader for interpretation and recording of seizure frequency/type.

Improvement or worsening of the patient's skin disease as compared to baseline was to be assessed with Physician's Global Assessment of Clinical Condition every 12 weeks.

Patients were treated until documented progression or unacceptable toxicity. If SEGA progression was documented (by independent central radiology review or unequivocally demonstrated according to the local radiologist), the patient was unblinded. If treated with placebo, the patient was offered the possibility to receive a treatment with open-label everolimus.

Randomisation

Patients who met the study eligibility criteria were randomized to receive either everolimus or matching placebo according to a 2:1 randomization ratio stratified by the use of EIAEDS.

Sample Size

The planned sample size of 99 patients had a 93% power to detect a 20% difference on SEGA response rates between everolimus and placebo (assuming the SEGA response rate of at least 20% in everolimus and 0% in placebo).

Statistical Methods

The primary endpoint and 3 key secondary endpoints were tested via a closed testing procedure using the following testing sequence (hierarchy):

1. Test primary endpoint SEGA response rate (using a one-sided exact CMH test).
2. Test change from baseline to Week 24 on total seizure frequency (using a rank analysis of Covariance, one-sided test).
3. Test time to SEGA progression (using a one-sided stratified log-rank test).
4. Test skin lesion response rate (using a one-sided exact CMH test).

Results

Overall, 117 patients were randomized between 20-Aug-2009 and 02-Sep-2010. The final primary analysis used data up to the cut-off date of 02-Mar-2011, which was 6 months after the last patient was randomized. The database was locked and unblinded on 05-May-2011. As the superiority of everolimus was shown at the end of the core treatment phase, the Study Steering Committee (SSC) met on 13-May-2011 and recommended that the study be unblinded and that all patients be offered the opportunity to receive open-label treatment with everolimus. The study is currently ongoing.

A total of 86 patients (73.5%) have at least one protocol deviation (62 patients [79.5%] and 24 patients [61.5%] in the everolimus and placebo arms, respectively). Only one major protocol violation was observed in a patient randomized to the placebo arm. And the other deviations, reported by the highest number of patients (in everolimus arm and placebo arm, respectively), were related to pharmacokinetic (PK) collection time (PK not at trough: 38.5% vs. 20.5%, two week post dose change PK collected outside of protocol window: 14.1% vs. 5.1%) and to the co-administration of inhibitors or inducers of isoenzyme CYP3A and/or P-glycoprotein (PgP) other than anti-epileptics, most of which being antibiotics (33.3% vs. 28.2%).

Baseline data

Tables 30-32 below summarize demographics and patient disposition and prior anti-SEGA therapy.

Table 30: Demographic characteristics (Full Analysis Set) – Study M2301

	Everolimus N=78	Placebo N=39	All patients N=117
Age (years)			
n	78	39	117
Mean (SD)	10.07 (5.903)	10.33 (7.305)	10.16 (6.374)
Median	9.53	7.09	9.46
Range	1.0- 23.9	0.8- 26.6	0.8- 26.6
Age - n (%)			
<3	13 (16.7%)	7 (17.9%)	20 (17.1%)
3 - < 18	55 (70.5%)	26 (66.7%)	81 (69.2%)
>= 18	10 (12.8%)	6 (15.4%)	16 (13.7%)
Gender - n (%)			
Male	49 (62.8%)	18 (46.2%)	67 (57.3%)
Female	29 (37.2%)	21 (53.8%)	50 (42.7%)
BSA (m^2)			
n	78	39	117
Mean (SD)	1.171 (0.4621)	1.180 (0.5340)	1.174 (0.4850)
Median	1.074	0.956	1.071
Range	0.42- 2.16	0.40- 2.14	0.40- 2.16
Race - n (%)			
Caucasian	73 (93.6%)	36 (92.3%)	109 (93.2%)
Black	3 (3.8%)	1 (2.6%)	4 (3.4%)
Asian	0	0	0
Native American	0	0	0
Pacific Islander	1 (1.3%)	0	0
Other	1 (1.3%)	2 (5.1%)	3 (2.6%)

Table 31: Patient and disease characteristics at baseline (Full Analysis Set) – Study M2301

	Everolimus N=78 n (%)	Placebo N=39 n (%)	All patients N=117 n (%)
Diagnosis of TSC	78 (100.0)	39 (100.0)	117 (100.0)
At least two major features	78 (100.0)	39 (100.0)	117 (100.0)
Only one major feature and at least two minor features	0	0	0
TSC diagnosis criteria (modified Gomez)			
Major Features			
Facial angiofibromas or forehead plaque	60 (76.9)	30 (76.9)	90 (76.9)
Nontraumatic ungual or periungual fibroma	12 (15.4)	14 (35.9)	26 (22.2)
Hypomelanotic macules (three or more)	70 (89.7)	36 (92.3)	106 (90.6)
Shagreen patch (connective tissue nevus)	37 (47.4)	23 (59.0)	60 (51.3)
Multiple retinal nodular hamartomas	11 (14.1)	9 (23.1)	20 (17.1)
Cortical tuber[1]	71 (91.0)	38 (97.4)	109 (93.2)
Subependymal nodule	73 (93.6)	37 (94.9)	110 (94.0)
Subependymal giant cell astrocytoma	78 (100.0)	39 (100.0)	117 (100.0)
Cardiac rhabdomyoma, single or multiple	49 (62.8)	22 (56.4)	71 (60.7)
Lymphangioleiomyomatosis[2]	1 (1.3)	0	1 (0.9)
Renal angiomyolipoma[2]	47 (60.3)	28 (71.8)	75 (64.1)
Minor Features			
Multiple, randomly distributed pits in dental enamel	10 (12.8)	6 (15.4)	16 (13.7)
Hamartomatous rectal polyps	0	0	0
Bone cysts	2 (2.6)	0	2 (1.7)
Cerebral white matter radial migration lines[1]	14 (17.9)	6 (15.4)	20 (17.1)
Gingival fibromas	10 (12.8)	10 (25.6)	20 (17.1)
Nonrenal hamartoma	6 (7.7)	4 (10.3)	10 (8.5)
Retinal achromic patch	4 (5.1)	3 (7.7)	7 (6.0)
Confetti' skin lesions	9 (11.5)	7 (17.9)	16 (13.7)
Multiple renal cysts	31 (39.7)	9 (23.1)	40 (34.2)

[1] The co-occurrence of cortical tuber and cerebral white matter radial migration lines is considered as one major feature.

[2] In patients with both 2 major features Lymphangioleiomyomatosis and Renal angiomyolipoma, another feature must be identified to assign TSC diagnosis.

Table 32: Prior anti-SEGA therapy (Full Analysis Set) – Study M2301

	Everolimus N=78 n (%)	Placebo N=39 n (%)	All patients N=117 n (%)
Any prior anti-SEGA medication/surgery	6 (7.7%)	2 (5.1%)	8 (6.8%)
Medication	0	0	0
Surgery	6 (7.7%)	2 (5.1%)	8 (6.8%)

Numbers Analysed

The Full Analysis Set (FAS) (N=117), consisted of all randomized patients. Following the intent-to-treat principle patients were analyzed according to the treatment and stratum that they were assigned to at randomization. A total of 78 patients were randomized to everolimus arm and 39 to placebo arm. The Safety Set (N=117), included all patients who received at least one dose of the double-blind study medication with a valid post-baseline safety assessment. Patients were analyzed according to the treatment they actually received.

A total of 78 patients were actually treated with everolimus and 39 with placebo, no patient received another treatment than the randomized one.

The Per Protocol Set (PPS) (N=113), consisted of all patients from the FAS without any major protocol deviation, who were evaluable for efficacy and who had completed a minimum exposure requirement. However, if a patient had SEGA progression, discontinued due to an AE, or died before the minimum exposure requirement could be met, or before he/she could become evaluable for efficacy, that patient was still included in the PPS.

Table 33: Patient disposition (Full Analysis Set) – Study M2301

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

n(%)=n(%) of patients

Outcomes and Estimations

The response rate was 34.6% (95% CI: 24.2% - 46.2%) for everolimus and 0% (95% CI: 0% - 9.0%) for placebo (Table 34). The difference in response rates was 34.6% (95% CI: 15.1% -52.4%). The difference in response rates was statistically significant (p< 0.0001, one-sided exact CMH test).

No statistically significant difference was observed in seizure frequency (one-sided rank ANCOVA, p=0.2004). The median of the change from baseline to Week 24 (Last observation-carried-forward (LOCF) approach) was 0 (95% CI: 0 - 0) in both treatment arms (Table 35). Time to progression and skin lesion response could not be interpreted from a formal statistical point of view since the test on seizure frequency in the fixed sequence strategy failed to yield a statistical significance.

Preliminary data from the phase III for time-to-progression are shown in Figure 3.

Skin lesion response was only determined among patients with at least one skin lesion at baseline (N=110), and was defined as proportion of patients with a best overall skin lesion response of either complete clinical response (100% improvement in the appearance of skin lesions) or partial response (≥ 50% to < 100% improvement in the appearance of skin lesions). The response rate was 41.7% (95% CI: 30.2% - 53.9%) for the everolimus arm and 10.5% (95% CI: 2.9% - 24.8%) for placebo (Table 36).

Table 34: Preliminary results best overall SEGA response as per central radiological review (Full Analysis Set) – Study M2301

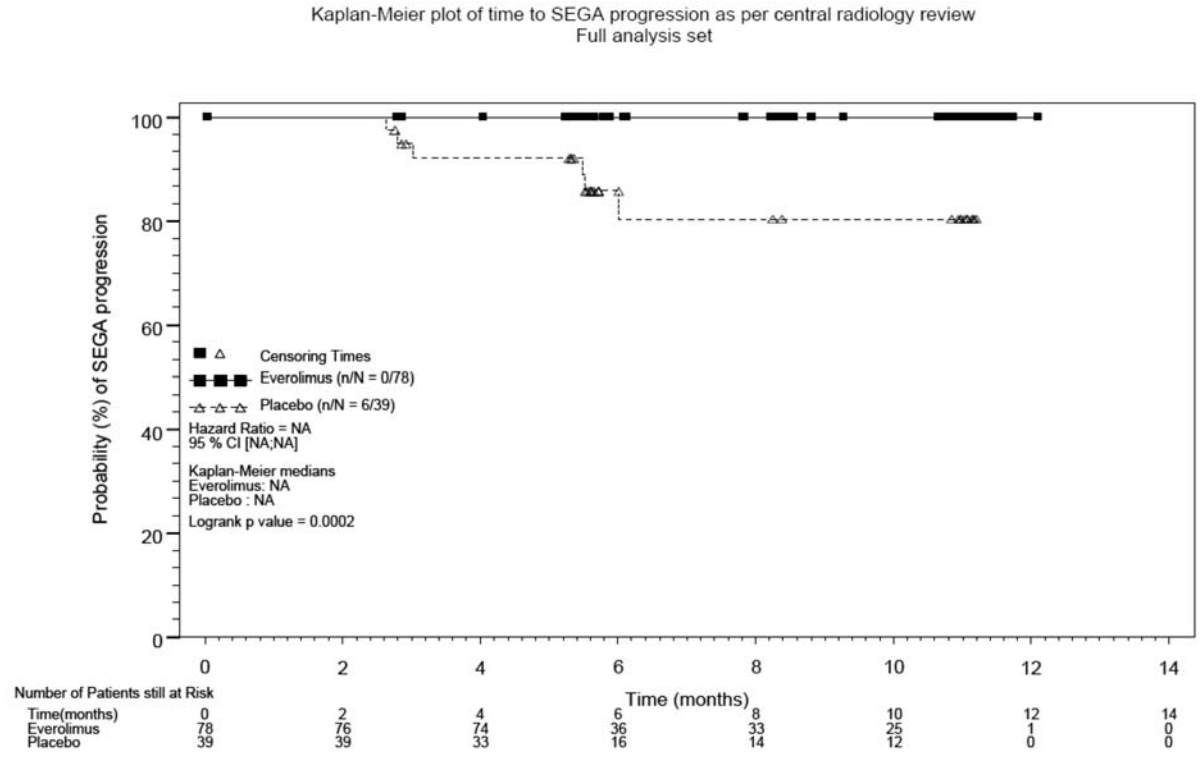
	Everolimus N= 78	Placebo N= 39	p-value [1]	Difference in response rates [95% CI] [2]
Best Overall SEGA Response				
Response	27 (34.6)	0		
Stable Disease	49 (62.8)	36 (92.3)		
Progression	0	3 (7.7)		
Not Evaluable	2 (2.6)	0		
Primary Analysis				
SEGA Response Rate	27 (34.6)	0	< 0.0001	34.6 [15.1;52.4]
95% CI for SEGA Response Rate [3]	[24.2;46.2]	[0.0; 9.0]		

[1] p-value is obtained from the one-sided exact CMH test, stratified by the protocol stratification factor (EIAED use versus EIAED non-use).

[2] Difference in response rates (everolimus minus placebo). Exact 95% confidence interval obtained from the exact unconditional confidence limits.

[3] Exact 95% confidence interval obtained from the Clopper-Pearson method.

Figure 3: Preliminary results for time to SEGA progression (Full Analysis Set) – Study M2301



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

Table 35: Change from baseline to week 24 (LOCF approach) in total seizure frequency per 24 hours from video EEG (Full Analysis Set) – Study M2301

	Everolimus N= 78	Placebo N= 39
Baseline [1]		
N	78	39
Mean (SD)	3.41 (8.355)	5.58 (14.976)
Median	0	0
Range	0 – 42.6	0 – 78.9
Week 24/LOCF [1]		
N	78	39
Mean (SD)	2.17 (4.838)	5.33 (15.567)
Median	0	0
Range	0 – 31.6	0 – 91.5
Change from baseline to Week24/LOCF		
N	78	39
Mean (SD)	-1.24 (6.116)	-0.24 (5.702)
Median	0	0
Range	-34.0 – 13.0	-15.9 – 14.4
95% CI for median [2]	[0; 0]	[0; 0]
p-value for treatment effect [3]	0.2004	

Seizure frequency per 24 hours is calculated as 24*(raw count/actual duration of EEG recording (hours)), missing if actual EEG recording duration less than 18 hours.

[1] Missing values were imputed as per LOCF (Last observation carried forward) method.

[2] 95% confidence intervals of the median based on bootstrap percentiles.

[3] 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).

Table 36: Best overall skin lesion response as per central radiology review: only patients with at least one skin lesion at baseline (Full Analysis Set) – Study M2301

	Everolimus N= 72	Placebo N= 38	p-value [1]
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)	
Progressive Disease (PD)	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 [2]	[30.2;53.9]	[2.9;24.8]	

[1] 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).

[2] Exact 95% confidence interval obtained from the Clopper-Pearson method.

2.5.3. Discussion on clinical efficacy

This application is based on a Phase II uncontrolled trial (C2485). This was a prospective, open-label, single-arm phase II study to evaluate the safety and efficacy of Votubia in patients with SEGA. Radiological evidence of serial SEGA growth was required for entry.

Change in SEGA volume during the core 6-month treatment phase, as assessed via an independent central radiology review, was the primary efficacy endpoint. After the core treatment phase, patients could be enrolled into an extension phase where SEGA volume was assessed every 6 months.

In total, 28 patients received treatment with Votubia; median age was 11 years (range 3 to 34), 61% male, 86% Caucasian. Thirteen patients (46%) had a secondary smaller SEGA, including 12 in the contralateral ventricle.

Primary SEGA volume was reduced at month 6 compared to baseline ($p<0.001$). No patient developed new lesions, worsening hydrocephalus or increased intracranial pressure, and none required surgical resection or other therapy for SEGA.

The robustness and consistency of the primary analysis were supported by the:

- change in primary SEGA volume as per local investigator assessment ($p<0.001$), with 75.0% and 39.3% of patients experiencing reductions of ≥30% and ≥50%, respectively.
- change in total SEGA volume as per independent central review ($p<0.001$) or local investigator assessment ($p<0.001$).

One patient met the pre-specified criteria for treatment success (>75% reduction in SEGA volume) and was temporarily taken off trial therapy; however, SEGA re-growth was evident within 3 months and treatment was restarted.

The CHMP acknowledged the limitations of the phase II study (C2485) and the inherent challenges of determining the relationship between volume or size reduction of SEGA and treatment with everolimus due to the lack of a control arm. Preliminary, high level results of the ongoing placebo controlled phase III trial (M2301) were submitted. The preliminary data supported the data from the phase II trial. The response rate in the phase II was 75.0% for patients that experienced reductions in primary SEGA volume of ≥ 30% during the 6-month treatment phase, including 9 patients (32.1%) who experienced ≥ 50% reductions. The response rate in phase III was 34.6% (95% CI: 24.2% - 46.2%) for everolimus arm and 0% (95% CI: 0% - 9.0%) for placebo arm for patients who experienced ≥ 50% reductions.

The CHMP had concerns with respect to the applicant's definition of treatment success and the clinical relevance of the findings. When the individual patient plots of SEGA volume were analysed, a number of patients only exhibited an initial extensive decrease in size. The CHMP noted the importance of prevention of further SEGA growth for at least 12 months in patients with documented serial SEGA growth not amenable to neurosurgery observed in both the phase II and III trials. For study C2485, no patients of the 24 patients with a ≥ 30% reduction in primary SEGA volume met the definition for progression and median time from first response to censoring was 15.1 months (5.7 – 31.1). According to the preliminary analysis presented for the phase III trial, no progression was observed in 78 patients vs. 6 progressions in 39 patients within 12 months for everolimus and placebo treatment, respectively. The CHMP considered that the duration of response was clinically significant.

The CHMP discussed the patient population which could benefit the most from treatment with everolimus and determined that, as resection was still the best therapeutic option for a curative treatment in patients who's tumours are amenable for resection, based on the evidence presented in the phase II and III studies, everolimus could become an additional option or complement to neurosurgical resection, but not a replacement to neurosurgery for the SEGA patient population.

Assessment of paediatric data on clinical efficacy

The European Medicines Agency has deferred the obligation to submit the results of studies with Votubia in one or more subsets of the paediatric population in subependymal giant cell astrocytoma (see section 4.2 of the SmPC for information on paediatric use).

In accordance with the timelines as set out in a modified PIP P/105/2010 as of 28 July 2010, more mature results of phase III trial M2301 should be reported to the CHMP not later than September 2012.

Additional efficacy data needed in the context of a conditional MA

There is a need to confirm the long-term clinical benefits expected from the reduction of SEGA volume, as well as potential risks. The applicant is applying for a conditional approval where the most relevant condition will be to report on the long term result of the ongoing controlled phase III trial.

The CHMP considered the following measures necessary to address the missing clinical data in the context of a conditional MA:

- Provide long-term follow-up on duration of response and time to progression for study C2485 and M2301.
- The MAH shall complete the ongoing pivotal clinical study M2301 and provide the interim and final safety and efficacy results within the stated timeframe. Within the interim analysis, the MAH shall:
    - analyse the adverse event incidence as a function of plasma drug concentration with and without inducer stratified by age,
    - readdress the starting dose strategy, utilising what is understood about the relationship between Cmin and dose in this patient population, as well as the experience gained on the need for dosage adjustment during study C2485
    - provide a new simulation that predicts the mean and confidence interval around C_{min} as a result of the recommended posology in appropriate subgroups of patients, keeping in mind that the population pharmacokinetic analysis of everolimus in children may lead the applicant to different age stratification than in the current analysis (i.e., a cut-off of 10 years may not be optimal).

These conditions are part of the specific obligations in Annex II.

2.5.4. Conclusions on the clinical efficacy

In summary, whilst there is a need for less invasive therapeutic options in the treatment of SEGA, as compared to neurosurgery, the submitted Phase II trial (C2485) and the preliminary result of the ongoing phase III trial (M2301) provided sufficient evidence of efficacy of everolimus against SEGA lesions and skin lesions.

The results from the single arm, uncontrolled phase II trial C2485 show that everolimus is an effective mTOR (mTORC1) inhibitor. The main effect observed is primarily the shrinkage of primary SEGA volume at month 6. The response was observed in nearly all patients although there was variation that was seemingly dependent on absolute SEGA volume at baseline. This response appears durable taking into account that median duration of response was not reached while median time from first response

to censoring was 15.1 months (5.7 to 31.1 months) and no progression was observed in the 24 patients in whom a ≥30% tumour volume reduction was observed.

2.6. Clinical safety

The overall safety evaluation was based on the 28 patients with SEGA associated with TSC who were recruited to Study C2485 and exposed to treatment with everolimus. In addition, supportive long-term safety data resulting from the use of everolimus in a paediatric renal transplant population (study B351) were presented as supportive data (of note, transplant patients received concurrent administration of cyclosporine and corticosteroids). Preliminary safety data from study M2301 and post-marketing safety data were also submitted.

Patient exposure

The exposure to everolimus in the pivotal SEGA study C2485 was 49.0 patient-years. As of the 09-December-2009 data cut-off, 27 of the 28 patients (96.4%) had completed ≥ 12 months of treatment, with 1 patient having voluntarily discontinued after 4.7 months of everolimus therapy. All 27 patients completing the core 6-month treatment phase subsequently continued everolimus therapy. The median duration of treatment was 21.5 months (range: 4.7 to 34.4). The 12-month analyses of Cohorts 1 and 2 from the Phase II renal transplant study (B351) corresponded to median durations of exposure of 12.3 and 13.3 months, respectively. It is important to note that while the everolimus dose (based on body surface area [BSA]) appeared to be considerably lower in the transplant group (B351), everolimus trough concentrations were similar as a result of cyclosporine potentiation (Table 38, 39).

Table 38: Duration of exposure to everolimus (safety population) - Study C2485 and B351

	SEGA C2485	Renal transplantation B351			
		Cohort I			Cohort II
	12-mo N=28	12-mo N=19	36-mo N=15	60-mo N=10	12-mo N=18
Exposure categories (months) (n [%])					
< 3	0	2 (10.5)	0	0	1 (5.6)
3 - < 6	1 (3.6)	0	0	0	0
6 - < 12	2 (7.1)	6 (31.6)	0	0	5 (27.8)
12 - < 24	17 (60.7)	11 (57.9)	4 (26.7)	0	12 (66.7)
24 - < 36	8 (28.6)	0	6 (40.0)	0	0
36 - < 48	0	0	5 (33.3)	0	0
48 - < 60	0	0	0	2 (20.0)	0
≥ 60	0	0	0	8 (80.0)	0
Duration of exposure (months)					
Mean (standard deviation)	21.0 (7.26)	11.3 (4.00)	30.9 (8.47)	61.7 (2.39)	13.1 (4.26)
Median	21.5	12.3	35.1	61.0	13.3
Range	4.7 - 34.4	0.4 - 16.0	14.3 - 37.2	59.1 - 66.2	0.1 - 18.4
Total exposure (years)	**49.0**	**17.8**	**38.6**	**51.4**	**19.7**

SEGA Subependymal giant cell astrocytoma

Includes interruptions (i.e., days on which the patient was not treated)

C2485: everolimus monotherapy; B351: Cohort I - full-dose cyclosporine plus fixed-dose everolimus; Cohort II - low-dose cyclosporine plus everolimus trough concentrations ≥ 3 ng/mL

Table 39: Average daily dose of study medication, including days without medication (safety population) – Study C2485 and B351

	SEGA C2485	Renal transplantation B351			
		Cohort I			Cohort II
	12-mo N=28	12-mo N=19	36-mo N=15	60-mo N=10	12-mo N=18
Everolimus (mg/m^2 BSA)					
Mean (standard deviation)	5.14 (2.212)	1.51 (0.153)	1.53 (0.145)	1.49 (0.148)	1.45 (0.215)
Median	5.29	1.54	1.51	1.49	1.50
Range	1.48-12.03	0.93-1.66	1.37-1.89	1.19-1.70	0.95-1.70
Cyclosporine (mg/kg)					
Mean (standard deviation)	-	6.04 (2.825)	4.45 (2.114)	3.84 (1.706)	4.40 (2.301)
Median	-	6.28	3.69	3.45	4.27
Range	-	2.47-11.29	1.77-8.99	1.69-6.65	0.00-8.15
Prednisone-equivalent corticosteroids (mg/kg)					
Mean (standard deviation)	-	0.93 (2.538)	0.21 (0.081)	0.18 (0.070)	0.72 (2.006)
Median	-	0.27	0.20	0.17	0.26
Range	-	0.13-11.34	0.09-0.38	0.08-0.31	0.10-8.75

BSA Body surface area; SEGA Subependymal giant cell astrocytoma

Average dose is calculated over the entire treatment duration for C2485, and from start of treatment up to 12 mo, 36 mo, or 60 mo (as per column headers) for B351, where 12 mo refers to Day 450, 36 mo to Day 1170, and 60 mo to Day 1890

Includes interruptions (i.e., days on which the patient was not treated)

C2485: everolimus monotherapy; B351: Cohort I - full-dose cyclosporine plus fixed-dose everolimus; Cohort II - low-dose cyclosporine plus everolimus trough concentrations ≥ 3 ng/mL

Adverse events

The adverse events that are suspected to be related to the study drug in the investigators' view in trial C2485 and B351 are shown below in Table 40.

In Study C2485, the most frequently reported AEs suspected as being drug-related for the SEGA patient population included stomatitis, upper respiratory tract infection, sinusitis, otitis media, pyrexia and acneiform dermatitis. In Study B351, 3 events in the renal transplant population (12-month analyses of Cohorts I or II) were suspected to be drug related at a frequency ≥ 10%: hyperlipidemia, hypercholesterolemia, and hypertriglyceridemia. All 3 are common toxicities reported in association with a class effect reflecting the inhibition of mTOR-regulated lipid metabolism. As a result, lipid profile monitoring is recommended prior to commencing everolimus therapy and periodically thereafter (see SmPC section 4.4).

The severity of infections in the population of SEGA patients treated with everolimus is shown in Table 41. Infections were experienced by the majority of patients, with a total of 159 events over the course of the study. This corresponds to a mean of 6.4 episodes per patient (range: 1 to 19). Of the 159 episodes, 15 were grade 1, 140 were grade 2, and 4 were grade 3. Complete resolution was evident for 13 of the 15 grade-1 episodes, 127 of 140 grade-2 events, and all 4 grade-3 episodes. Upper respiratory tract infection and otitis media were the predominant events leading to both dose

reduction/temporary interruption and the administration of concomitant medication. No patient discontinued treatment as the result of an infection.

Table 40: Adverse events suspected as study drug related by preferred term (safety population) – Study C2485 and B351

MedDRA preferred term	SEGA C2485	Renal transplantation B351			
		Cohort I			Cohort II
	12-mo N=28 n (%)	12-mo N=19 n (%)	36-mo N=15 n (%)	60-mo N=10 n (%)	12-mo N=18 n (%)
Any preferred term	**28 (100.0)**	**11 (57.9)**	**11 (73.3)**	**9 (90.0)**	**9 (50.0)**
Stomatitis	22 (78.6)	0	0	0	0
Upper respiratory tract infection	22 (78.6)	0	0	0	0
Sinusitis	11 (39.3)	0	0	0	0
Otitis media	10 (35.7)	0	0	0	0
Pyrexia	8 (28.6)	1 (5.3)	1 (6.7)	0	0
Dermatitis acneiform	7 (25.0)	0	0	0	0
Cellulitis	6 (21.4)	0	0	0	0
Diarrhoea	6 (21.4)	0	0	0	0
Body tinea	4 (14.3)	0	0	0	0
Gastroenteritis	4 (14.3)	0	0	0	0
Otitis externa	4 (14.3)	0	0	0	0
Hypertriglyceridaemia	3 (10.7)	2 (10.5)	2 (13.3)	2 (20.0)	0
Acne	3 (10.7)	0	0	0	0
Cough	3 (10.7)	0	0	0	0
Gastric infection	3 (10.7)	0	0	0	0
Skin infection	3 (10.7)	0	0	0	0
White blood cell count decreased	3 (10.7)	0	0	0	0
Blood triglycerides increased	2 (7.1)	1 (5.3)	1 (6.7)	0	1 (5.6)
Pneumonia	2 (7.1)	0	2 (13.3)	2 (20.0)	0
Urinary tract infection	2 (7.1)	0	1 (6.7)	1 (10.0)	0
Vomiting	2 (7.1)	0	0	0	1 (5.6)
Gastritis	2 (7.1)	0	0	0	0
Mucosal inflammation	2 (7.1)	0	0	0	0
Pharyngeal inflammation	2 (7.1)	0	0	0	0
Pharyngitis	2 (7.1)	0	0	0	0
Hypercholesterolaemia	1 (3.6)	2 (10.5)	2 (13.3)	1 (10.0)	0
Blood cholesterol increased	1 (3.6)	1 (5.3)	1 (6.7)	0	2 (11.1)
Hypertension	1 (3.6)	0	2 (13.3)	1 (10.0)	0
Anaemia	1 (3.6)	0	1 (6.7)	1 (10.0)	0
Headache	1 (3.6)	0	0	0	1 (5.6)
Insomnia	1 (3.6)	0	0	0	1 (5.6)
Hyperlipidaemia NOS	0	5 (26.3)	0	0	0
Hyperlipidaemia	0	0	5 (33.3)	4 (40.0)	2 (11.1)
Aphthous stomatitis	0	0	1 (6.7)	2 (20.0)	0
Sepsis	0	0	1 (6.7)	1 (10.0)	0

MedDRA Medical Dictionary for Regulatory Activities; NOS Not otherwise specified; SEGA Subependymal giant cell astrocytoma

Preferred terms are presented by descending frequency in the C2485 column, and in the case of ties, by descending frequency in each subsequent column, starting with the B351 Cohort I 12-mo column

A patient with multiple occurrences of an AE is counted only once in that AE category

AEs are not included if occurring > 28 days after discontinuation of study treatment in C2485, or > 7 days after discontinuation of study treatment in B351

C2485: everolimus monotherapy; B351: Cohort I- full-dose cyclosporine plus fixed-dose everolimus; Cohort II - low-dose cyclosporine plus everolimus trough concentrations ≥ 3 ng/mL

Table 41: Grading (severity) of infections by preferred term irrespective of relationship to treatment (safety population) – Study C2485

MedDRA preferred term	Everolimus N=28				
	All grades n (%)		Grade 3 n (%)		Grade 4 n (%)
Any infection	**25**	**(89.3)**	**4**	**(14.3)**	**0**
Upper respiratory tract infection	22	(78.6)	0		0
Sinusitis	11	(39.3)	1	(3.6) [a]	0
Otitis media	10	(35.7)	0		0
Cellulitis	6	(21.4)	0		0
Body tinea	5	(17.9)	0		0
Gastroenteritis	4	(14.3)	0		0
Otitis externa	4	(14.3)	0		0
Skin infection	4	(14.3)	0		0
Gastric infection	3	(10.7)	0		0
Conjunctivitis infective	2	(7.1)	0		0
Pharyngitis	2	(7.1)	0		0
Pneumonia	2	(7.1)	1	(3.6) [a]	0
Urinary tract infection	2	(7.1)	0		0
Acarodermatitis	1	(3.6)	0		0
Bronchitis	1	(3.6)	0		0
Bronchitis viral	1	(3.6)	1	(3.6) [a]	0
Catheter site cellulites	1	(3.6)	0		0
Eyelid infection	1	(3.6)	0		0
Gastroenteritis viral	1	(3.6)	0		0
Helicobacter infection	1	(3.6)	0		0
Hordeolum	1	(3.6)	0		0
Impetigo	1	(3.6)	0		0
Infection	1	(3.6)	0		0
Laryngitis	1	(3.6)	0		0
Lymph gland infection	1	(3.6)	0		0
Rhinitis	1	(3.6)	0		0
Tooth infection	1	(3.6)	1	(3.6) [a]	0
Vulvovaginal mycotic infection	1	(3.6)	0		0

[a] Event suspected as study drug related; note, all infections were mandated by the protocol to be suspected to be drug related

Each patient has only been represented with a maximum reported intensity for each preferred term

Serious adverse event/deaths/other significant events

No deaths were reported during the course of trial C2485 and B351. In trial C2240, deaths 'on-treatment' were recorded for 28 patients (6.8%). Of the 28 patients who died, 21 (7.7%) had received treatment with everolimus and 7 (5.1%) with placebo. Twenty-three of the 28 deaths (82.1%) were attributed to the underlying malignancy. The remaining five cases were attributed to acute respiratory failure (2 patients) and bronchopulmonary aspergillosis, sepsis, and myocardial infarct, respectively.

The incidence of specific individual SAEs was low for both patient populations for study C2485 and B351. Overall, 4 patients (14.3%) with SEGA reported a total of 6 non-fatal SAEs. Two of the 6 SAEs (both infections) were suspected to be drug-related (Table 42).

Table 42: Serious adverse events by system organ class and preferred term irrespective of relationship to treatment (safety population) – Study C2485

System organ class MedDRA preferred term	Everolimus N=28 n (%)	
Any SAE	**4**	**(14.3)**
Infections and infestations	**2**	**(7.1)**
Bronchitis viral	1	(3.6)
Pneumonia	1	(3.6)
Nervous system disorders	**2**	**(7.1)**
Convulsion	2	(7.1)
Gastrointestinal disorders	**1**	**(3.6)**
Vomiting	1	(3.6)

System organ classes are presented in descending order of frequency; preferred terms are also sorted within SOC in descending order of frequency
A patient with multiple occurrences of an SAE is counted only once in that SAE category

In Study C2485, infections and stomatitis were the most common reasons leading to dose reduction and/or temporary interruptions in therapy (Table 43). Dose interruptions rather than dose reduction appeared to be the favoured method for managing AEs in this single-center study, with a median of 2 interruptions per patient (range: 0 to 15). Interruptions lasted for between 1 and 131 days.

Table 43: Adverse events requiring dose reduction and/or temporary interruption by preferred term irrespective of relationship to treatment (safety population) – Study C2485 and B351

MedDRA preferred term	SEGA C2485	Renal transplantation B351			
		Cohort I			Cohort II
	Everolimus N=28 n (%)	12-mo N=19 n (%)	36-mo N=15 n (%)	60-mo N=10 n (%)	12-mo N=18 n (%)
Any AE requiring dose reduction and/or temporary interruption	**22 (78.6)**	**0**	**0**	**0**	**2 (11.1)**
Upper respiratory tract infection	15 (53.6)	0	0	0	0
Sinusitis	9 (32.1)	0	0	0	0
Otitis media	7 (25.0)	0	0	0	0
Stomatitis	5 (17.9)	0	0	0	0
Pyrexia	4 (14.3)	0	0	0	0
Cellulitis	3 (10.7)	0	0	0	0
Cough	3 (10.7)	0	0	0	0
Diarrhoea	3 (10.7)	0	0	0	0
White blood cell count decreased	3 (10.7)	0	0	0	0
Otitis externa	2 (7.1)	0	0	0	0
Pneumonia	2 (7.1)	0	0	0	0
Urinary tract infection	2 (7.1)	0	0	0	0
Vomiting	2 (7.1)	0	0	0	0
Blood alkaline phosphatase increased	0	0	0	0	1 (5.6)
Adenovirus and cytomegalovirus infection	0	0	0	0	1 (5.6)

Preferred terms are sorted in descending order of frequency
A patient with multiple occurrences of an AE is counted only once in that AE category
This table uses a cut-off of 5%

In the C2240 study, SAEs were reported more frequently for patients receiving everolimus (110 [40.1%] and 31 [22.6%] for the everolimus and placebo groups, respectively). The most frequently reported SAEs are dyspnea, pyrexia, pneumonitis, pneumonia, pleural effusion, and anemia. Events within the 'respiratory, thoracic, and mediastinal disorders' SOC (17.5% versus 2.9% for placebo-treated patients) and 'infections and infestations' SOC (11.3% versus 1.5% for placebo-treated patients) are more evident for patients receiving everolimus therapy.

Laboratory findings

In the study C2485, no consistent laboratory abnormalities were noted, with the exception of increases in total and low-density lipoprotein cholesterol, and triglycerides.

Haematology

No newly occurring grade 3-4 hematologic toxicity was reported in patients with SEGA; although further examination of the data identified a single ANC value that corresponded to a grade-3 neutropenia. Of the 15 patients with leukopenia, 13 patients experienced grade-1 events and 2

patients experienced grade-2 events (one of whom had a grade-2 abnormality at baseline). All cases of anaemia were grade 1. Thrombocytopenia was grade 1 for 5 patients and grade 2 for 1 patient.

Changes for the transplant recipients (trial B351) were consistent with those expected post-transplantation, including increased leukocytes and decreased haemoglobin.

Nearly all patients in trial C2240 reported changes in laboratory results. Grade 3 and 4 changes were observed in 29.2% of patients receiving everolimus therapy and 10.9% of placebo-treated patients. Low haemoglobin occurred in 92.3% and 78.8% of patients receiving everolimus and placebo, respectively. Anaemia was reported as an AE in 37.6% and 14.6% of patients, respectively. Lymphopenia was observed in 50.7% of patients receiving everolimus and 28.5% from the placebo arm, respectively. While there was more grade 3 and grade 4 lymphopenia in the everolimus treatment group (17.9% versus 5.1% in the placebo group), the incidence of grade 3 and grade 4 leukopenia, thrombocytopenia, and neutropenia did not differ between the 2 treatment groups.

Clinical chemistry

All patients in the pivotal SEGA study had ≥ 1 abnormal clinical chemistry value; however, grade 3 changes were evident in only 1 patient. AST concentrations fluctuated widely in this patient. However, the patient's final value was within normal range, which reflected an improvement relative to baseline (1.2 x ULN).

For the renal transplant population, elevated lipid and creatinine concentrations were evident from baseline.

Concerning trial C2240, nearly all patients reported changes in clinical chemistry laboratory results. Grade 3 and 4 changes were observed in 30.7% of patients receiving everolimus and 3.6% of the placebo treatment group. The proportion of patients experiencing grade 3 or grade 4 changes for hyperglycemia, hypophosphatemia, and hypercholesterolemia were higher with everolimus than with placebo therapy. Although increases in serum creatinine, AST, and ALT concentrations were reported more often for everolimus, the incidence of grade 3-4 toxicities did not differ.

Preliminary safety data from Study M2301

With the exception of amenorrhea, AEs were similar to those identified in Study C2485 and were consistent with what is known about the safety profile of everolimus.

Infections (71.8% vs. 66.7% on everolimus and placebo, respectively) were characterized primarily by different kinds of upper respiratory infections (e.g. nasopharyngitis, upper respiratory tract infection). No opportunistic infections were reported. One case of Grade 4 gastroenteritis was observed. Stomatitis/oral mucositis/ulcers was frequent (59% vs. 25.6% on everolimus and placebo, respectively), consistent with the known safety profile of everolimus. No cases of Grade 4 stomatitis were observed. Pneumonia was seen in 7.7% of patients on everolimus vs. 0% on placebo: 2.6% on everolimus and 0% on placebo were considered Grade 3. No Grade 4 pneumonia was observed. One case of non-infectious pneumonitis was observed in the everolimus arm. One case of proteinuria was observed at frequencies of 1.3% and 0% in the everolimus and placebo arms, respectively. Information regarding changes in creatinine or glomerular filtration was not available at the time of submission. Decreased platelet count was seen in 1.3% and 0% of patients on everolimus and placebo, respectively. No Grade 3 or 4 platelet count decreased AE was observed. Hemorrhagic events were seen in 9% of patients on everolimus (most commonly, epistaxis, in 5.1%) and 5.1% on placebo (most commonly, epistaxis, in 2.6%). Amenorrhea was seen in 3 patients on everolimus out of a total of 8 females aged 13 years and older on everolimus.

Safety in special populations

The median age of patients included in trial C2485 was 11.0 years of age. The incidence of AEs was generally similar for patients aged 3 to < 12 years, 12 to <18 years, and ≥ 18 years. Rash and gastric infection were only reported in the youngest age group, while urinary tract infection was evident only in those ≥ 18 years.

Too few non-Caucasians were included to draw conclusions on safety in different ethnic groups.

No new safety data in patients with severe hepatic and renal impairment were submitted.

The incidence of most AEs was generally similar for both males and females.

Safety related to drug-drug interactions and other interactions

Drug-drug interactions are described in the section on clinical pharmacology. Drug-drug interactions did not raise additional safety concerns.

Discontinuation due to adverse events

In the study C2485, no AEs led to discontinuation of everolimus.

Post marketing experience

There are no post-marketing experiences with everolimus in the TSC setting. At the time of submission, 3,275 oncology patients had received treatment with everolimus in Novartis sponsored studies. The total combined worldwide cumulative market exposure to Afinitor was 3400 PTYs (30 March 2009 – 30 September 2010).

2.6.1. Discussion on clinical safety

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

The most frequently reported drug-related AEs in the phase II study (C2485) were stomatitis, upper respiratory tract infection, sinusitis, otitis media, pyrexia, and acneiform dermatitis. All these AEs are known side effects of everolimus and thus, no new major safety concerns were identified.

Non-infectious pneumonitis is a class effect of rapamycin derivatives, including everolimus. Non-infectious pneumonitis (including interstitial lung disease) was described very commonly in patients taking everolimus in the advanced RCC setting (see section 4.8 of the SmPC). 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 Votubia 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. Votubia may be reinitiated at a daily dose approximately 50% lower than the dose previously administered. For cases where symptoms of non-infectious pneumonitis are severe, Votubia

therapy should be discontinued and the use of corticosteroids may be indicated until clinical symptoms resolve. Votubia may be reinitiated at a daily dose approximately 50% lower than the dose previously administered depending on the individual clinical circumstances.

Everolimus has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoal infections, including infections with opportunistic pathogens (see section 4.8 of the SmPC). 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 everolimus in the oncology setting. 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 Votubia. Pre-existing infections should be treated appropriately and should have resolved fully before starting treatment with Votubia. While taking Votubia, 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 Votubia.

If a diagnosis of invasive systemic fungal infection is made, Votubia treatment should be promptly and permanently discontinued and the patient treated with appropriate antifungal therapy.

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 of the SmPC).

Mouth ulcers, stomatitis and oral mucositis have been observed in patients treated with Votubia (see section 4.8 of the SmPC). 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 of the SmPC).

Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with everolimus (see section 4.8 of the SmPC). Renal function of patients should be monitored particularly where patients have additional risk factors that may further impair renal function (see section 4.2 and 4.4 of the SmPC).

Elevations of serum creatinine, usually mild, and proteinuria have been reported in clinical trials (see section 4.8 of the SmPC). Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein or serum creatinine, is recommended prior to the start of Votubia therapy and periodically thereafter.

Hyperglycaemia, hyperlipidaemia and hypertrigylceridaemia have been reported in clinical trials (see section 4.8 of the SmPC). Monitoring of fasting serum glucose is recommended prior to the start of Votubia therapy and periodically thereafter. When possible optimal glycaemic control should be achieved before starting a patient on Votubia.

Decreased haemoglobin, lymphocytes, neutrophils and platelets have been reported in clinical trials (see section 4.8 of the SmPC). Monitoring of complete blood count is recommended prior to the start of Votubia therapy and periodically thereafter.

Votubia should not be used in patients with severe hepatic impairment (Child-Pugh class C) (see sections 4.2 and 5.2 of the SmPC).

Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Impaired wound healing is a class effect of rapamycin derivatives, including Votubia. Caution should therefore be exercised with the use of Votubia in the peri-surgical period.

The immune response to vaccination may be affected and, therefore, vaccination may be less effective during treatment with Votubia. The use of live vaccines should be avoided during treatment with Votubia (see section 4.5 of the SmPC). Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG (Bacillus Calmette-Guérin), yellow fever, varicella, and TY21a typhoid vaccines.

Women of childbearing potential must use a 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.

Everolimus is not recommended during pregnancy and in women of childbearing potential not using contraception. Male patients should not be prohibited from attempting to father children.

It is not known whether everolimus is excreted in breast milk. However, in rats, everolimus and/or its metabolites readily pass into the milk (see section 5.3 of the SmPC). Therefore, women taking everolimus should not breast-feed.

No studies on the effects on the ability to drive and use machines have been performed. Patients should be advised to be cautious when driving or using machines if they experience fatigue during treatment with Votubia.

Reported experience with overdose in humans is very limited. Single doses of up to 70 mg have been given with acceptable acute tolerability in the adult population. It is essential to assess everolimus blood levels in cases of suspected overdose. General supportive measures should be initiated in all cases of overdose. Everolimus is not considered dialysable to any relevant degree (less than 10% was removed within 6 hours of haemodialysis).

A limited number of paediatric patients have been exposed to doses higher than 10 mg/m^2/day. No signs of acute toxicity have been reported in these cases.

The potential for growth/developmental delays with long-term treatment is unknown (see section 5.3 of the SmPC).

In the non-clinical studies, the major target organs in all species were the reproductive organs. As SEGA patients are likely to be of reproductive age and will require longterm treatment, these are of major concern. Histopathological findings consisted of depletion of germ cells and tubular vacuolation in testes, reduced sperm content in epididymides, reduced ovarian follicular development, and uterine atrophy. In addition, developmental delay was also observed in juvenile rat studies with both everolimus and rapamycin. These issues have been resolved and are adequately addressed in the SmPC and RMP.

Lens fibre swelling also occurred in the non-clinical studies but the pre-clinical lens fibre disruption appeared to be species specific and observed only in rats. Ocular hyperaemia was observed in one patient in the Phase II trial (C2485) but was resolved with gentamicin treatment.

Both rapamycin and everolimus are known to cause thrombocytopenia. In one phase I trial (Bissler et al 2008) angiomyolipoma bleeding and uterine bleeding was observed and was considered to be drug related. There is therefore concern regarding the potential risk of bleeding that may occur in SEGA patients. However, none of the patients in study C2485 with thrombocytopenia experienced any

bleeding. Routine pharmacovigilance including detailed cumulative review in the PSURs will be implemented to address the risk of haemorrhage (see RMP). The issue was considered resolved.

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 Votubia may be required (see section 4.5 of the SmPC).

Concomitant treatment with potent CYP3A4 inhibitors result in dramatically increased blood concentrations of everolimus (see section 4.5 of the SmPC). There are currently not sufficient data to allow dosing recommendations in this situation. Hence, concomitant treatment of Votubia and potent inhibitors is not recommended.

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 (see also section 5.3 for preclinical observations on the male and female reproductive systems).

The overall safety profile of Votubia is based on a phase II study for the treatment of SEGA (n=28) and a randomised phase III study for the treatment of metastatic renal cell carcinoma (everolimus, n=274; placebo, n=137) and in further studies in cancer patients. In the pivotal phase II study, 16 of the 28 SEGA patients were exposed to Votubia for ≥21 months. Total exposure was 49.0 patient-years. The median age of patients was 11 years (range 3-34). In the renal cell carcinoma study, a total of 165 patients were exposed to everolimus 10 mg/day for ≥4 months. The median age of patients was 61 years (range 27-85). The median duration of blinded study treatment was 141 days (range 19-451) for patients receiving everolimus and 60 days (range 21-295) for those receiving placebo.

The most common adverse reactions (incidence ≥10%) in SEGA patients were infections, increased aspartate transaminase (AST), stomatitis, increased cholesterol, decreased white blood cell count, increased alanine transaminase (ALT), increased triglycerides, decreased haemoglobin, pyrexia, decreased glucose, acneiform dermatitis, increased glucose, diarrhoea, decreased platelet counts, acne, cough, and increased creatinine. The only grade 3 adverse reactions were infections (single cases of sinusitis, pneumonia, tooth infection and viral bronchitis), and single cases of stomatitis, elevated aspartate transaminase (AST) concentrations and low absolute neutrophil count (ANC). No grade 4 adverse reactions were reported. The grades follow CTCAE Version 3.0.

Table 44 shows the incidence of adverse reactions reported in at least one of the pivotal studies, showing the highest frequency reported. Adverse reactions are listed according to MedDRA system organ class. Frequency categories are defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 44 Adverse reactions reported in a phase II study for the treatment of SEGA and in phase III studies

Infections and infestations	
Very common	Infections [a,*], upper respiratory tract infections, sinusitis, otitis media
Blood and lymphatic system disorders	
Very common	White blood cell count decreased, platelets decreased [b], haemoglobin decreased [b]
Immune system disorders	
Not known	Hypersensitivity
Metabolism and nutrition disorders	
Very common	Glucose decreased [b], cholesterol increased [b], triglycerides increased [b], glucose

	increased [b], phosphate decreased [b], anorexia
Common	Dehydration
Uncommon	New-onset diabetes mellitus
Psychiatric disorders	
Common	Anxiety, insomnia
Nervous system disorders	
Very common	Abnormal taste
Common	Somnolence, headache
Eye disorders	
Common	Ocular hyperaemia, conjunctivitis, eyelid oedema
Cardiac disorders	
Uncommon	Congestive cardiac failure
Vascular disorders	
Common	Hypertension
Uncommon	Flushing
Not known	Haemorrhage
Respiratory, thoracic and mediastinal disorders	
Very common	Pneumonitis [c], dyspnoea, epistaxis, cough
Common	Pharyngeal inflammation, respiratory disorder, haemoptysis
Uncommon	Pulmonary embolism
Gastrointestinal disorders	
Very common	Stomatitis [d], diarrhoea, mucosal inflammation, vomiting, nausea
Common	Gastritis, dry mouth, abdominal pain, dysphagia, dyspepsia
Hepatobiliary disorders	
Very common	Alanine aminotransferase increased [b], aspartate aminotransferase increased [b]
Common	Bilirubin increased [b]
Skin and subcutaneous tissue disorders	
Very common	Rash, acne, acneiform dermatitis, dry skin, pruritus
Common	Pityriasis rosea, palmar plantar erythrodysaesthesia, erythema, skin exfoliation, nail disorder, onychoclasis
Uncommon	Angioedema
Renal and urinary disorders	
Very common	Creatinine increased [b]
Common	Renal failure (including acute renal failure)*, proteinuria*
Reproductive system and breast disorders	
Common	Secondary amenorrhoea / LH/FSH imbalance
General disorders and administration site conditions	
Very common	Fatigue, asthenia, peripheral oedema, pyrexia
Common	Chest pain
Uncommon	Impaired wound healing
Investigations	
Common	Blood immunoglobulin G decreased, weight decreased

* see also SmPC section 4.8, subsection "c) Description of selected adverse reactions"

[a] Includes all events within the 'infections and infestations' system organ class (such as pneumonia, sepsis, and opportunistic infections [e.g. aspergillosis and candidiasis (see also SmPC section 4.4)]. The protocol of the study in patients with SEGA mandated that all infections be classified as adverse drug reactions

[b] Frequency based on determination of abnormal laboratory value (as part of routine laboratory assessment)

[c] Includes interstitial lung disease, lung infiltration, pulmonary alveolar haemorrhage, pulmonary toxicity, and alveolitis

[d] Includes aphthous stomatitis, and mouth and tongue ulceration

In clinical studies, everolimus has been associated with serious cases of hepatitis B reactivation, including fatal outcome. Reactivation of infection is an expected reaction during periods of immunosuppression.

In clinical studies and post-marketing spontaneous reports, everolimus has been associated with renal failure events (including fatal outcome) and proteinuria. Monitoring of renal function is recommended (see section 4.4 of the SmPC).

In the pivotal phase II study, 22 of the 28 SEGA patients studied were below the age of 18 years. Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

The CHMP considers the following measures necessary to address the missing safety data (See Risk Management Plan):

- The applicant shall provide long-term follow-up data from studies C2485 and M2301 for the assessment of reproductive/sexual and developmental toxicities.

2.6.2. Conclusions on clinical safety

In conclusion, the safety of everolimus treatment is already well established in several indications. The phase II trial in the SEGA indication does not add new safety concerns. Recommendations for reproductive toxicity are included in section 4.6 of the SmPC. All other relevant safety concerns are covered either in the RMP or the SmPC. The preliminary results of the trial M2301 raised safety concerns in terms of amenorrhoea. These have been addressed in the RMP and the SmPC section 4.8.

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.

Risk management plan

The applicant submitted a risk management plan.

Table 45: Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
Important identified risks		
Non-infectious pneumonitis	Routine pharmacovigilance activities including cumulative analysis in PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, post-marketing surveillance study reports, reports from other programs where data are being handled as solicited and all clinical trial SAE reports using a targeted product questionnaire/checklist.	Warning in SPC Section 4.4: "Non-infectious pneumonitis is a class effect of rapamycin derivatives, including everolimus. Non-infectious pneumonitis (including interstitial lung disease) was described very commonly in patients taking everolimus in the advanced renal cell carcinoma (RCC) setting (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

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
		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 Votubia 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. Votubia may be reinitiated at a daily dose approximately 50% lower than the dose previously administered. For cases where symptoms of non-infectious pneumonitis are severe, Votubia therapy should be discontinued and the use of corticosteroids may be indicated until clinical symptoms resolve. Votubia may be reinitiated at a daily dose approximately 50% lower than the dose previously administered depending on the individual clinical circumstances." Pneumonitis is included as ADR in SPC Section 4.8.
Severe infections	Routine pharmacovigilance including detailed cumulative review in the PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, serious reports from other programs where data is being handled as solicited and all clinical trial SAE reports, using a targeted product questionnaire/checklist.	Warning in SPC Section 4.4: "Everolimus has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoal infections, including infections with opportunistic pathogens. 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 everolimus in the oncology setting. 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 Votubia. Pre-existing infections should be treated appropriately and should have resolved fully before starting treatment with Votubia. While taking Votubia, be vigilant for symptoms and signs of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
		consider interruption or discontinuation of Votubia. If a diagnosis of invasive systemic fungal infection is made, Votubia treatment should be promptly and permanently discontinued and the patient treated with appropriate antifungal therapy." Infections is included as ADR in SPC Section 4.8.
Hypersensitivity (anaphylactic reactions)	Routine pharmacovigilance including detailed cumulative review in the PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-serious marketing surveillance study reports, reports from other programs where data is being handled as solicited and all clinical trial SAE reports, using a targeted event questionnaire/checklist.	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. Dyspnoea, flushing, angioedema, chest pain are included as ADRs in SPC Section 4.8.
Stomatitis	Routine pharmacovigilance including detailed cumulative review in the PSUR.	Warning in SPC Section 4.4: "Mouth ulcers, stomatitis and oral mucositis have been observed in patients treated with Votubia (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.
Increased creatinine/Proteinuria/ Renal failure	Routine pharmacovigilance including detailed cumulative review in the PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, serious reports from other programs where data is being handled as solicited and all clinical trial SAE reports, using a targeted event questionnaire/checklist.	Warning in SPC Section 4.4: Elevations of serum creatinine, usually mild, have been reported in clinical trials. Monitoring of renal function, including measurement of blood urea nitrogen (BUN) or serum creatinine, is recommended prior to the start of Votubia therapy and periodically thereafter. Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with everolimus. Renal function of patients should be monitored particularly where patients have additional risk factors that may further impair renal function. Increased creatinine, renal failure and proteinuria included as ADRs in SPC

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
		Section 4.8.
Hyperglycemia/New onset diabetes mellitus	Routine pharmacovigilance including detailed cumulative review in the PSUR.	Warning in SPC Section 4.4: "Hyperglycaemia, hyperlipidaemia and hypertrigylceridaemia have been reported in clinical trials. Monitoring of fasting serum glucose is recommended prior to the start of Votubia therapy and periodically thereafter. When possible optimal glycaemic control should be achieved before starting a patient on Votubia." Glucose decreased, glucose increased and new-onset diabetes mellitus included as ADRs in SPC Section 4.8.
Dyslipidemia	Routine pharmacovigilance including detailed cumulative review in the PSUR.	Warning in SPC Section 4.4: "Hyperglycaemia, hyperlipidaemia and hypertrigylceridaemia have been reported in clinical trials." Cholesterol increased, triglycerides increased are included as ADRs in SPC Section 4.8.
Hypophosphatemia	Routine pharmacovigilance including detailed cumulative review in the PSUR.	Phosphate decreased included as ADR in SPC Section 4.8.
Hemorrhages	Routine pharmacovigilance including detailed cumulative review in the PSUR.	Haemorrhage included as ADR in SPC Section 4.8.
Thromboembolism	Routine pharmacovigilance including detailed cumulative review in the PSUR.	Pulmonary embolism included as ADR in SPC Section 4.8.
Cardiac failure	Routine pharmacovigilance including detailed cumulative review in the PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, serious reports from other programs where data is being handled as solicited and all clinical trial SAE reports, using a targeted event questionnaire/checklist.	Congestive cardiac failure included as ADR in SPC Section 4.8.
Lymphopenia	Routine pharmacovigilance including detailed cumulative review in the PSUR.	Warning in SPC Section 4.4: "Decreased haemoglobin, lymphocytes, neutrophils and platelets have been reported in clinical trials. Monitoring of complete blood count is recommended prior to the start of Votubia therapy and periodically thereafter." White blood cell count decreased included as ADR in SPC Section 4.8.
Important potential risks		
Developmental toxicity	Routine pharmacovigilance including detailed cumulative review in the PSUR.	Relevant information included in SPC Section 5.3: "In juvenile rat toxicity studies,

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
	Additional activities Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, and serious reports from other programs where data are being handled as solicited and all clinical trial SAE reports, using a targeted event questionnaire/checklist. Study CRAD001M2301: A randomized, double-blind, placebo-controlled study of RAD001 in the treatment of patients with subependymal giant cell astrocytomas (SEGA) associated with tuberous sclerosis complex (TSC). Study M2301 includes a trial extension phase to follow-up of all patients until they reach Tanner stage V, or until the age of 15 for females and 16 for males, regardless of end of trial therapy. Study CRAD001C2485: Everolimus (RAD001) therapy of giant cell astrocytomas in patients with tuberous sclerosis complex (including children). Assessments include the collection of weight and height (before and after enrollment into the study), changes in hormones (LH and FSH, all patients; estrogen, females; testosterone, males) as well as Tanner staging until sexual maturation. For study M2301, these potential developmental effects will continue to be assessed until patients reach Tanner stage V, or until the age of 15 for females and 16 for males, regardless of end of trial therapy.	systemic toxicity included decreased body weight gain, food consumption, and delayed attainment of some developmental landmarks, with full or partial recovery after cessation of dosing. With the possible exception of the rat-specific lens finding (where young animals appeared to be more susceptible), it appears that there is no significant difference in the sensitivity of juvenile animals to the adverse reactions of everolimus as compared to adult animals. Toxicity study with juvenile monkeys did not show any relevant toxicity. The potential for growth/developmental delays with long-term treatment in SEGA patients is unknown.”
Reproductive (teratogenicity) toxicity	Routine pharmacovigilance including detailed cumulative review in the PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, and serious reports from other programs where data are being handled as solicited and all clinical trial SAE reports, using a targeted event and pregnancy questionnaire/checklist.	Relevant information in SPC Section 4.6: “There are no adequate data from the use of everolimus in pregnant women. Studies in animals have shown reproductive toxicity effects including embryotoxicity and foetotoxicity. The potential risk for humans is unknown.” 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.

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
		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."
Intestinal obstruction/ileus	Routine pharmacovigilance including detailed cumulative review in the PSUR.	None.
Secondary amenorrhea in post-adolescent females	Routine pharmacovigilance including detailed cumulative review in the PSUR. **Additional activities** Presentation of the results of a retrospective study and an updated review of amenorrhoea within 2 months including a detailed description of the proposals to further mechanistically define the observations and to characterise the reversibility taking into account the findings from the preclinical studies on the male and female reproductive organs.	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 and LH/FSH imbalance included as ADRs in SPC Section 4.8.
Infertility	Routine pharmacovigilance including detailed cumulative review in the PSUR.	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."
Overexposure due to concomitant administration of CYP3A4 or PgP inhibitors	Routine pharmacovigilance including detailed cumulative review in the PSUR.	Relevant information in SPC Section 4.2: "Trough concentrations should be assessed approximately 2 weeks after the initial dose, after any change in dose or after initiation of or change in co-administration of CYP3A4 inducers or 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 Votubia may be required. Concomitant treatment with potent CYP3A4 inhibitors result in dramatically increased blood concentrations of everolimus (see

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
		section 4.5). There are currently not sufficient data to allow dosing recommendations in this situation. Hence, concomitant treatment of Votubia 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 2 in the same SPC section."
Important missing information		
Pediatric patients less than 3 years old	Routine pharmacovigilance including cumulative analysis in PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, and serious reports from other programs where data are being handled as solicited and all clinical trial SAE reports, using a targeted event questionnaire/checklist.	Indication in SPC section 4.1 limited to patients aged 3 years and older. Appropriate dosing information in SPC Section 4.2: "The safety and efficacy of Votubia in children aged 0 to less than 3 years have not been established. No data are available." Relevant information in SPC Section 5.1: "In total, 28 patients received treatment with Votubia; median age was 11 years (range 3 to 34), 61% male, 86% Caucasian. Thirteen patients (46%) had a secondary smaller SEGA, including 12 in the contralateral ventricle."
Off-label use in pediatric and adolescent patients	Routine pharmacovigilance including cumulative analysis in PSUR.	Statement included in SPC Section 4.2 that the safety and efficacy of Votubia in children aged 0 to less than 3 years and in paediatric cancer patients have not been established and that no data are available. Relevant information in SPC section 5.1 about patient population studied.
Pregnant or breast-feeding women	Routine pharmacovigilance including cumulative analysis in PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, and serious reports from other programs where data are being handled as solicited and all clinical trial SAE reports, using a targeted event and pregnancy questionnaire/checklist.	Relevant information included in SPC Section 4.6: "Everolimus is not recommended during pregnancy and in women of childbearing potential not using contraception. It is not known whether everolimus is excreted in breast milk. However, in rats, everolimus and/or its metabolites readily pass into the milk. Therefore, women taking everolimus should not breast-feed."
Hormonal contraceptive use	Routine pharmacovigilance.	Relevant information included in SPC

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
		Section 4.6: "Women of childbearing potential must use a highly effective method of contraception (e.g. oral, injected, or implanted non-oestrogen-containing hormonal method of birth control, progesterone-based contraceptives, hysterectomy, tubal ligation, complete abstinence, barrier methods, intrauterine device [IUD], and/or female/male sterilisation) while receiving everolimus, and for up to 8 weeks after ending treatment."
Patients with renal impairment	Routine pharmacovigilance including cumulative analysis in PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, and serious reports from other programs where data are being handled as solicited and all clinical trial SAE reports, using a targeted event questionnaire/ checklist.	Information in SPC Section 4.2 that no dose adjustment is required. Further information in SPC Section 5.2 that no significant influence of creatinine clearance (25-178 ml/min) was detected on CL/F of everolimus was detected in a population pharmacokinetic analysis of 170 patients with advanced solid tumours.
Patients with pre-existing infections (other than systemic invasive fungal infections) Patients with CNS metastases Patients with HIV, or hepatitis B or C seropositivity Patients with bleeding diathesis (hemorrhages) Patients with coagulation disorders (thromboembolism) Patients with uncontrolled or significant cardiac disease Patients with impairment of GI function Patients undergoing chronic treatment with steroids or another immunosuppressive agent Patients who have undergone surgery within 2 weeks prior to treatment Race other than Caucasian	Routine pharmacovigilance including cumulative analysis in PSUR.	Warning in Section 4.4: Everolimus 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 everolimus in the oncology setting. 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 Votubia. Pre-existing infections should be treated appropriately and should have resolved fully before starting treatment with Votubia. While taking Votubia, 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 Votubia. Relevant information in SPC section 4.8: In clinical studies, everolimus has been associated with serious cases

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
		of hepatitis B reactivation, including fatal outcome. Reactivation of infection is an expected reaction during periods of immunosuppression.
Patients with severe hepatic impairment	Routine pharmacovigilance including cumulative analysis in PSUR.	Information in SPC Section 4.2: Dose should be reduced by approximately 50% to maintain target trough concentrations of 5 to 15 ng/ml. Patients with severe hepatic impairment (Child-Pugh class C): Everolimus has not been evaluated in patients with severe hepatic impairment (Child-Pugh class C) and is not recommended for use in this patient population Warning 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 Plasma protein binding is approximately 74% both in healthy subjects and in patients with moderate hepatic impairment.
Long-term safety	Routine pharmacovigilance including cumulative analysis in PSUR. **Additional activities** Study CRAD001M2301: Follow-up of all patients until they reach Tanner stage V, or until the age of 15 for females and 16 for males, regardless of end of trial therapy. Study CRAD001C2485: Follow-up of all patients for 5 years after last patient randomized.	None
Reactivation of background diseases	Routine pharmacovigilance including cumulative analysis in PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, serious reports from other programs where data is being handled as solicited and all clinical trial SAE reports, using a targeted product questionnaire/checklist.	Relevant information 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 reaction during periods of immunosuppression.

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
Submission of clinical study report CRAD001M2301: A randomized, double-blind, placebo-controlled study of RAD001 in the treatment of patients with subependymal giant cell astrocytomas (SEGA) associated with tuberous sclerosis complex (TSC). Study M2301 includes a trial extension phase.	Initial study: 4Q 2011

Description	Due date
	Extension phase: 2Q 2014
Submission of clinical study report CRAD001C2485: Everolimus (RAD001) therapy of giant cell astrocytomas in patients with tuberous sclerosis complex	4Q 2014

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

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

1. Section 1.5.2, rows „Seriousness/outcome": The EU-RMP template (Doc.Ref. EMEA/192632/2006) categories should be added.
2. Table 2-1: The targeted follow-up should be classified as routine pharmacovigilance, just like the cumulative PSUR review.
3. Section 1.5.2: Pertinent SMQs should be added.
4. Section 5, summary table: The SmPC entries should be described in detail, per EU-RMP template (e.g., "Warning in SmPC section 4.4 that ...").

2.8. 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. Benefit-Risk Balance

Benefits

Beneficial effects

In the C2485 phase II study, a statistically significant ($p<0.001$) reduction in SEGA volume was shown in patients treated with everolimus. Primary SEGA volume was reduced by a median 0.80 cm^3 (0.06 – 6.25) at Month 6 relative to baseline (median primary SEGA volume at baseline and at 6 months was 1.74 cm^3 and 0.93 cm^3, respectively) on independent central review. Out of the 28 treated patients, no patient developed worsening hydrocephalus or signs of increased intracranial pressure and none required surgical resection or other therapy for SEGA. Furthermore, no patient developed a new lesion within 12 months of observation.

Preliminary analyses of data of phase III trial M2301 support the observations derived from phase II trial C2485: a response rate (response defined as a >50% reduction of primary SEGA volume) of 34.6% compared with 0% (95%CI: 15.1 – 52.4; $p<0.0001$) was observed for everolimus and placebo, respectively. Out of 78 patients, there was no progression of disease in patients treated with everolimus compared to 6 patients in 39 patients for placebo.

SEGA volume reduction is expected to provide a clinical benefit to patients by reducing the risk of hydrocephalus or signs of increased intracranial pressure including seizure and other symptoms deriving from TSC, decrease the frequency of surgical interventions and may potentially affect overall survival. Further clinical benefit, such as improvement in disease-related symptoms, has not been demonstrated. The final results of the ongoing phase III trial M2301 are expected to provide statistically robust and comparable results to confirm the long term clinical benefit of SEGA volume reduction.

Concerning the beneficial effects in subgroups, there was no difference observed based on gender, age, or race as the sample size was too small to draw any conclusions.

Uncertainty in the knowledge about the beneficial effects

Currently, long-term comparative efficacy data in terms of duration of response, prevention of intracranial surgery, and overall survival are lacking. Preliminary results of trial M2301 have shown that there is an estimated median 40% SEGA volume reduction achieved after 6 months with everolimus whereas serial growth of SEGA continues in the placebo treated group. Long term follow-up from studies C2485, and M2301 may provide useful additional information about the long term outcomes associated with everolimus.

It is unclear whether patients with very small SEGA lesions at baseline can benefit from everolimus treatment. However, this poses no major concern because delaying further growth of small lesions may in principle be considered equally beneficial. Again, long-term follow-up from studies C2485, and M2301 may provide useful additional information about the long-term outcomes associated with everolimus.

The safety and efficacy of Votubia in children aged 0 to less than 3 years have not been established. No data are available. The safety and efficacy of Votubia in paediatric cancer patients have not been established. No data are available. This information has been adequately reflected in the SmPC.

Risks

Unfavourable effects

The main AEs in the everolimus safety database are infections and stomatitis which are manageable and are not considered serious.

Overall, there was no new safety information in addition to what has already been identified in the RMP and SmPC.

It should be highlighted that everolimus could decrease exposure to antiepileptic agents such as, for example carbamazepine, phenobarbital and phenytoin. This information is adequately reflected in the SmPC. PK monitoring, which is always required during antiepileptic treatment, may counter the risk.

Uncertainty in the knowledge about the unfavourable effects

SEGA patients, which are likely to be of reproductive age, face the prospect of long term treatment with everolimus to delay the growth or reduce the volume of SEGA lesions. The effect of everolimus on the maturation of children is unknown and it still not investigated. However, there may also be indirect beneficial effects on maturation with everolimus treatment through its effect on reducing SEGA volume and, as a consequence, providing relief from sequelae such as hydrocephalus, intracranial pressure, seizure and neuropsychological retardation. The applicant shall provide long term follow-up from studies C2485 and M2301 to assess the reproductive/sexual developmental toxicities.

Another uncertainty is the oncogenic potential of everolimus in the long term treatment of such a young SEGA patient population suffering from a mutation in a tumour suppressor gene. This is considered a well established risk of immunosuppressant agents in general. Long-term safety of everolimus will be addressed through pharmacovigilance including cumulative analysis in PSURs.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

SEGA volume reduction is expected to provide a clinical benefit to patients by reducing the risk of hydrocephalus or signs of increased intracranial pressure including seizure and other symptoms deriving from TSC, decrease the frequency of surgical interventions and may potentially affect overall survival. The main AEs in the everolimus safety database are infections and stomatitis which are manageable and are not considered serious.

Neurosurgery is still the currently accepted curative treatment option for SEGA lesions. The studies C2485 and M2301 did not investigate everolimus as an alternative therapy to neurosurgery, or as a kind of adjuvant or neo-adjuvant treatment in relation to neurosurgery. Thus, it is uncertain whether there are any clinical benefits from everolimus administration in SEGA patients that are eligible to undergo surgical resection of SEGA lesions. For this reason, the indication in SEGA patients was restricted to patients "who are not amenable to surgery".

Benefit-risk balance

During the 12 months of treatment reported in the phase II study C2485, the benefits of everolimus treatment (SEGA volume reduction, duration of response) clearly outweighed the rather mild adverse events (mild infections and manageable stomatitis).

Discussion on the Benefit-Risk Balance

Although the preliminary results of the randomised, placebo controlled, phase III trial M2301 fully support this balance of benefits and risks, there is still the need to obtain mature data from the M2301 study to confirm long term effects.

Following consultation with the applicant, the CHMP considered the granting of a conditional marketing authorisation for everolimus in SEGA patients. Everolimus was designated as an orphan medicinal product and falls within the scope of Commission Regulation 507/2006 on the conditional marketing authorisation. The Committee found that although comprehensive clinical data referring to the safety and efficacy of the medicinal product had not been supplied, all of the following requirements were met:

- The risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive

During the 12 months of treatment reported in the phase II study C2485, the benefits of everolimus treatment (SEGA volume reduction, duration of response) clearly outweighed the rather mild adverse events (mild infections and manageable stomatitis). The CHMP determined that, based on the evidence presented in the phase II and III studies, everolimus could represent an additional option or complement to neurosurgical resection, but not a replacement to neurosurgery for the SEGA patient population. Thus, the indication was restricted to patients with patients with SEGA associated with TSC who require therapeutic intervention but are not amenable to surgery.

- It is likely that the applicant will in a position to provide comprehensive clinical data

The applicant should provide long term follow-up data from studies C2485 and M2301 for the assessment of reproductive/sexual and developmental toxicities. A final clinical study report from the core phase of study M2301 will be submitted before 30/09/2012. Thus the CHMP concluded that it is likely that the applicant will be in a position to provide the comprehensive clinical data from the phase III with a view to confirming that the benefit-risk balance is positive and providing the additional comprehensive clinical data referring to the safety and efficacy of the medicinal product.

- Unmet medical needs to be fulfilled

Surgical resection is the current standard of treatment. However, the deep location of these tumours can make resection difficult and such procedures carry a significant risk of peri- and post-operative complications[21] which can include meningitis, persistent memory deficits and death[22]. Incompletely-resected SEGAs can recur, necessitating repeat operative procedures. There exists no satisfactory method of treatment authorised in the Community for patients with subependymal giant cell

[21] Levine NB, Collins J, Franz DN, et al (2006). Gradual formation of an operative corridor by balloon dilation for resection of subependymal giant cell astrocytomas in children with tuberous sclerosis: specialized minimal access technique of balloon dilation. Minim Invasive Neurosurg; 49: 317-20.
[22] de Ribaupierre S, Dorfmüller G, Bulteau C, et al (2007). Subependymal giant-cell astrocytomas in pediatric tuberous sclerosis disease: when should we operate? Neurosurgery; 60: 83-9.

astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not amenable to surgery.

The CHMP concluded that the product fulfils an unmet medical need in a SEGA patient population in relation to the lack of available non-invasive pharmacological treatments for SEGA.

- The benefits to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required

The CHMP considered that the potential risks inherent in marketing everolimus for the specific indication while additional, more comprehensive data will be available in the future would be offset by the benefit to patients with SEGA associated with TSC who require therapeutic intervention but are not amenable to surgery. The CHMP agreed that the RMP for everolimus in the approved indication was adequate to address any identified and unknown risks.

The CHMP concluded that all the requirements for the granting of a conditional marketing authorisation had been met.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers that the risk-benefit balance of Votubia in the indication "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." is favourable and therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the marketing authorisation

Risk management system and PSUR cycle

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

The PSUR submission schedule should follow the PSUR submission schedule for Afinitor.

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

Not applicable

Obligation to complete post-authorisation measures

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

Description	Due date
The applicant shall adequately document the population pharmacokinetics of everolimus in children (CL/F, apparent volumes, C_{max}, C_{min}, AUC, etc), including (but not limited to) the impact of age, weight, BSA, co-administration of enzyme inducers to complement the current sparse understanding of the disposition of everolimus in this patient group.	31/12/2012
The MAH shall re-evaluate the genotoxic potential of the impurities in the active substance everolimus.	31/05/2012

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
The MAH shall complete the ongoing pivotal clinical study M2301 and provide the interim and final safety and efficacy results within the stated timeframe. Within the interim analysis, the MAH shall: • analyse the adverse event incidence as a function of plasma drug concentration with and without inducer stratified by age, • readdress the starting dose strategy, utilising what is understood about the relationship between Cmin and dose in this patient population, as well as the experience gained on the need for dosage adjustment during study C2485 • provide a new simulation that predicts the mean and confidence interval around Cmin as a result of the recommended posology in appropriate subgroups of patients, keeping in mind that the population pharmacokinetic analysis of everolimus in children may lead the applicant to different age stratification than in the current analysis (i.e., a cut-off of 10 years may not be optimal).	Interim CSR due by: 30 /12/2011 Final CSR due by: 30 /09/ 2012

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 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.