European Medicines Agency
Evaluation of Medicines for Human Use

London, 29 May 2009
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CHMP ASSESSMENT REPORT

FOR

Afinitor

International Nonproprietary Name: everolimus

Procedure No. EMEA/H/C/001038

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

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Novartis Europharm Ltd. submitted on 01 July 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) through the centralised procedure for Afinitor, which was designated as an orphan medicinal product EU/3/07/449 on 5 June 2007. Afinitor was designated as an orphan medicinal product in the following indication: treatment of renal cell carcinoma. The calculated prevalence of renal cell carcinoma in the EU is 3.48 per 10,000 population with about 171,340 EU residents affected by the condition (based on the population as of January 1st 2004).

The applicant applied for the following indication:

> Afinitor is indicated for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.

The legal basis for this application refers to:

A - Centralised / Article 8(3) / New active substance.

The application submitted is a complete dossier composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information relating to Orphan Market Exclusivity

Similarity
Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application contained a critical report addressing the possible similarity with authorised orphan medicinal products.

Protocol Assistance:
The applicant received protocol assistance from the CHMP on 30 June 2006. The protocol assistance pertained to the clinical development aspects of the dossier.

Licensing status:
Afinitor has been given a Marketing Authorisation in the USA on 30 March 2009.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: **Harald Enzmann** Co-Rapporteur: **Tomas P Salmonson**

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 01 July 2008.
- The procedure started on 23 July 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 October 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 October 2008.
- During the meeting on 17-20 November 2008, 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 21 November 2008.
- A clarification meeting on the CHMP List of Questions with the Applicant and the Rapporteurs was held on 08 January 2009.

- The Applicant submitted the responses to the CHMP consolidated List of Questions on 16 January 2009 and additional responses on 4 February 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 02 March 2009.
- During the CHMP meeting on 16-19 March 2009, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- During a SAG meeting on 08 April 2009, experts were convened to address questions raised by the CHMP.
- The Applicant submitted the responses to the CHMP Day 180 List of Outstanding Issues on 24 April 2009.
- The Rapporteurs circulated an updated Joint Assessment Report on the Applicant's responses to the List of Outstanding Issues to all CHMP members on 12 and 13 May 2009.
- During the meeting on 26-29 May 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Afinitor on 29 May 2009 The Applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 28 May 2009.
- The CHMP adopted a report on similarity of Afinitor with Nexavar and Torisel on 21 November 2008.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Renal cell carcinoma (RCC) represents approximately 2% of all adult malignancies. More than 208,000 cases of kidney cancer are diagnosed per annum worldwide[1]. RCC affects more males than females (ratio of 1.6:1)[1,2]. The median age at diagnosis is 65 years, while that at death is 71 years[3] . In Europe, the highest incidence is observed in eastern European countries and in Germany[4]. Clear cell is the most common histological subtype, accounting for approximately 75-80% of the cases[5]. The incidence of RCC has increased annually by an estimated 2% over the past 2 decades[6] and by 126% over the past 50 years[7]. RCC is currently the sixth leading cause of cancer death and is responsible for >100,000 deaths worldwide each year [1.]

Patients diagnosed early in the disease process and whose disease remains local have a more favourable prognosis compared with those diagnosed with advanced or metastatic disease, with 5-year survival rates of 89.6% vs 9.5% [6]. The most important prognostic determinants of 5-year survival are evidence of metastatic disease at presentation, presence of regional nodal metastases, local extent of the tumour, and tumour grade[3]. Approximately 25-30% of patients present with metastatic RCC (mRCC) at the time of the initial diagnosis. The typical presentation of RCC involves a symptomatic triad: haematuria, flank pain, or abdominal mass. Patients with evidence of metastatic disease may present with signs and symptoms of bone pain, adenopathy, or pulmonary distress[3].

Chemotherapy and radiation therapy demonstrate little efficacy in advanced disease, and the 5-year survival rate ranges from 5-10%[8] . Until recently, standard therapy for advanced RCC consisted of cytokine therapy with interleukin-2 (IL-2) and/or interferon-alfa (IFN-α). However, cytokine therapy only benefits a minority of patients[9,10]. The critical role of angiogenesis in RCC led to the development of treatments specifically targeting VEGF signalling. The VEGF receptor protein tyrosine kinase acts at the level of the endothelial cell to drive new blood vessel formation. New options for therapy, which have become available over the past 2 years, and which are associated with antitumour efficacy include sorafenib, sunitinib, temsirolimus and bevacizumab.

In the initial application, the proposed indication for everolimus/ Afinitor was:

> "for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy".

The recommended posology for Afinitor is 10 mg once daily at the same time every day, consistently either with or without food. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

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[1] Ferlay J, Bray F, Pisani P, Parkin DM. (2004). GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide. IARC CancerBase No. 5. version 2.0, IARCPress, Lyon. Available at: www-dep.iarc.fr/globocan/database.htm.

[2] Jemal A, Siegel R, Ward E, et al (2008). Cancer statistics, 2008. CA Cancer J Clin; 58: 71-96.

[3] National Comprehensive Cancer Network. (2007) NCCN Clinical Practice Guidelines in Oncology. Kidney Cancer. V.2.2007. Available at: http://www.nccn.org/professionals/physician_gls/PDF/kidney.pdf.

[4] Rubagotti A, Martorane G, Boccardo FM (2006). Epidemiology of kidney cancer. Eur Urol Suppl; 5: 558-65.

[5] Jones J, Libermann TA (2007). Genomics of renal cell cancer: the biology behind and the therapy ahead. Clin Cancer Res; 13(2 Suppl): 685s-92s.

[6] Ries LAG, Harkins D, Krapcho M, et al, eds. (2007) SEER Cancer Statistics Review, 1975-2004. Bethesda, MD: National Cancer Institute. Available at: http://seer.cancer.gov/csr/1975_2004.

[7] Pantuck AJ, Zisman A, Belldegrun AS (2001). The changing natural history of renal cell carcinoma. J Urol; 166: 1611-23.

[8] Garcia JA, Rini BI (2007). Recent progress in the management of advanced renal cell carcinoma. CA Cancer J Clin; 57: 112-25.

[9] Bukowski RM (1997). Natural history and therapy of metastatic renal cell carcinoma: the role of interleukin-2. Cancer; 80: 1198-220.

[10] Motzer RJ, Bacik J, Murphy BA, Russo P, Mazumdar M (2002). Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J Clin Oncol; 20: 289-96.

2.2 Quality aspects

Introduction
Everolimus (INN) 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 with Sweden as Reference Member State, for the indication "Prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving an allogeneic renal or cardiac transplant" (MRP-number: SE/H/356/01-06).

Since November 2002, Everolimus has also been in development in the oncology setting. This application in advanced renal cell carcinoma is based in some parts, i.e. active substance, non-clinical (mainly pharmacokinetics and toxicology) and clinical pharmacology on Everolimus transplant data, since this information does also apply to Everolimus in the oncology setting. This information was previously submitted under the Mutual Recognition Procedure, and is submitted again in this *e*CTD application.

The full active substance section is presented as well as the full medicinal product section of everolimus in oncology (Afinitor) in module 3 of the dossier. Data is presented for 5 mg and 10 mg strengths and although the 2.5 mg strength is not applied for, data has been included since it was not known at that time which strengths would be marketed.

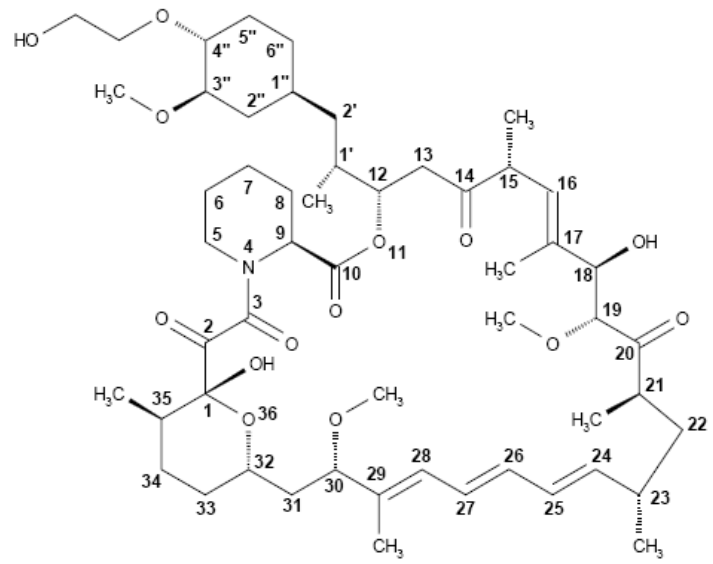
Active Substance

The active substance Everolimus is a hydroxyethyl derivative of rapamycin, which is a macrolide, isolated from the micro-organism *Streptomyces hygroscopicus*.
The guideline, impurities in new active substances ICHQ 3A (R), does not apply to active substance of fermented origin.

Everolimus (INN) or 42-O-(2-hydroxyethyl)-rapamycin (chemical name) or $C_{53}H_{83}NO_{14}$ has been fully described.
The molecule is amorphous and is stabilised with an antioxidant. Its physico-chemical properties including parameters such as solubility, pH, specific rotation, potential polymorphism and potential isomerism have been fully characterised.
Everolimus is a white to faintly yellow amorphous powder. It is almost insoluble in water, is unstable at temperatures above 25 °C and is sensitive to light.

In addition, possible isomerism has been investigated. Everolimus contains 15 asymmetric carbon atoms and 4 substituted double bonds. The configuration of the asymmetric carbon atoms and the double bonds is guaranteed by the microbial origin of Rapamycin. The configuration is not affected by the chemical synthesis.

Polymorphism has been comprehensively discussed and it was demonstrated that the molecule domain remains amorphous.



- Manufacture

Synthesis of Everolimus
The manufacturing process 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 the stabilizer has been sufficiently explained and justified by experimental results. Interactions products of Everolimus and the antioxidant were not detected, or were below detection limit.

Rapamycin, obtained by a fermentation process, was used as the starting material.
Reaction conditions and the necessary in-process controls are described in detail.
Adequate specifications for starting materials and isolated intermediates and descriptions of the test procedures have been submitted.
Control of the quality of solvents, reagents and auxiliary materials used in the synthesis has been adequately documented. It is stated by the manufacturer of rapamycin solution that no starting material of animal or human origin is used in the fermentation.

Elucidation of structure and other characteristics
The structure of Everolimus has been fully elucidated using several 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.

Related substances
An extensive discussion was presented on the related substances. The complex structure of Everolimus allows several possible degradation pathways to occur at various positions of the molecule.
Everolimus alone is extremely sensitive to oxidation. By the addition of an antioxidant, the sensitivity to oxidation is significantly reduced (the antioxidant is known to react as a scavenger of peroxide radicals). It is assumed that oxidation of Everolimus proceeds via a radical mechanism. All the requirements set in the current testing instruction valid for Everolimus are justified on the basis of the results obtained during development and manufactured at the production scale.

- Specification

There is no monograph for Everolimus 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 four commercial 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 is packaged in either in
- triple laminated aluminium foil bags or
- quadruple laminated aluminium foil bags

The inner 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, to protect the material from humidity, light and oxidation. The bags are 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 or amber glass bottles placed in aluminium bags have been placed under ICH stability studies: long term conditions (-20°C and +5°C°) and accelerated conditions (25°C/60% RH and 30°C/70 % RH).
The test methods and their validation were 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 alteration 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.

All quality characteristics were found to be within specifications after storage up to
- 60 months at -20°C and at 5°C in aluminium bags
- 12 months at 25°C/60 %RH in aluminium bags
- 3 months at 25°C/60% RH in amber glass bottles and in aluminium bags
- 3 months at 30°C/70 % RH in aluminium bags

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 the antioxidant was observed only after storage at higher temperature or when the active substance was unpacked.

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 kept in triple laminated aluminium foil bags or in quadruple laminated aluminium foil bags. Everolimus was stable for 60 months at - 20°C or 5°C. Storage of the same batches under accelerated conditions documented a 6 months stability at 25°C / 60 %RH.

Re-test period

Based on the above results, a satisfactory re-test period of Everolimus has been established when in the recommended storage conditions in a very tight packaging.

Medicinal Product

Afinitor 5 mg and 10 mg tablets are white to slightly yellowish, elongated tablets with bevelled edge and without breaking score.

- 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 5 mg and 10 mg tablets has been adequately detailed.

Compatibility with excipients:
During the early stages of development of everolimus tablets, stress tests 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), lactose anhydrous (filling agent).

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 states 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 preparation of the tablets.

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 dispersion 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. All intermediate batches consistently met the specified the acceptance criteria.
Based on the stability data, a satisfactory shelf life can be assigned for the Everolimus solid dispersion when stored 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 5 mg and 10 mg Tablets
The manufacture of Everolimus 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 5 mg and 10 mg tablets

Everolimus 5 mg and 10 mg 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 both strengths 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. 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 of Everolimus 5 mg and 10 mg tablets are common pharmaceutical excipients used for tablets such as BHT, Magnesium stearate, Lactose monohydrate, Hypromellose, Crospovidone and Lactose anhydrous. 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 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 of each strength (5 mg and 10 mg) have been provided. All batches consistently met the release specifications.

Analytical results of three batches tested at the development for another site have been presented. The results document, that analytical testing is equivalent at both testing sites and that method transfer has been carried out successfully.

The tablets will be packed in double sided aluminium blister consisting of an aluminium covering (or lidding) foil with a heat seal lacquer 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:

Since the registration stability study was designed and initiated, before a final decision was made on the tablet strengths to be marketed, studies were conducted on three pilot batches of Everolimus 2.5 mg tablets and three pilot 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 Afinitor 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.

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 SPC.

Discussion on chemical, pharmaceutical and biological aspects
The quality of this medicinal product is considered satisfactory when used within the conditions defined in the SPC. 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 2 years.
At the time of the CHMP opinion, there were two outstanding quality issues with no impact on the benefit/risk. The applicant undertook to provide the necessary information as follow-up measures within an agreed timeframe and to submit variations if required following the evaluation of this additional information.

2.3 Non-clinical aspects

The nonclinical studies for everolimus (also known as RAD001) presented in this submission were performed between 1992 and 2008 and were either performed by Novartis Pharma AG, by a contract research laboratories or described from the published literature. Relevant toxicity studies were performed in compliance with Good Laboratory Practices (GLP).

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. The monkey was selected as a non-rodent species because gastrointestinal intolerability of everolimus was seen in the oral rising-dose study in the dog [Study 41DED] precluding this species from treatment for longer periods. Similar findings have been reported with rapamycin in this species [11, 12].

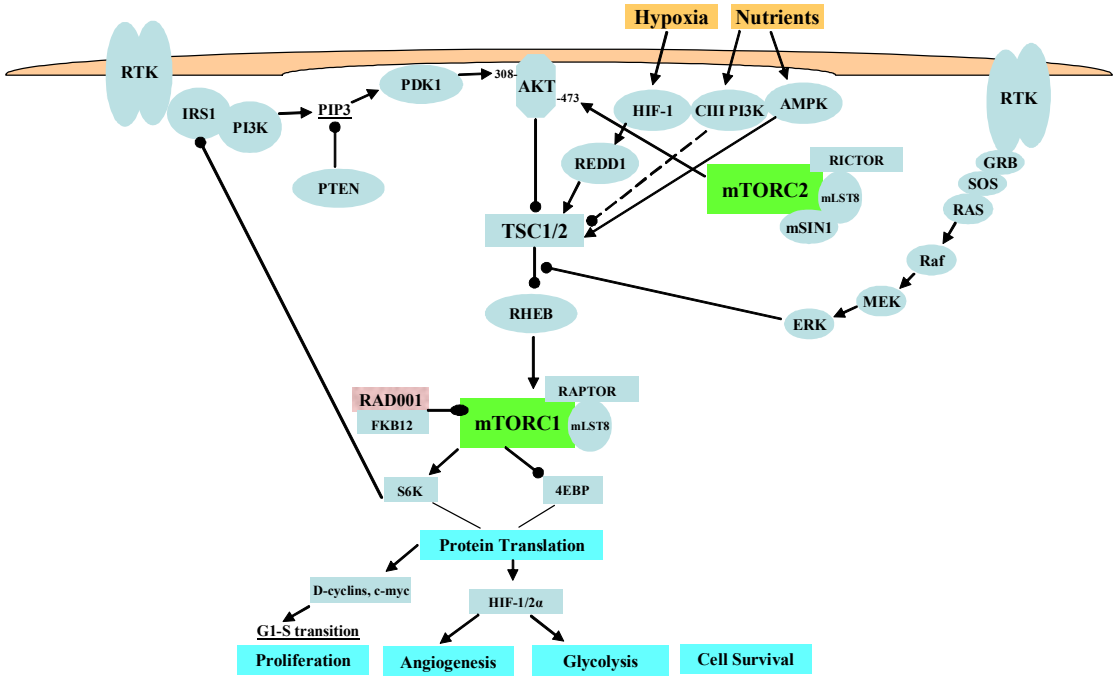
ADME and toxicity studies were performed with ^{3}H- or ^{14}C-radiolabeled and non-radiolabeled everolimus in the mouse, rat and monkey after oral (p.o.) and intravenous (i.v.) administration and repeated i.v. administration of everolimus were performed in rats, minipigs and monkeys. The blood/plasma distribution and plasma protein binding of ^{3}H-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*. Since the proposed route of administration of everolimus in patients with advanced renal cell carcinoma is oral, the i.v studies are of low relevance.

Introduction

Everolimus is a derivative of rapamycin. These two compounds are part of a family of specific inhibitors of mTOR (Figure 1). mTOR is a serine-threonine kinase acting as a signal transducing protein, which signals information via the regulation of multiple downstream pathways. mTOR regulates cellular metabolic state, protein synthesis, cell proliferation (including angiogenesis) and cell survival. Everolimus and other mTOR inhibitors achieve inhibition of mTOR by binding the cytoplasmic immunophilin receptor FKBP-12. mTOR is downstream of PI3K, and is considered a component in the PI3K/AKT/mTOR pathway which is known to be involved in numerous human cancers [13].

Figure 1 The mTOR pathway and everolimus

[11] Calne RY, Collier DSJ, Lim S, et al (1989). Rapamycin for immunosuppression in organ allografting. The Lancet; 22:227.
[12] Collier DSJ, Calne R, Thiru S, et al (1990). Rapamycin in experimental renal allografts in dogs and pigs. Transplant Proc; 22(4):1674-1675.
[13] Luo J, Manning BD, Cantley LC (2003). Targeting the PI3K-Akt pathway in human cancer: rationale and promise. Cancer Cell; 4:257-62.



Pharmacology

- Primary pharmacodynamics

Everolimus binds to FKBP-12 with an affinity (IC_{50} = 5.3 nM) similar to rapamycin (IC_{50} = 3.3 nM) and was inactive in tumour cell lines expressing mutant mTOR lacking the appropriate binding site [14]. Everolimus showed no inhibitory activity *in vitro* against 10 different protein kinases at 10 µM or below. Everolimus showed antiproliferative effects against most of the tested tumour cell lines *in vitro*. Most of the cell lines (80%) showed IC_{50} values of between 0.3 and 70 nM. There was a correlation between basal phospho-AKT/Phospho-S6 levels and anti-proliferative activity of everolimus in these tumour cell lines which could be useful indicators of the mTOR pathway activation and sensitivity to everolimus. Everolimus inhibited proliferation of endothelial cells (HUVECs) with IC_{50} values of 120 pM, 841 pM and > 10 nM for VEGF-, bFGF-, and foetal bovine serum stimulated proliferation, respectively. Normal haematopoietic stem cells were not as sensitive to everolimus, with an IC_{50} about 15-fold higher than the tumour cell lines.

Everolimus was evaluated for anti-tumour activity in 81 different human tumour xenografts grown *in vitro* using a clonogenic assay. Everolimus inhibited tumour colony formation in a broad concentration-dependent manner, resulting in low IC_{50}-values (0.18 µm). Anti-tumour activity of everolimus was studied in a wide range of different tumour xenografts grown in athymic mice. At doses (0.1 to 10 mg/kg, p.o., once per day) below the maximally tolerated dose of > 60 mg/kg, p.o., once per day, everolimus was capable of reducing the tumour growth rate and final tumour volume, and was active against 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). Everolimus treatment rarely significantly reduced mouse body weights and no deaths could be directly attributable to everolimus.

There were 6 RCC lines which demonstrated that in two tumour models, everolimus caused regressions in 50% of the treated mice. Overall in all 6 lines, everolimus caused impairment of tumour growth producing T/C values (tumour value (change) divided by control value (change)) of between 0.03 and 0.63 (mean±SEM of 0.29±0.1) and the treatment was very well tolerated.

[14] Beuvink I, Boulay A, Fumagalli S, et al (2005). Sensitization of Tumor Cells to Cisplatin- Induced Apoptosis By RAD001 Through mTOR Dependent Inhibition of p21 Protein Expression. Cell; 25:747-59.

The *in vivo* efficacy of everolimus against tumour growth was established using different xenograft models of human tumours (including pancreatic, colon, epidermoid, lung and melanoma) and three syngeneic models (rat pancreatic CA20948 and GH3 prolactinoma and murine B16/BL6 melanoma). In the xenograft models, everolimus (10 mg/kg, p.o., once per day) was effective at producing a mean T/C of 0.27 and a median value of 0.24 with a minimum value of -0.11 (regression) and a maximum value of 0.73. The activity of everolimus was mostly cytostatic but transient tumour regressions were also observed occasionally with durable regressions in two tumour models (one mammary and one lung adenocarcinoma: 3% of total). In the syngeneic models (Lewis and Wistar-Furth rats bearing rapidly growing well-vascularised s.c. CA20948 and s.c. GH3 prolactinoma tumours respectively), everolimus was well tolerated and exhibited a dose-dependent anti-tumour activity. Significant tumour growth suppression was observed at a dose of 0.5 and 2.5 mg/kg/day and 5 mg/kg once, twice or three times per week. Further experimentation indicated that weekly everolimus doses exhibited dose-dependency, with significant anti-tumour responses at doses >1 mg/kg/week.

To address the mechanism of tumour growth reductions in these models, the vascular parameters of these tumours were studied. Reduced VEGF levels, blood vessel density (BVD) and smooth muscle actin coverage of tumour blood vessels (one of the markers of blood vessel maturity) were observed. However, everolimus did not affect endothelial cell migration or reduce vascular permeability.

- Secondary pharmacodynamics

Everolimus prevents acute allograft rejection in rat and non-human primate allotransplantation models, especially when used in combination with CsA. This was confirmed in a rat model where two different schedules (2.5 mg/kg daily or 5 mg/kg weekly) reduced IgG levels in response to a T-cell dependent antigen but much less so using the 5 mg/kg schedule. 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).

Everolimus reduced mouse osteoclast and osteoblast differentiation *in vitro* and also osteoclast bone-resorbing activity at concentrations similar to that of sensitive human tumour cell lines (0.6-1.3 nM). Similar activity *in vitro* was also observed against human osteoclast activity and formation.

- Safety pharmacology programme

The studies related to safety pharmacology observed that everolimus was devoid of 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 fibres, in stable transfected HEK293 cells (hERG currents) and with conventional ECG monitoring in minipigs and monkeys.

Although everolimus passes the blood-brain barrier, there was no indication of relevant changes in the behaviour of rodents, even after single oral doses up to 2000 mg/kg.

- Pharmacodynamic drug interactions

Combinations of everolimus with other anticancer agents were tested using both *in vitro* and *in vivo* models. Investigations included using established drugs involving the more traditional targets of microtubules (paclitaxel, patupilone), anti-metabolites (gemcitabine and 5-fluorouracil) and DNA (cisplatinum, doxorubicin and temozolomide) and targeted compounds/drugs for the oestrogen receptor (ER) (letrozole), human epidermal growth factor (Her-2, ErbB1/2) (gefitinib, erlotinib, NVP-AEE788) and vascular endothelial growth factor receptor (VEGFR) (NVP-AEE788, vatalanib, bevacizumab) signal transduction pathways.

There was weak additivity or synergy observed with the combination compounds and this was attained *in vivo* using tolerable combination schedules. There were no cases where anti-tumour antagonism was observed *in vitro*. *In vivo* antagonism was only observed for the combination with paclitaxel when the taxane was administered 24 hr before or after everolimus. There were no consistent patterns of any advantage in terms of schedule other than concomitant treatments.

Pharmacokinetics

Absorption - Bioavailability
The absorption and intestinal metabolism of everolimus was studied *in vitro* and *in vivo*. 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. The absolute bioavailability of everolimus was 5% in the mouse, 6% in the monkey and 14%-26% in the rat.

Multiple daily oral doses (0.5 mg/kg/day) of ^{3}H everolimus given to rats increased the AUC_{0-24h} exposure of everolimus radioactivity moderately 2.4-fold on Day 21 compared to Day 1, which was expected from the observed apparent half-life of 96 hours for radioactivity elimination. Systemic exposure to everolimus in blood was substantial in the mouse and human (63% and 40% of total radioactivity AUC_{0-24h}) and moderate to low in the rat and monkey (8%-14%).

Everolimus is a substrate for P-glycoprotein mediated efflux systems. Studies in Caco-2 cells showed that everolimus was a substrate for the prominent trans-membrane efflux transporter system P glycoprotein (P-gp; MDR1; ABCB1). Inhibitors of P-gp might decrease the efflux of everolimus from some organs or tumours and, therefore, increase the everolimus concentrations in these tissues.

Distribution
The blood/plasma distribution and plasma protein binding of ^{3}H-radiolabeled everolimus in the mouse, rat, monkey and human was studied *in vitro*.

The *in vitro* blood distribution of 5 ng/ml everolimus was concentration-dependent, being 76% in rat and 79% in monkey. However, the blood cell uptake decreased to 11% in rat and 29% in monkey at an everolimus concentration of 1000 ng/ml. In the mouse blood, the majority of everolimus (~ 98%) was located in plasma. The concentration dependency of the blood/plasma partitioning suggests the presence of saturable high-affinity/low-capacity binding sites for everolimus in the blood cells. As a consequence, in almost all of the pharmacokinetic studies the determination of unchanged everolimus was performed in whole blood. In plasma, the free fraction of everolimus was independent of concentration (50 and 100 ng/ml) and averaged 7.6% in the rat and 16% in the monkey, but only 0.1% in mouse indicating higher protein binding in the mouse than in the other species tested.

The volume of distribution at steady-state (Vss) was species dependent and ranged from high in the rat (44-52 l/kg), moderate in monkeys (4.3 l//kg) to very low in the mouse (0.42 l/kg). In rats, ^{14}C everolimus tissue distribution studies, 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 tissues radioactivity of rats after single oral or intravenous administration. In the rat, the blood-brain passage of everolimus and/or its metabolites was found to be dose-dependent. Similar distribution patterns were obtained in the rat with ^{3}H-radiolabeled everolimus.

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. The transfer of radioactivity from blood into milk was rapid and very pronounced, as radioactivity 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. ^{3}H-everolimus-related radioactivity passed the placenta of pregnant rats to a limited degree and was readily transferred into milk of lactating rats.

Everolimus and/or its metabolites showed no affinity for melanin-containing tissues (choroid plexus of the eye) or persistent binding to any organ or tissue.

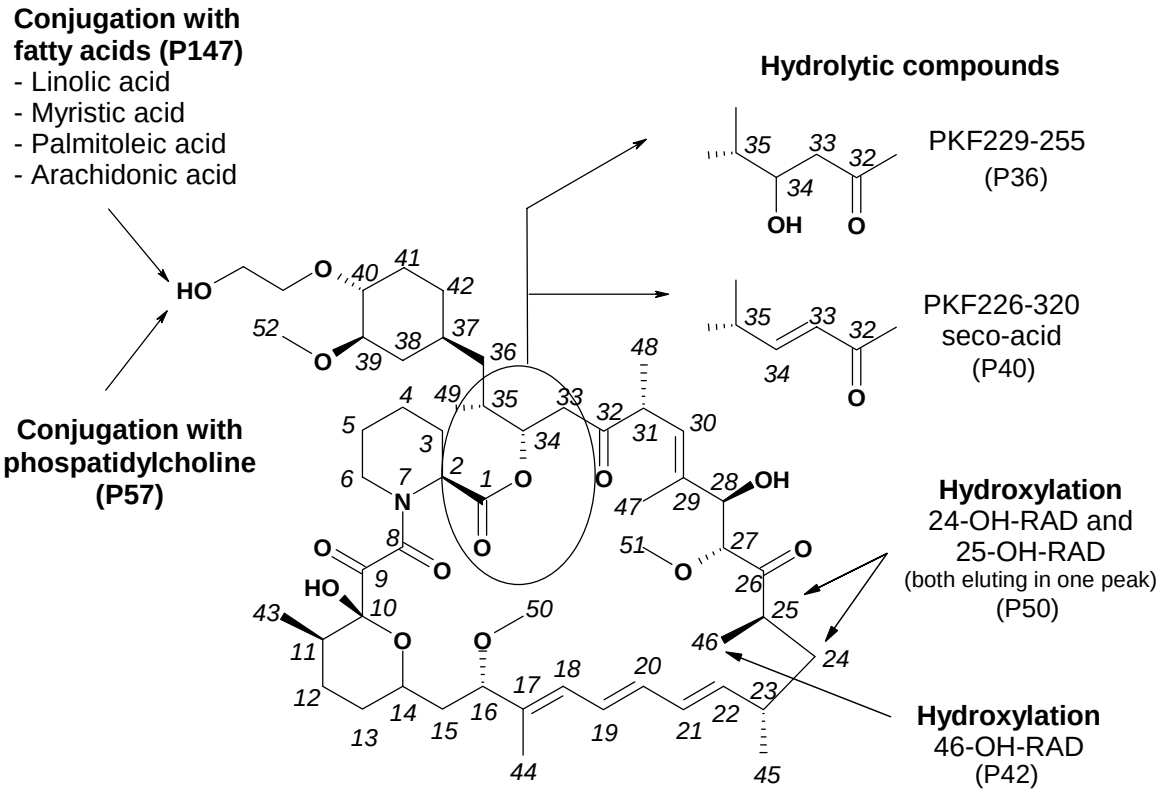
Metabolism
The metabolism of everolimus was investigated *in vitro* using animal and human liver microsomal fractions and liver slices and *in vivo* in the mouse, rat and monkey after single oral and intravenous doses.

The major enzyme responsible for the oxidative metabolism of everolimus in human liver microsomes was CYP3A4. Other cytochrome P450 enzymes did not or at very low rates metabolize everolimus. *In vitro* incubations of everolimus with liver microsomes from mouse, rat, monkey and human resulted in metabolite patterns which were comparable to those observed *in vivo* in the corresponding species, except P57 (ATG181) and P147, which were not formed *in vitro.*

In the blood of all investigated species including human, everolimus was generally the major circulating component, averaging in mice, rats and humans between 31% and 63% of the total AUC(0-24h) radioactivity, and 12% in the monkey. In human blood, five major metabolite peaks were present, covering together with unchanged drug, more than 80% of the total ^{14}C-AUC. These metabolite peaks were also detected in blood of the mouse, rat and monkey. Two of the metabolites were formed by ring-opened hydrolysis of everolimus e.g. PKF229-255, and subsequent dehydration with an additional double-bond (between carbon 33 and 34), the seco acid of everolimus, PKF226-320. Two other main metabolites were identified as 46-hydroxy-everolimus and 24/25-hydroxy- everolimus (the 24/25-hydroxy metabolites are eluded in one peak. The above mentioned major metabolites contribute to 13% (46-hydroxy- everolimus), 12% (24/25-hydroxy- everolimus), 6.5% (PKF226-320) and 4.1% (PKF229-255) of the total AUC in humans respectively.

The metabolic pathways *in vivo* are illustrated in Figure 2.

Figure 2 Proposed *in vivo* biotransformation pathways of everolimus in human, monkey, rat and mouse



A further metabolite peak (P147) of very lipophilic nature was present in considerable amounts in the milk of the rat. This peak was also present in a few tissues (e.g. duodenum), and occasionally in blood and in faecal samples of the rat, monkey and human.
Unchanged everolimus was the main component in blood and all tissues investigated, followed by metabolite peaks P40, P50 and P57. Peak P147 was most prominent in the duodenum, and Peak P57 was most prominent in the kidney.

In the rat, a large number of metabolites were excreted almost exclusively via the bile into faeces. Only trace amounts of everolimus could be detected in urine, bile, and faeces. Rapamycin, which may

be formed by cleavage of the 40-hydroxyethyl side chain of everolimus, was detected in monkey studies after multiple doses of 0.5 mg/kg/day (7.8%-10.7% of the everolimus blood concentration).

The pharmacological activity of the hydrolysis products of everolimus PKF229-225 and PKF226-320, and the hydroxylated metabolites 46-hydroxy- everolimus and 24/25-hydroxy- everolimus were tested and were compared to everolimus and rapamycin for their activity in the mixed lymphocyte reaction (MLR) assay. Everolimus was found to be 3-fold less active compared to rapamycin. PKF 226-320 and 229-255 were about 60- to 145-fold less active than everolimus. The hydroxy metabolites, 46-hydroxy- everolimus and 42-/25-hydroxy- everolimus were about 533-fold and 97-fold less active than everolimus respectively. Hence, primary metabolites of everolimus did not show any significant pharmacological activity.

Excretion
The excretion of everolimus was investigated in the mouse, rat and monkey following intravenous and oral administration of ^{3}H- or ^{14}C-labeled everolimus.

Everolimus was predominantly eliminated through metabolic biliary/faecal clearance in mouse and rat species. Excretion was essentially complete in all species. Renal excretion was a minor component (0.05%-0.5% of dose for rat). No unchanged drug was detected in urine or faeces. In the mouse, excretion of everolimus (either oral or i.v. dose) was almost complete (95%) within 48 hours in the faeces. The apparent systemic elimination half-life of everolimus in the mouse was 9.8 hours (period: 24-72 h), although the total blood clearance was low at 0.79 ml/min/kg compared to rat (21 and 32 ml/min/kg).

In a rat study, the administered ^{3}H-radioactivity (1 or 10 mg/kg, i.v.) was recovered predominantly in the faeces (69 to 82% of dose). In bile duct-cannulated rats, biliary excretion amounted to 71% of the dose. Thus, the observed systemic clearances of 21 and 32 ml/min/kg consisted almost exclusively of metabolic clearance. The terminal half-life of everolimus was 60 hours after intravenous dosing (1 and 10 mg/kg) and 61 and 47 hours after oral doses (1.5 and 15 mg/kg). Oral dosing of 1.5 mg/kg of ^{14}C-radiolabeled everolimus in the rat yielded a similar tissue distribution pattern as obtained with the ^{3}H-radiolabeled compound, the recovery of radioactivity being nearly complete (95%) within 7 days . The excretion via urine was almost negligible (0.05% of dose) and in bile (0.5% of dose). After multiple daily oral doses of 0.5 mg/kg/day ^{3}H-everolimus given to rats for 21 consecutive days, the excretion of radioactivity was almost complete within 7 days after the last dose.

In the monkey (1 mg/kg; i.v.), the radioactivity was excreted mainly in faeces (67% of dose, i.v.; 76% of dose, p.o.). Balance of excretion was not yet complete after 7 days, due to slow and continuing faecal excretion. The terminal half-life of the parent drug in blood was 27 hours and the systemic clearance was 3.1 ml/min/kg, smaller than that observed in the rat but in the range of the apparent systemic clearance observed in human (CL/F= 2.4 ml/min/kg).

A substantial enrichment of everolimus and/or metabolites was observed in the milk compartment: from 30 min to 8 hours post-dose the M/B ratio increased by a factor of 11. Thus, everolimus and/or its metabolites were readily transferred/excreted into the milk of lactating rats.

Pharmacokinetic drug interactions

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. Other CYP isoenzymes, such as CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A5 did not metabolize everolimus.

The effect of a series of compounds on the metabolism of everolimus (1 µM) was investigated in human liver microsomes. 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 concomitant medication 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 substrate CsA *in vitro* (K_i = 2.3 µmol/l) and was also a mixed inhibitor of the CYP2D6 substrate dextromethorphan (Ki = 1.7 µmol/l). Everolimus had no effect on phenacetin and chloroxanone metabolism by CYP1A2 and CYP2E1, respectively. Everolimus had little or no effect on the metabolism of paclitaxel, tolbutamide and s-mephenytoin by 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 no interaction was observed *in vitro* in human liver microsomes. 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) 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 µmol/l, 9-fold higher than that of the positive control CsA. 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. Therefore, it is unlikely that everolimus would affect the distribution of P-gp substrates in tissues.
Potential of everolimus to induce the liver drug-metabolizing enzymes
There were no signs of relevant *in vivo* induction of the liver drug metabolizing enzymes by everolimus, although no data from hepatocytes were available.

Potential of co-administrated drugs to induce the metabolism of everolimus
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, and by 3- to 7-fold in the monkey. Conversely, everolimus did not increase significantly the AUC of CsA.

Toxicology
Acute oral and intravenous toxicity studies were conducted in mice and rats. Repeated-dose toxicity studies were performed with durations up to 4 weeks in minipigs, 13 weeks in mice, 26 weeks in rats and up to 52 weeks in monkeys. The monkey was selected as a non-rodent species, since gastrointestinal intolerability of everolimus in the dog was seen after rising-doses between 2 and 18 mg/kg during only 9 days, precluding this species from treatment for longer periods.

- Single dose toxicity

The acute toxicity of everolimus was assessed in mice and rats. Everolimus was well tolerated after single oral administration in acute toxicity studies. No lethality or severe toxicity was observed after single oral doses of 2000 mg/kg in either mice or rats. In rats, intravenous administrations at 10 and 40 mg/kg were lethal, but at 2.5 mg/kg all animals survived.

- Repeat dose toxicity (with toxicokinetics)

Repeated dose oral toxicity studies were performed in mice, rats, minipigs, and monkeys. Major target organs in all animal species were reproductive organs. 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. These findings were accompanied by a decrease in circulating testosterone plasma levels.

There was a slight depletion of cortical bone mass only in the rat in the 4-week rat studies at ≥ 5.0 mg/kg. There were findings in the lungs (increased alveolar macrophages) in mouse and rat studies. 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. Electron microscopic examinations of rat lungs revealed vacuoles and multilamellar bodies in the macrophages. Pituitary gland (decrease in weight) and eye lesions (lenticular anterior suture line opacities and swelling/disruption of cortical lens fibres) were considered either species-specific or rodent-specific target organ. The finding of dilated lateral ventricles in the brain of rats treated with everolimus or rapamycin was exacerbated at higher dosages only in the 2-week studies, but not at longer duration or in other species. 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. There was no indication of kidney toxicity in mice after life-long treatment up to 0.9 mg/kg. In rats, incidence and severity of lipofuscin in renal tubular epithelial cells was more pronounced in treated animals at ≥ 0.3 mg/kg than in controls of the oncogenicity study, and occurred already after 26 weeks of treatment at ≥ 0.5 mg/kg. Increased incidence of hydronephrosis was observed in male rats at ≥ 0.5 mg/kg in the 26-week study. Increased incidence of hydronephrosis was observed in a small number of male rats at ≥ 0.5 mg/kg in the 6-month study which were considered reversible and were not seen in rats of the 2 year carcinogenicity study at doses up to 0.9 mg/kg. There were no indications of kidney toxicity in monkeys or minipigs. 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 were observed in relation to an affected general health condition of the animals. This was partly associated with necrosis in minipigs at 15.0 mg/kg, when animals died or were sacrificed early due to poor condition consequent to gastrointestinal problems. Pancreatic islet cell vacuolation has been reported for rapamycin in rats in association with cataracts and hyperglycemia. Hyperglycemia without pancreas findings also occurred in monkeys treated with rapamycin. Hyperlipidemia was increased in most species at ≥ 0.5 mg/kg.

Immunosuppressant effects of everolimus included changes in lymphatic organs such as thymus, spleen and lymph node associated with a decrease in circulating lymphoid as well as white blood cells, and a variety of skin alterations in mouse and monkey (e.g. abrasions, ulceration, inflammation, scabs). These showed full or at least partial reversibility after a 2- or 4-week recovery period. There were increased spontaneous background diseases. In the rat, spontaneous heart lesions (myocardial degeneration, also reported as chronic myocarditis) were exacerbated by the treatment with everolimus, in general at doses ≥ 1.5 mg/kg. Degenerative myocardial lesions were noted in the monkey at ≥ 5 mg/kg in the 2-week study and at 1.5 and 5 mg/kg in the 26-week study. Intestinal disorders associated with diarrhoea led to poor general health condition and some early sacrifices in minipigs and monkeys. This was evident in the 4-week study in minipigs from an exacerbation of coccidial infestation in the intestine and in the 52-week study in monkeys from inflammatory changes in the gastrointestinal tract which contributed to the premature termination of the high-dose group at 0.9 mg/kg after 39 weeks.

After multiple oral dosing for 13 weeks and in a carcinogenicity study in mice the systemic exposure to everolimus in blood was approximately proportional to the dose. In rat studies, the systemic exposure of everolimus in blood increased over-proportional to the dose by a factor between 3 and 6, whereas in a 26-week toxicity study about a linear increase to the dose was observed.

Adult and juvenile monkeys were exposed similarly with slightly under-proportional increases with dose. Pregnant rabbits were exposed to everolimus in a dose-proportional manner.

There was no gender effect and everolimus did not accumulate in the blood of any species.

Comparison of exposure levels at the NTEL or NOAEL in animals with those at the proposed therapeutic dosage in humans of 10 mg/day resulted in similar or even lower ratios.

- Genotoxicity

Everolimus is not genotoxic as indicated by *in vitro* and *in vivo* genetic toxicology studies.

- Carcinogenicity

Carcinogenicity studies were not required for the present indication. However, studies investigating carcinogenicity with everolimus showed an increase in the incidence of malignant granulocytic leukaemia in mice. The high dose in the mouse carcinogenicity study provides an AUC levels < 0.2 times higher than the expected clinical exposure at a dose of 10 mg/day and an AUC of 514 ng.h/ml.

- Reproduction Toxicity

The reproductive and developmental toxicity was evaluated in male fertility studies in rats, female fertility 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. In fertility studies in rats, everolimus caused testicular morphology changes, and a decrease in male fertility but had no effect on female fertility. After a recovery period, there was reversibility in only half of the animal. In rats, everolimus caused embryofoetal toxicity comprising mortality and reduced foetal weight. The incidence of skeletal variations and malformations were increased. In rabbits, embryo toxicity was evident by an increase in late resorptions at the maternally toxic dose of 0.8 mg/kg. The NTEL for embryotoxicity was 0.2 mg/kg, although maternal toxicity was observed at this dose. Effects of everolimus on the pre- and postnatal development of rats were limited to slight effect on body weight and survival in the F1-generation at ≥0.1 mg/kg, and did not indicate a specific toxic potential. Exposure ratios animal/man were estimated to be <1, which might indicate a potential risk in patients during pregnancy. In juvenile monkeys (approximately 1 year old), the oral treatment with everolimus at dosages up to 0.5 mg/kg for 4 weeks did not cause relevant toxicity.

- Toxicokinetic data

In oral juvenile toxicity studies in rats and monkeys a similar toxicity profile to that observed in adult animals was found except for the rare specific lens findings where young animals appeared to be more susceptible.

- 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. Everolimus was not irritant to the skin of rabbits or guinea pigs. For intravenous administration, all solutions were locally well tolerated

- Other toxicity studies

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 and thus was considered to have no antigenicity potential.

No specific immunotoxicity study was conducted with everolimus.

Ecotoxicity/environmental risk assessment

Considering the orphan drug designation of everolimus for the treatment of renal cell carcinoma, the predicted environmental concentration of everolimus is below the trigger value for a phase II assessment (10 ng/l). The method used for the determination of logKow was a High Performance Liquid Chromatography (HPLC) method following OECD guideline for testing of chemicals No. 117. The HPLC method was chosen based on the low water solubility of everolimus (< 0.01%). The pH value of everolimus dissolved in water is 7.2. Determination of a pH dependent distribution coefficient (logD) is not applicable for this active pharmaceutical ingredient, as everolimus does not possess any ionisable groups. The $\log K_{ow}$ is of 4.

Discussion on the non-clinical aspects

Everolimus is a selective mTOR (mammalian target of rapamycin) inhibitor. mTOR is a key serine-threonine kinase whose activity is known to be upregulated in a number of human cancers. Everolimus binds to the intracellular protein FKBP-12, forming a complex then inhibits mTOR complex-1

(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*.

There were no major objections raised during the assessment of the non-clinical part of the application.

Everolimus is a derivate of rapamycin. Everolimus, like rapamycin, is a specific inhibitor of mTOR. Inhibition of mTOR occurs via the binding of everolimus to the intracellular protein FKBP-12. mTOR is downstream of PI3K and is considered a component in the PI3K/AKT/mTOR pathway which is known to be involved in numerous human cancers.

Antiproliferative activity of everolimus was tested in a broad range of human tumour cells *in vitro*. Most cell lines (80%) were considered sensitive with IC_{50} values of between 0.3 and 70 nM.

Everolimus also showed significant anti-tumour activity in a wide range of different human xenografts grown in athymic mice. The anti-tumour activity observed of everolimus was typically that of reduction of tumour growth rates rather than producing regression. Anti-tumour activity was also demonstrated in xenografts models bearing tumours that were insensitive *in vitro*. Due to the insensitivity of some tumour cell lines to everolimus a number of biomarkers of sensitivity and resistance to everolimus were investigated. S6 kinase and other biomarkers were sensitive to everolimus treatment. Taken together, these data show that the broad anti-tumour activity of everolimus is not limited to human tumour xenograft models but extends also to well-vascularised syngeneic rat tumour models.

Safety pharmacology studies indicated that everolimus has no adverse effects on the function of vital organs including CNS, cardiovascular and respiratory system. However, everolimus showed immunosuppressive and reduced bone activity, which could be attributed to the anti-proliferative activity of everolimus and to an hormonal imbalance.

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, suggesting considerable first-pass metabolism. First-pass metabolism is also implied by the difference between absorption and bioavailability across species. Everolimus is a substrate for P-glycoprotein mediated efflux systems.

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. Except for the mouse, blood distribution of everolimus was concentration-dependent, being 66% and 79% in rat and monkey respectively.

The volume of distribution (Vss) was species dependent and ranged from high in the rat (44-52 l/kg) to very low in the mouse (0.37 l/kg). An intermediate value could be estimated for human (Vz/F= 14.2 l/kg). 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 tissues radioactivity of rats after single oral or intravenous administration. In the rat, the blood-brain passage of everolimus and/or its metabolites was found to be dose-dependent.

Everolimus-related radioactivity passed the placenta of pregnant rats to a limited degree and was readily transferred into milk of lactating rats suggesting that nursing infants of mothers administered everolimus would ingest parent compound and/or metabolites. There was decreased male fertility, which was partially reversible after a washout period following withdrawal of everolimus

administration. These findings suggest a relationship to an endocrine imbalance, which was evidenced in rats by a decrease in circulating testosterone levels after everolimus.

Everolimus is mainly eliminated by metabolism in the mouse, rat and monkey. In all species everolimus formed a large number of metabolites. Everolimus is essentially metabolized CYP3A4 in the liver and to some extent in the gut wall. Therefore, co-medications that are strong CYP3A4 have the potential to reduce everolimus metabolism *in vivo*. Conversely, 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*.

Everolimus was predominantly eliminated through metabolic biliary/faecal clearance in all animal species. Excretion was essentially complete in all species. Renal excretion was a minor component. No unchanged drug was detected in urine or faeces.

Repeat dose toxicity in the mouse, rat, minipigs and monkey was observed. The major target organ was the reproductive system where males were generally more affected than females. These findings were accompanied by a decrease in circulating testosterone which could be caused by a down-regulation of testicular mRNA levels encoding key proteins involved in the early steps of testosterone synthesis. There was also a depletion of cortical bone mass in the rat which could be due to hormonal imbalance. Minor kidney changes were seen in the rat (exacerbation of age-related lipofuscin in tubular epithelium) and in the mouse (exacerbation of background lesions). The aetiology and toxicological relevance of an increased incidence of pancreatic islet cell degeneration in the 26-week monkey study at 5.0 mg/kg is unknown; there were no similar findings in all the other studies, including all species. As there might be a class effect on the pancreatic islet cell function due to mTOR inhibition, a concern was raised by the CHMP as this may be of clinical relevance. To minimize the risk for hyperglycemia in humans, a recommended monitoring of fasting serum glucose prior to the start of Afinitor therapy and periodically thereafter was included in the SPC section 4.4 and 5.3. In addition, optimal glycaemic control has also been communicated before starting a patient on Afinitor.

In monkeys, degenerative myocardial lesions were noted at ≥5 mg/kg in the 2-week study and at 1.5 and 5 mg/kg in the 26 week study. The pathogenesis of the heart lesions observed in monkeys is unknown and this was of concern to the CHMP. Similar findings were reported for other mTOR inhibitors (rapamycin) [15, 16] and were attributed to pre-existing parvovirus infection [17]. In the latter study, virological examinations of plasma identified high titres of Coxsackie virus B4 in samples collected before and after the treatment period, which were increased in the samples collected from the high-dose animals at 5 mg/kg. Immunostaining with antibodies to Coxsackie virus in heart, pancreas and lymph nodes revealed positive results in heart tissues, although a positive immunoreaction against coxsackievirus in plasma and heart did not show a clear correlation to histopathological findings in the heart. Therefore, these findings could be considered as secondary to the anticipated immunosuppression of everolimus which permitted a detectable opportunistic viral infection and contributed to the poor health of the animals.

All by- and degradation products have been appropriately qualified in the toxicology study program on everolimus.

Everolimus is considered an immunosuppressant which affects the lymphatic organs and circulating white blood cells and thus is expected to modulate immune function.

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[15] Chan CC, Martin DF, Xu D, et al (1995). Side effects of rapamycin in the rat. J Ocul Pharmacol Ther; 11(2):177-181.

[16] DiJoseph JF and Sehgal SN (1996). Sirolimus: Side effect profile in animal studies. Principles of drug development in transplantation and auto-immunity, [ed. by Liebermann R and Mukherjee A]; R.G. Landes Company, Chapter 12,3:289-294.

[17] Vu MD, Qi S, Xu D, et al (1997). Tacrolimus (FK506) and sirolimus (rapamycin) in combination are not antagonistic but produce extended graft survival in cardiac transplantation in the rat. Transplantation; 64(12):1853-1856.

The $\log K_{ow}$ is of 4, therefore the persistent bioaccumulative and toxic (PBT) screening assessment is considered not necessary.

2.4 Clinical aspects

Introduction
Everolimus has been in clinical development as an immunosuppressant for solid organ transplantation since 1996.

The applicant received scientific advice on the study design for renal cell carcinoma patients from the CHMP in 2006 on clinical issues. The CHMP scientific advice focussed on the importance of showing benefit in overall survival (OS) and questioned progression free survival (PFS) as the choice for the primary endpoint. The appropriateness of placebo was questioned with reference to other treatments as comparators considered possible by CHMP. The trial design as a crossover of placebo to active treatment was also discussed in the context of patient recruitment. Additionally, the acceptability of efficacy data (PFS data) from an interim analysis was identified as an important issue since interim analyses are usually acceptable for overall survival and relate to the maturity of the data. In the end, the view of the SAWP/CHMP regarding OS as the choice of endpoint for final and interim analysis (OS) was not followed by the company.

On 5 June 2007, orphan designation (EU/3/07/449) was granted by the European Commission to Novartis Europharm Limited, United Kingdom, for everolimus for the treatment of renal cell carcinoma.
For the indication in renal cell carcinoma, the applicant submitted a pivotal phase III, double-blind, placebo-controlled study (Study C2240). The development program supporting this indication consisted of 3 dose-finding and phase-I pharmacokinetic studies in patients with advanced solid tumours ([Study C2101 monotherapy/C2102], [Study C2107], and [Study C1101]). The clinical development program was conducted taking into consideration relevant current guidelines. The recommended dose is 10 mg everolimus once daily. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

GCP

The Clinical trials were performed in accordance with GCP and all applicable regulatory requirements and the guiding principles of the Declaration of Helsinki, 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.

Pharmacokinetics
A number of studies with elements of clinical pharmacokinetics have been performed. Some of the studies were performed in the transplantation setting which have thus been performed at a lower dose (food effect, hepatic impairment and in vivo interaction studies) and some in combination with cyclosporine (e.g. mass-balance study and study in transplant patients with renal impairment). The more formal bio-equivalence trials (in healthy volunteers) have been performed as a randomised, open-label, two to four-period crossover trials with a sufficient long wash-out period between the periods. A typical sampling frequency in these more formal trials was about 10 times blood drawn in 12 hours. Furthermore, population PK approaches and meta-analysis have been used for solving some specific questions.

Table 1 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
[2120]	light-fat meal vs. high-fat meal vs. fasting	24	three-period, six-sequence crossover study of single dose	10 mg

Reference: [Synopses of Individual Studies], [Tabular Listing of all Clinical Studies]

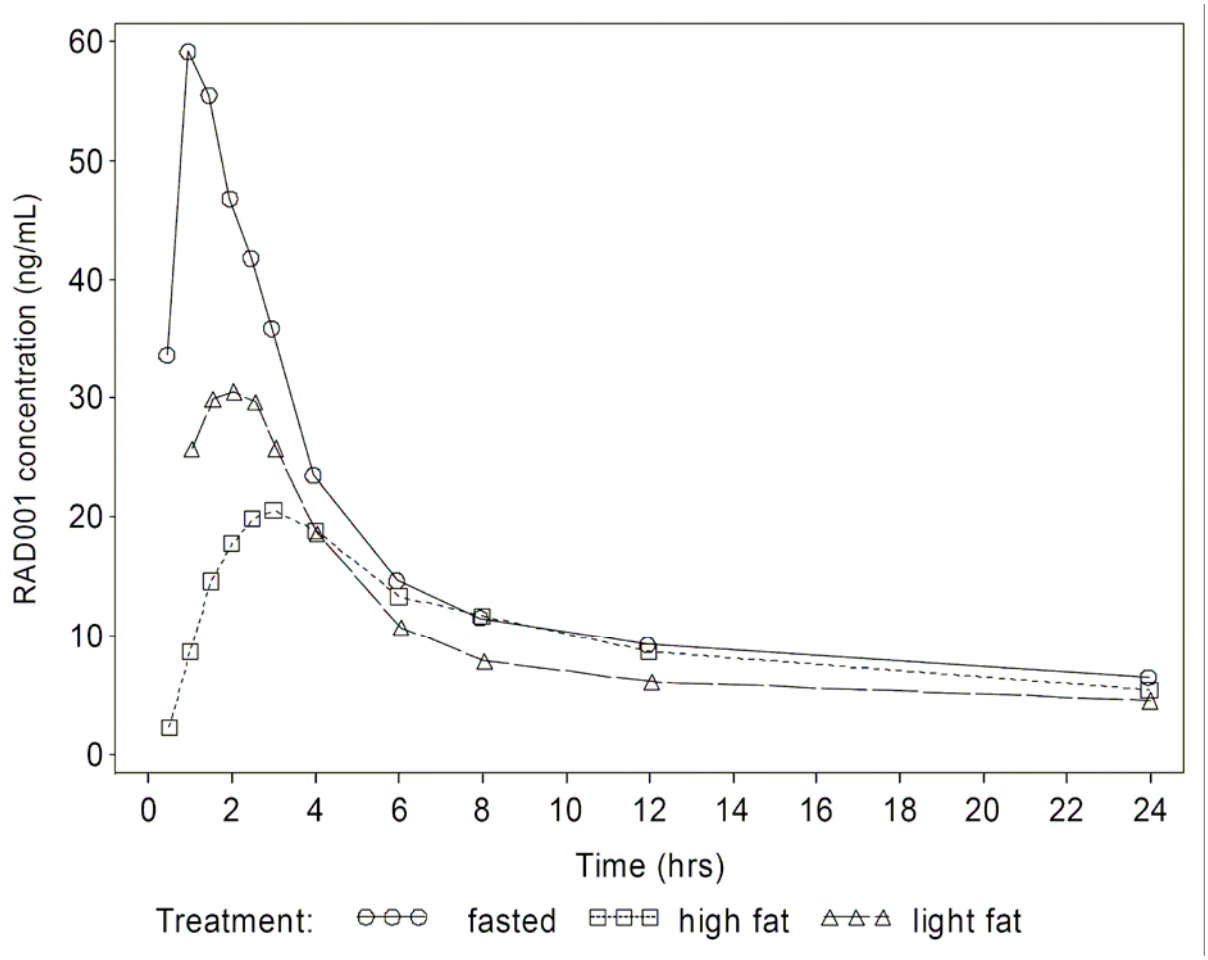
Everolimus pharmacokinetics has been evaluated utilizing non-compartmental methods and nonlinear mixed effects modelling.

- Absorption and bioavailability

Everolimus is rapidly absorbed after oral administration of the 10 mg tablet. Maximum concentration was obtained after median 1 h range (0.5-2.5 hrs). Absolute bioavailability has not been determined. Lower limits of absolute bioavailability estimates are 5% and 11% based on the mass balance trial W107. The 5% represents the recovery of radioactivity in urine while the estimate of 11% derives from a calculation of the radioactive dose (parent drug and metabolites) circulating in the blood stream at C_{max} (calculated with the mean maximal blood concentration of radioactivity and an assumed blood volume of 5L). Bioequivalence has been demonstrated for AUC and C_{max} between the final marketing formulations (5 and 10 mg) and the formulation used in the pivotal clinical study after administration of single dose 10 mg under fasting conditions.

Food effect was studied at a 2 mg dose (study W302). Intake of everolimus with food resulted in a 60% lower C_{max} and a 16% lower AUC. A study in healthy subjects (study C2120) confirmed the effects of food on oral absorption of everolimus using the 10 mg everolimus. Taking everolimus with a high-fat meal or light meal respectively decreases C_{max} by 54% and 42% and $AUC_{0-\infty}$ by 22% and 32% in comparison to the fasted state, but has no apparent effects on post-absorption phase concentration-time profiles (Figure 3).

Figure 3 Geometric mean concentration-time profile for everolimus in whole blood on a short time scale (24 hours) – linear view (PK population) – Study C2120



RAD001=everolimus; hrs=hours

- Distribution

Everolimus blood-to-plasma ratio is concentration dependent and a large portion of everolimus is bound to blood cells. Therefore, concentrations of everolimus were determined in blood. Distribution to blood cells is high and saturation of blood cell uptake of everolimus was evident at concentrations above 100 ng/ml. With the concentrations obtained after daily dose of 10 mg, about 20% of blood concentration is confined to plasma and blood to plasma ratio is fairly constant. Plasma protein binding is around 74%. In the population analysis based on patients with advanced cancer, the typical value of apparent volume of distribution V/F were 209 L and 530 L for the central and peripheral compartments respectively. In human, the apparent volume of distribution (Vss) expressed as Vz/F was 14.2 l/kg.

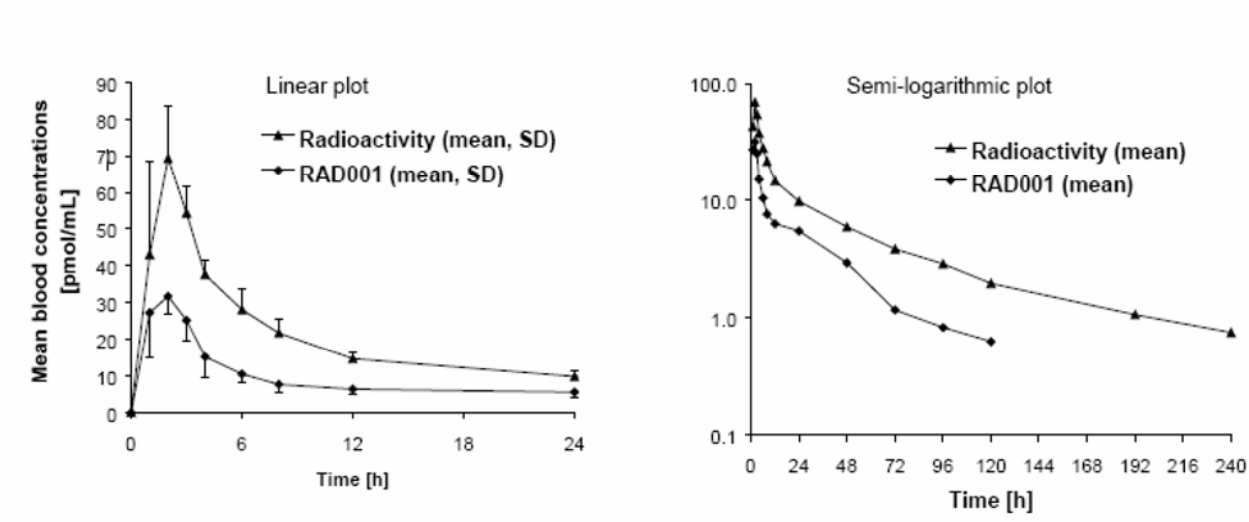
Metabolism

In vitro investigations suggest that the major and nearly exclusive enzyme responsible for the metabolism of everolimus in man is CYP3A4. Other CYP isoenzymes either do not metabolize everolimus or do so at very low rates. Five major metabolite peaks (P36, P40, P42, P50, P57, containing 6 metabolites) were detected in blood: three mono-hydroxylated metabolites resulting from hydroxylation at carbon positions 24, 25, and 46 and two hydrolytic ring opened products. One metabolite peak was identified as a direct phosphatidylcholine conjugate of everolimus (metabolite P57). As investigated, these metabolites are approximately 100-times less active than the parent compound.

In human, the metabolism of everolimus was investigated in stable renal transplant patients after a single oral dose of 3 mg ^{14}C everolimus (Study W107) (Figure 4). Patients were under concomitant treatment of the immunosuppressant CsA microemulsion (Neoral). Pharmacokinetic profiles of

metabolites after administration of everolimus 10 mg without cyclosporine was not provided. It is likely that the metabolite profile will differ when administered without cyclosporine which affects first -pass formation of metabolites, elimination and distribution of everolimus. It is unknown whether cyclosporine also affects the elimination and distribution of the metabolites.

Figure 4 Mean blood concentrations time profile of radioactivity and parent substance – Study W107



Rapamycin, which may be formed by cleavage of the 40-hydroxyethyl side chain of everolimus, was detected in human blood samples at very low amounts. In patients treated with 3 mg ^{14}C-radiolabeled everolimus, rapamycin accounted for about 1% of the total ^{14}C-AUC. Moreover, in pharmacokinetic studies in human after single (25 mg, p.o.) and multiple (0.75 mg/day; 22 days) dosing of everolimus, rapamycin blood concentrations were only 2.7%-5.4% and 3.8%-5.2% of the everolimus blood concentration, respectively.

- Elimination and excretion

The elimination half-life is around 30 hours in patients with advanced cancer. CL/F was around 20 l/h in healthy subjects and patients with advanced cancer of different origin.

Excretion and metabolism have been investigated in the mass balance trial W107 in 4 male stable renal transplant patients on treatment with cyclosporine. After an oral ^{14}C-labelled dose of everolimus, 85% of the radioactivity was recovered in faeces (80%) and urine (5%) within 10 days. Unchanged everolimus accounted for about 40% of the AUC of total radioactivity in blood. In this trial terminal half-lives were determined to be in the range of about 30 to 37 h.

- 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.

The pharmacokinetics of everolimus at 5 mg, 10 mg, 20 mg, 30 mg, 50 mg, 70 mg given weekly, and at 5 mg and 10 mg given daily each as monotherapy was investigated in parallel groups of patients with advanced solid cancers. Pre-dose blood samples were obtained in Weeks 2, 3, 4, and 5 and a full concentration-time profile in Week 4. The result for the weekly dosing only (daily schedule allowed the same conclusion as regards dose proportionality/linear PK) are shown at steady state in Table 2. The 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.

Table 2 Summary statistics of everolimus steady-state pharmacokinetic parameters: Weekly dosing - Protocols C2101 and C2102

Parameter	5 mg	10 mg	20 mg	30 mg	50 mg	70 mg
N	4	4	2	5	5	6
tmax (h)	1 (1-2)	1 (1)	1 (1)	1 (1-2)	1 (1-2)	1 (1)
Cmax (ng/mL)	32.3 ± 15.4	69.1 ± 8.1	93.5 ± 0.4	90.5 ± 20.5	163 ± 63	174 ± 49
	(47.6%)	(11.8%)	(0.5%)	(22.7%)	(38.5%)	(28.5%)
Cmax/Dose (ng/mL per	6.46 ± 3.07	6.91 ± 0.81	4.68 ± 0.02	3.02 ± 0.68	3.26 ± 1.26	2.48 ± 0.71
mg dose)	(47.6%)	(11.8%)	(0.5%)	(22.7%)	(38.5%)	(28.5%)
AUC0-τ (ng·h/mL)	283 ± 48 (17.1%)	573 ± 258 (45.0%)	1002 ± 301 (30.0%)	1814 ± 823 (45.4%)	2622 ± 631 (24.1%)	3616 ± 1496 (41.4%)
AUC0-τ/Dose (ng·h/mL per mg dose)	56.6 ± 9.7 (17.1%)	57.3 ± 25.8 (45.0%)	50.1 ± 15.0 (30.0%)	60.5 ± 27.4 (45.4%)	52.4 ± 12.6 (24.1%)	51.7 ± 21.4 (41.4%)
t1/2 (h)	26.3 ± 2.9	38.8 ± 14.7	32.0 ± 8.6	36.2 ± 5.0	27.2 ± 6.5	26.0 ± 2.8
	(11.2%)	(38.0%)	(26.9%)	(13.9%)	(24.0%)	(10.8%)
CL/F (L/h)	18.1 ± 3.7	21.8 ± 13.5	20.9 ± 6.3	19.1 ± 7.8	20.1 ± 5.5	21.6 ± 7.1
	(20.3%)	(61.8%)	(30.0%)	(40.8%)	(27.4%)	(32.8%)
CL/F normalized to BSA (L/h/m2)	9.75 ± 1.30 (13.3%)	11.1 ± 7.3 (66.0%)	11.0 ± 3.3 (30.0%)	9.83 ± 4.63 (47.1%)	10.8 ± 2.9 (27.1%)	11.1 ± 3.4 (30.5%)

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

Inter-individual variability of PK parameters (in particularly C_{max} and AUC) is in the range of about 20 to 50%. Variability of C_{min} appeared to be even higher in the Phase III study but this might be caused by inaccurate recording of the sampling in some subjects.

- Special populations

Impaired renal function
In the population pharmacokinetic analyses in 168 patients with advanced cancer, no significant influence of creatinine clearance (25 – 178 ml/min) was detected on CL/F of everolimus. The data in patients with severe renal impairment is sparse but renal impairment is considered not to have a significant impact on the pharmacokinetics of everolimus. Based on the analyses and data presented no dosage adjustment for everolimus is required for renal impairment.

Impaired hepatic function
In trial A2303, 8 subjects with hepatic impairment (Child-Pugh B, score 7 to 9) and 8 healthy subjects matched for gender, age, height, and weight received a single 2 mg dose of everolimus. Everolimus absorption was not influenced by hepatic impairment as evidenced by comparable C_{max} and t_{max} to those in control subjects. Compared with healthy subjects, subjects with moderate hepatic impairment had higher mean values for $AUC_{0-\infty}$ (115%) and half-life (84%) and lower CL/F (53%) (Table 3).

Table 3 Everolimus pharmacokinetics with 2mg single dose – Study A2303

Parameter	Hepatic impaired	Healthy subjects	p-value
t_{max} (h)	0.5 (0.5-1.1)	0.5 (0.5-2.0)	*
$C_{max,b}$ (ng/ml)	11.7 ± 4.3	15.4 ± 8.6	0.32
AUC_b (ng·h/ml)	245 ± 91	114 ± 45	0.01
CL_b/F (L/h)	9.1 ± 3.1	19.4 ± 5.8	0.01
$t_{1/2}$ (h)	79 ± 42	43 ± 18	0.04
$V_{z,b}/F$ (L)	936 ± 301	1219 ± 593	0.19

There is no observed effect of gender, weight and age on the PK of everolimus.

Race
No significant difference in apparent clearance (CL/F) was detected for Asians (n = 17) in the population pharmacokinetic evaluation. Blacks (n = 65 transplant patients) had in average a 20 % higher apparent clearance compared with non-blacks. The difference was not considered clinically relevant for this indication. Data from Japanese healthy subjects resided in Japan (trial A1101) were comparable with those from non-Japanese healthy subjects resided outside Japan across all clinical pharmacology studies in which everolimus was administered under fasting conditions and without co-medications. There was comparable CL/F between Japanese and Caucasian patients with similar liver functions.

Paediatric population (<18 years)
Everolimus is not recommended for use in children below age 18 years due to insufficient data on safety and efficacy in paediatric cancer patients.

- Pharmacokinetic interaction studies

Everolimus is a substrate for CYP3A4 and P-gp, thus, inhibitors and inducers will affect the pharmacokinetics of everolimus. Table 4 summarizes the major findings of the interaction trials.

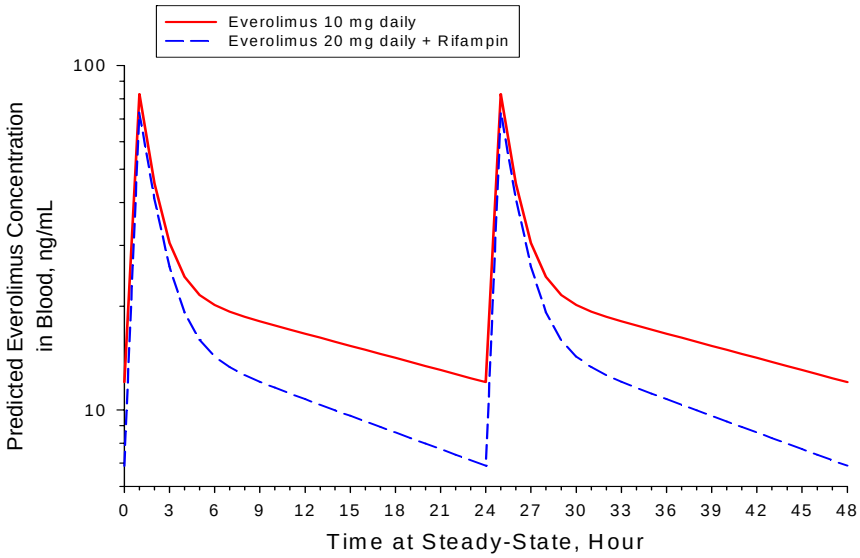
Table 4 Effects of CYP3A4 inhibitors, inducers and substrates on AUC of everolimus (mean AUC ± SD)

Co-administered drug	Everolimus dose	AUC (ng.h/mL) Everolimus alone	AUC (ng.h/mL) Everolimus + drug	Change in Everolimus AUC[c]
Strong CYP3A inhibitor and P-glycoprotein inhibitor:				
Ketoconazole (n=12)	1 or 2 mg sd	90 ± 23	1324 ± 232	15.0-fold increase
Moderate CYP3A inhibitors and P-glycoprotein inhibitor:				
Erythromycin (n=16)	2 mg sd	116 ± 37	524 ± 225	4.4-fold increase
Verapamil (n=16)	2 mg sd	115 ± 45	392 ± 142	3.5-fold increase
CYP3A substrate and and P-glycoprotein inhibitor:				
Cyclosporine (Neoral) (n=12)	2 mg sd	74 ± 26	193 ± 47	2.7-fold increase
CYP3A substrate and P-glycoprotein substrate:				
Paclitaxel (n=3)	15 mg qw	955 ± 336	792 ± 347	
Paclitaxel (n=3)	30 mg qw	1434 ± 1120	1668 ±1000	
CYP3A substrate:				
Atorvastatin (n=12)	2 mg sd	120 ± 37	118 ± 46	
letrozole	10 mg qd	514 ± 231 (n=6)[b]	541 ± 211 (n=9)	
CYP3A inducer and P-glycoprotein inducer:				
Rifampin (n=12)	4 mg sd	219 ± 69	83 ± 37	63% decrease

Effect of other drugs on everolimus
Large effects were observed with inhibitors of CYP3A4 and P-gp. The potent CYP3A4/P-gp inhibitor ketoconazole resulted in a 15-fold increase in AUC, i.e. a 1 mg dose of everolimus in combination with ketoconazole resulted in AUC values in the range obtained after 10 mg daily doses in oncology patients. Erythromycin increased everolimus exposure by 335% on average and Verapamil increased everolimus exposure by 249%. Orally administered cyclosporine increased everolimus exposure by 168%, while intravenously administered cyclosporine increased everolimus AUC by 74%.

The effect on everolimus pharmacokinetics of the inducer rifampicin was evaluated at day 8 and resulted in a 63% decreased AUC. Based on PK modelling, a 20 mg dose is predicted to adjust the AUC to the approximate range observed in the absence of an inducer, although there are no clinical data available with this dose adjustment in patients receiving potent CYP3A4 or PgP inducers (Figure 5).

Figure 5 Predicted concentration-time profiles of everolimus in blood at steady-state when administered alone or in combination with a potent CYP3A4 inducer rifampin



Concentrations for the everolimus 10 mg qd monotherapy were predicted using the pharmacokinetic parameters estimated by fitting the monotherapy data in Study A2302 to a 2-compartment open model. Concentrations for the everolimus 20 mg qd in combination with rifampin were predicted using the pharmacokinetic parameters estimated by fitting the combination data (everolimus + rifampin) in Study A2302 to a 2-compartment open model.

Effect of everolimus on other drugs
No significant effects of everolimus were seen on atorvastatin (CYP3A4) substrate and pravastatin but the effects were evaluated at a too low single dose of everolimus. A 10 mg daily dose of everolimus was used when evaluating the effect of everolimus on letrozole. It is unknown whether letrozole is a sensitive substrate for CYP3A4 *in vivo* as it is also metabolized by CYP2A6. Therefore an interaction study with orally administered midazolam is requested as a follow up measure. Although systemic inhibition of P-gp is unlikely everolimus may inhibit P-gp in the gut and hence affect bioavailability of co-administered drugs.

- Pharmacokinetics using human biomaterials

Pharmacodynamics

A number of studies have been used to investigate the pharmacodynamic (PD) properties of everolimus. Overall, there are 3 PD studies/sub-studies (studies C2107, C2239, and C2240) and side effects and efficacy have been correlated with exposure and/or dose. Furthermore, secondary pharmacology (cardiac toxicity) has been studied in a separate trial (study C2118).

- Mechanism of action

There were no clinical studies investigating the mechanism of action.

- Primary and Secondary pharmacology

The rationale for the daily 10 mg dose, which was the dose used in the pivotal trial C2240, is based on the PD (dose-marker responses) observations in trial C2107. Study C2107 was a Phase I, non-randomised, open label multi-centre trial in patients with advanced solid cancers to determine the optimal dose and dose schedule of everolimus based on safety, tolerability and pharmacodynamic effect. Daily (5 and 10 mg) and weekly (20, 50, 70 mg) regimens were investigated in parallel. Up to 6 patients were to be recruited to each cohort. Pharmacodynamic effects of everolimus were determined by measuring the activity of the molecular markers S6 (40S) ribosomal protein, 4EBP1, AKT, eIF-4G,

and Ki67. The most consistent dose-response relationship seen was a decrease in the presence of phospho-S6 kinase and phospho-eIF-4G in tumour biopsies from patients treated with everolimus 10 mg daily. Weekly dosing regimen did not show a consistent pattern of inhibition in the molecular markers.

However, the effects on molecular markers were not shown as significantly different by dose group and the predictive value of molecular markers of mTOR activity were not validated for surrogacy for response or duration of PFS in (m)RCC.

The response-exposure relationship was explored in study C2239 where there was a trend to higher estimates for PFS in the median C_{min} subgroup (10-35 ng/ml) compared to the low C_{min} subgroup (<10 ng/ml) (Table 5). It appears that there was no consistent relation between PFS and C_{min}, however, there is some uncertainty regarding whether C_{min} was accurately sampled in all subjects which could obscure any true relation.

Table 5 Analysis of PFS based on central radiological review using K-M method by Cmin subgroups – Study C2239

	C_{min} subgroup 0-10 ng/mL N = 32	C_{min} subgroup 10-35 ng/mL n = 130	C_{min} subgroup > 35 ng/mL n = 55
No. of PFS events	12 (37.5%)	44 (33.8%)	22 (40.0%)
No. of progression	9 (28.1%)	43 (33.1%)	17 (30.9%)
No. of death	3 (9.4%)	1 (0.8%)	5 (9.1%)
No. of censored	20 (62.5%)	86 (66.2%)	33 (60.0%)
Kaplan-Meier estimates [90% CI] at			
4 months	64.1 [44.6;83.7]	58.1 [46.7;69.6]	50.8 [32.8;68.8]
6 months	NA [NA;NA]	34.0 [16.5;51.4]	22.6 [2.1;43.0]
25th percentile for PFS [95% CI] (months)	1.87 [1.77;4.47]	3.19 [2.10;3.71]	1.84 [1.74;3.84]
Median PFS [95% CI] (months)	4.47 [3.35;NA]	5.55 [3.75;6.41]	4.30 [3.35;5.52]
75th percentile for PFS [95% CI] (months)	NA [4.01;NA]	7.39 [5.75;8.44]	5.52 [5.19;NA]

Analysis of AEs did not demonstrate a consistent correlation between C_{min} and AEs.

Trial C2118 was a single centre, blinded, randomised, placebo and active controlled, single dose crossover study to assess if everolimus had an effect on cardiac repolarization in male and female healthy volunteers. Overall, the result showed that everolimus had no clinically relevant effect on HR, QTcF, and other cardiac conduction intervals (QT, QTc, QTcB, QTcl, QRS, RR, and PR) in adult healthy male and female subjects.

Clinical efficacy

The clinical efficacy of everolimus in patients with advanced RCC is based on the pivotal phase-III study (Study C2240). The development program supporting this indication consisted of 3 dose-finding and phase-I pharmacokinetic studies in patients with advanced solid tumours ([Study C2101 monotherapy/C2102], [Study C2107], and [Study C1101]) (Table 6). There were no phase II studies presented in RCC.

Table 6 Overview of trial designs in support of the development programme for the RCC indication of everolimus

Study	Study design, objective, and population	Efficacy endpoints	No of patients	
			Everolimus 10 mg	Total
Pivotal, phase-III study				
C2240	Phase-III randomised, double-blind, placebo-controlled, efficacy and safety in patients with mRCC after failure of VEGFr-TKI therapy	Primary: PFS Secondary: ORR, OS, QoL	272	416
Dose selection trials				
C2101 Part 1/ C2102	Phase-I dose-escalation study in patients with advanced solid tumours	ORR	33	92
C2107	Phase-I investigation of safety, tolerability, and molecular pharmacodynamic effects in patients with advanced solid tumours	ORR	12	55
C1101	Phase-I dose-escalation study in Japanese patients with advanced solid tumours	ORR, PFS	3	9

- Dose response study (ies)

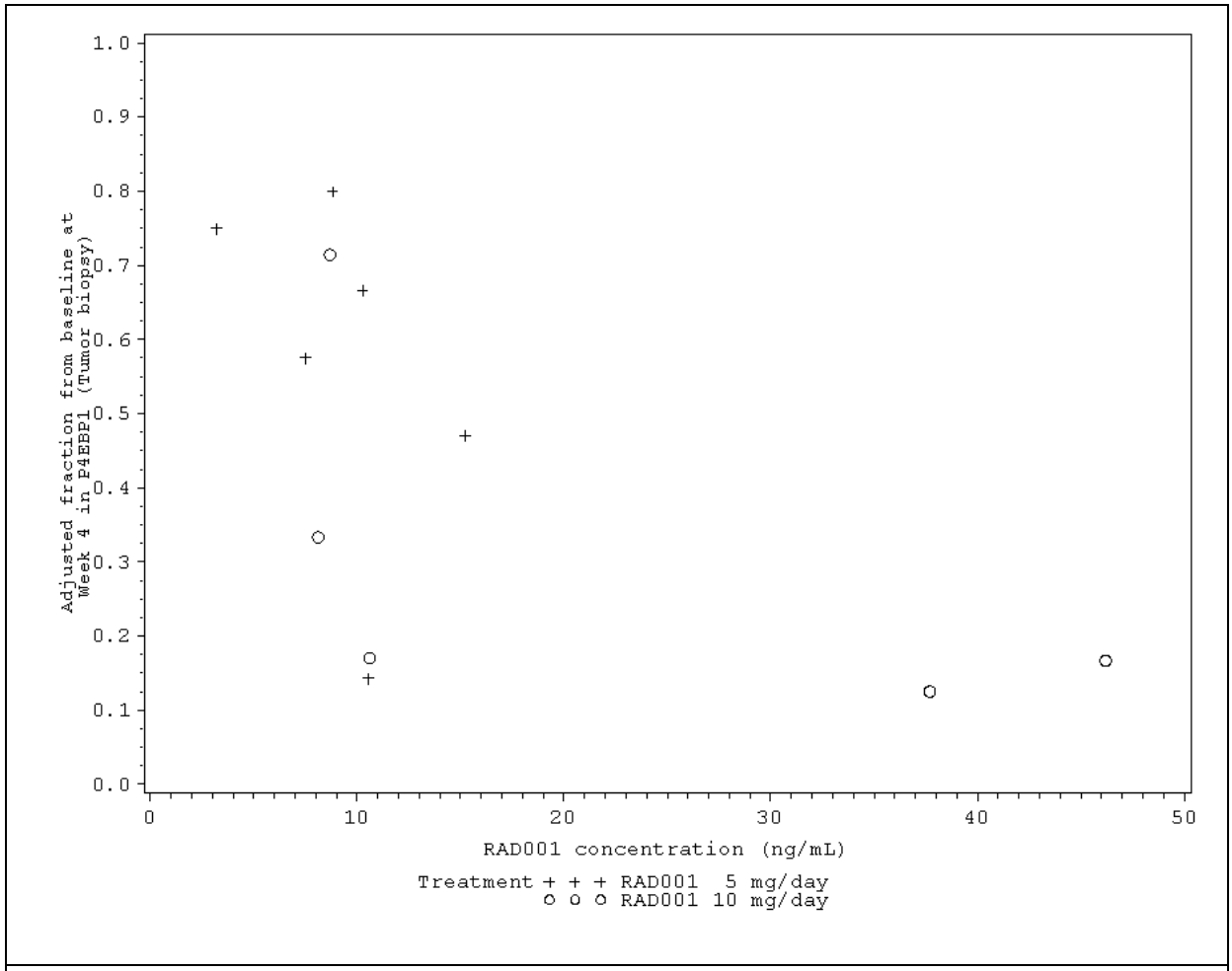
The monotherapy dose of 10 mg daily was established from three phase-I clinical studies ([Study C2101 monotherapy/C2102], and [Study C2107]) that explored daily dosing with everolimus monotherapy at 5 and 10 mg doses in addition to weekly dosing at 5, 10, 20, 30, 50, and 70 mg in patients with advanced solid tumours [18, 19].

Three phase I dose finding studies (C2101/2, C2107 and C1101) were investigated in patients with advanced solid tumours. A total of 156 patients were treated, 9 of which were from Japan (C1101). The primary aim of studies C2101/2 and C2107 were to investigate safety, tolerability, pharmacokinetics and pharmacodynamics in patients with advanced solid tumours and establish a dose and dose interval where marker proteins (p70S6 kinase, elF-4G and 4E-BP1 phosphorylation) downstream of the main target mTOR were effectively inhibited. Response according to RECIST-criteria was also recorded. 12 of 147 patients in C2101/2 and C2107 had RCC. Weekly doses of 5, 10, 20, 30, 50 and 70 mg and daily doses of 5 and 10 mg were tested. P70S6 kinase was inhibited at weekly doses of >20 mg and eIF-4G was inhibited at weekly doses >50 mg or daily doses >10 mg. There was a correlation between average plasma C_{min} and 4E-BP1 phosphorylation in tumour tissue with full inhibition at blood levels above approximately 10 ng/ml (Figure 6). The C_{min} after 5 and 10 mg was 7.3 ng/ml (90% C.I. 5.2-9.4) and 15.9 ng/ml (90% C.I. 8.6-23) respectively. In study 2101/2102 no dose-limiting toxicity was reported for doses up to 70 mg/weekly and 10 mg daily.

Figure 6 Relationship between phospho-4E-BP1 and average everolimus pre-dose concentration at steady-state

[18] O'Donnell A, Faivre S, Burris HA, et al (2008). Phase I pharmacokinetic and pharmacodynamic study of the oral mammalian target of rapamycin inhibitor everolimus in patients with advanced solid tumors. J Clin Oncol; 28(10): 1588-95.

[19] Tabernero J, Rojo F, Calvo E, et al (2008). Dose- and schedule-dependent inhibition of the mammalian target of rapamycin pathway with everolimus: a phase I tumor pharmacodynamic pathway study in patients with advanced solid tumors. J Clin Oncol; 26: 1603-10.



One data point with fraction change from baseline value of 20.5 is not shown in this plot.

Five of 147 patients in C2101/2 and C2107 had a partial response (PR) (Table 7) and 60 had disease stabilisation. 4/12 patients with RCC had a disease stabilisation and one had a PR 1/9 patients (oesophageal cancer) in the Japanese study had a PR and one (gastric cancer) an unconfirmed PR.

Table 7 Best overall tumour response in phase-I dose selection studies – Study C2101 monotherapy/C2102 and Study C2107

	Daily		Weekly			Total
	5 mg n=4	10 mg n=33	5-30 mg n=18	50 mg n=6	70 mg n=31	N=92
Study C2101 monotherapy/C2102						
Objective tumour response rate	1	1	1	0	1	4
Complete response	0	0	0	0	0	0
Partial response	1	1	1	0	1	4
Disease stabilization	1	16	5	4	16	42
Progressive disease	2	7	11	1	10	31
Unknown	0	9	1	1	4	15
	Daily		**Weekly**			**Total**
	5 mg n=12	**10 mg n=11**	**20 mg n=10**	**50 mg n=11**	**70 mg n=5**	**N=55**
Study 2107						
Objective tumour response rate	0	0	1	0	0	1
Complete response	0	0	0	0	0	0
Partial response	0	0	1	0	0	1
Disease stabilization	5	4	4	3	2	18
Progressive disease	7	7	5	7	3	29

	Daily		Weekly			Total
	5 mg n=4	10 mg n=33	5-30 mg n=18	50 mg n=6	70 mg n=31	N=92
Unknown	0	0	0	1	0	2

Dose limiting toxicity (4/6) was encountered at 70 mg/week in one study (C2107) while 10 mg daily was well tolerated, 2/12 patients had at least one, drug related grade 3 toxicity while there was 1/12 grade 3 toxicity in the 5 mg daily cohort. The most common grade 3 toxicity was stomatitis. 50/147 patients had at least one SAE.

Based on the results of biomarker studies, pharmacokinetic data and tolerability, 10 mg daily flat dose was chosen for the confirmatory phase III trial.

- Main study (ies)

Study RAD001C2240 (C2240) - *A randomised, double-blind, placebo-controlled, multicenter phase III study to compare the safety and efficacy of RAD001 plus Best Supportive Care (BSC) versus BSC plus Placebo in patients with metastatic carcinoma of the kidney which has progressed on VEGF receptor tyrosine kinase inhibitor therapy*

METHODS

Study Participants
The main inclusion and exclusion criteria in the study protocol included:
Inclusion criteria:
- Patients with metastatic carcinoma and with histological or cytological confirmation of clear cell RCC
- Patients must have progression on or within 6 months of stopping treatment with a VEGF receptor tyrosine kinase inhibitor (sunitinib and/or sorafenib). Patients may have received one or both agents.
- Prior therapy with cytokines (i.e., IL-2, Interferon) and/or VEGF-ligand inhibitors (i.e., bevacizumab) are permitted.
- Patients with at least one measurable lesion at baseline as per the RECIST criteria, either on physical exam or as determined by Computer Tomography (CT) Scan or Magnetic Resonance Imaging (MRI).
- Patients with a Karnofsky Performance Status $\geq$ 70%

Exclusion criteria:
- Patients currently receiving chemotherapy, immunotherapy, or radio-therapy or who have received these $\leq$ 4 weeks prior to Visit 1.
- Patients who have previously received mTOR inhibitors.
- Patients receiving chronic treatment with corticosteroids or another immunosuppressive agent
- Patients with a known hypersensitivity to RAD001 (everolimus) or other rapamycins (sirolimus, temsirolimus) or to its excipients.
- Patients with untreated CNS metastases or who are neurologically unstable despite treatment of the CNS metastases. (Patients with treated CNS metastases, who are neurologically stable off of corticosteroids, are eligible to enter study)

Treatments
Two treatment arms: everolimus 10 mg dose (two 5 mg tablets) plus Best Supportive Care (BSC) or Matching Placebo plus BSC. BSC was defined as drug and non-drug therapies, nutritional support, and/or physical therapy was allowed during the study. All medications including non-drug therapies (physical therapy, blood transfusions etc.) taken prior and after the start of the study drug were recorded on the appropriate case report forms (CRFs).

Best supportive treatments that were permitted during the study included:
• Bisphosphonate therapy for treatment of bone metastases which had to be started prior to the first dose of the study medication.
• Pain medications to allow the patient to be as comfortable as possible.
• Localized radiotherapy for the treatment of pre-existing, painful bone metastases was allowed only in the absence of radiological progression.
• Nutritional support as recommended by the investigator.
• Megestrol acetate could be prescribed as an appetite stimulant.
• Oxygen therapy and blood transfusions.
• Leukocyte growth factors (e.g. CSF and GM-CSF) could be prescribed for severe neutropenia.
The following therapies were not allowed during the entire duration of the study:
• Other investigational therapies.
• Other anticancer agents with the exception of study medication. The use of other anticancer agents required discontinuation from the study
The following therapies were to be avoided while on study drug:
• Drugs or substances known to be inhibitors or inducers or substrates of the isoenzyme CYP3A4 as these could alter the metabolism of the study drug. In addition, patients were advised not to drink grapefruit juice which is considered to be a potent CYP3A4-inhibitor.

Everolimus 10 mg dose (two 5 mg tablets) or matching placebo was to be taken by the patients themselves orally daily at once with a glass of water, at the same time each day in a fasting state or with a light fat-free meal. On days when pharmacokinetic (drug concentration levels) assessments occur, study drug administration was to be supervised by the investigators.

Detailed procedures for dose reduction and the management of specific side affects were provided. Dose modification guidelines were given on the study protocol for dose reduction in case of toxicity:

Dose level	Dose and schedule
0 (starting dose)	10 mg daily
Decrease 1 dose level	5 mg daily
Decrease 2 dose levels	5 mg every other day

Study drug was to be taken daily until progression or unacceptable toxicity.

Compliance was to be assessed by the investigator or his/her designee at each visit using pill counts and to be captured in the source document at each visit. Drug accountability was to be monitored by the field monitors.

Objectives
Primary objective
- To compare progression-free survival (PFS) in patients who receive everolimus plus BSC versus patients who receive Matching Placebo plus BSC.

Secondary objectives
- To compare the overall survival (OS) for patients who received everolimus plus BSC versus Matching Placebo plus BSC
- To compare the objective response rate (ORR) and duration in patients who receive everolimus plus BSC versus Matching Placebo plus BSC
- To describe the safety profile of everolimus versus Placebo
- To assess disease-related symptoms (DRS) and overall quality of life (QoL) in patients treated with everolimus plus BSC and to compare their reported outcomes to the Matching Placebo plus BSC treatment group.
- To describe the pharmacokinetics (PK) of everolimus in patients with metastatic renal cell cancer (mRCC).
- To explore the relationships between everolimus blood levels and efficacy/safety endpoints.

A number of exploratory objectives were included such as mutation analysis of PI3KCA, and immunohistochemistry evaluation of PTEN, pS6, and pAKT, characterization of VHL tumour suppressor and Glut-1 glucose transporter levels and changes from baseline in secreted VEGF, bFGF, PLGF, VEGFR2 and LDH total in serum samples.

Outcomes/endpoints
For the evaluation of the primary endpoint, PFS and the secondary endpoint ORR, the tumour response and progression was assessed using the RECIST Criteria Guidelines. The primary endpoint was defined as the time from the date of randomisation to the date of the first documented disease progression or death due to any cause. The primary analysis of PFS was based on central radiological assessments. The assessment was done independently at the site (by a local radiologist) and by the central radiology review. A CT Scan of the Chest, Abdomen and Pelvis (CAP) obtained within 2 weeks of the first dose of the study medication was used as the baseline tumour assessment. Tumour response was assessed every 8 weeks (±1 week) during the first year of treatment and every 12 weeks (±1 week) during and after the second year of treatment. The methods of tumour assessment were CT Scans or MRIs with contrast. Patients who were allergic to radiographic contrast media were permitted to have a CT scan of the chest without contrast and an MRI of the abdomen and pelvis without contrast.

Health-related QoL was assessed via two independent, reliable, and validated tools (European Organization for the Research and Treatment of Cancer [EORTC] QLQ-C30 [Version 3.0] and Functional Assessment of Cancer Therapy Kidney Symptom Index – Disease-Related Symptoms [FKSI-DRS]). The EORTC instrument assesses the patients' symptoms, functional status, and QoL, while the FKSI-DRS evaluates symptoms related to renal cancer.

Sample size
An unstratified 1-sided sequential log-rank score test with a cumulative type I error of α=0.025 and a cumulative power 1-β= 90% was used for a 3-look group sequential plan. Assuming a hazard ratio of 1.5 (corresponding to a median PFS of 3 months for the Placebo plus BSC and 4.5 months for everolimus plus BSC), and using a 2:1 randomisation to everolimus vs. Placebo a total of 290 PFS events were required. Considering a recruitment time of 16 months and an additional follow-up of 5 months, a total of 362 patients were required. This number included the assumption that about 10% of patients are lost to follow-up during the study.

Randomisation
The randomisation was performed by an Interactive Voice Response System (IVRS), the randomisation ratio was 2:1, with two patients randomly assigned to everolimus treatment for every one patient randomly assigned to Placebo. Randomisation was stratified by prior VEGFR therapy taken by the patient prior to study entry (one vs. two VEGFR TKIs, namely sunitinib and sorafenib) and by 3 Risk factors (Memorial Sloan Kettering Cancer Center/MSKCC) which are believed to be associated with survival:
• Low Karnofsky Performance Status (< 80%),
• Low haemoglobin (≤ 13 g/dl for males and ≤ 11.5 g/dl for females)
• High corrected serum calcium (≥ 10 mg/dl).

Blinding (masking)
The study was conducted as a double-blind study. Patients randomised to the placebo group received matching placebos that identically appeared in tablet size, colour, unit dose, label and packaging. The protocol allowed for unblinding on an individual patient basis in the case of documented progression (as assessed locally). Patients randomised to placebo could crossover to open-label everolimus. An extension study was set up to enrol patients treated with everolimus when the core study was stopped due to meeting the statistically defined primary efficacy endpoint of PFS at either of the two planned interim analyses. As a consequence, some members of the Novartis clinical team became unblinded at the first occurrence of disease progression. The independent Central Radiologists, ICON Medical Imaging, remained blinded to the identity of the treatment assignment.

All patients enrolled in the extension study continue to have safety and efficacy assessments until disease progression.

Statistical methods

The primary endpoint was PFS, defined as the time from the date of randomisation to the date of the first documented disease progression or death due to any cause. Assessment of PFS was based on the central radiological assessment on the FAS/ITT population. The Full Analysis Set (FAS population) was defined as all randomised patients. Following the intent-to-treat (ITT) principle, patients were analyzed according to the treatment and stratum they were assigned to at randomisation. The primary statistical analysis to compare PFS was performed using a one-sided log-rank test stratified by strata defined by the MSKCC risk criteria. The hazard ratio of the treatment effect estimated in a stratified Cox proportional hazard model, using the strata defined by the MSKCC criteria, was provided with two-sided 95% confidence interval.

The secondary endpoints (OS, ORR, and the three PROs: FKSI-DRS, PF and global QL) were tested in a hierarchical testing order adjusting for multiple testing with a gate keeping strategy to control the multiple significance level at 2.5%.

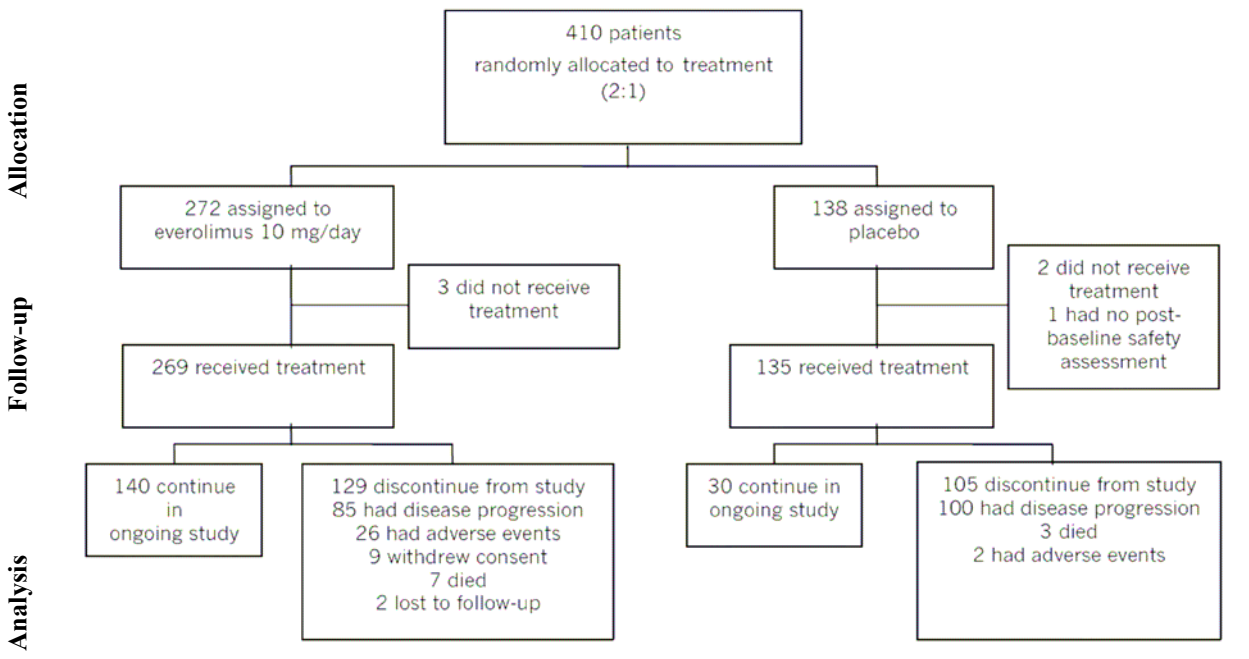
Two interim analyses were prospectively planned that allowed for stopping on the grounds of futility or outstanding efficacy. A group sequential design was implemented using a spending function approach for both futility and efficacy. A conservative approach was adopted where the derivation of efficacy boundaries was not affected by the presence of the futility stopping rule. The procedure selected ensured that the overall probability of type-I error was controlled at the desired level.

RESULTS

Participant flow

Figure 7 shows the participant flow:

Figure 7 Patient disposition in the pivotal trial for the full analysis set – Study C2240



Recruitment
416 patients with advanced, clear-cell RCC at 88 centers in 10 countries were recruited and entered into the study. No single center enrolled >24 patients. The first patient was included Dec 6, 2006 and the study was stopped on 28 February 2008. Cut-off date for the 2nd interim analysis was 15 October 2007.

Conduct of the study
Two interim analyses were planned in the protocol: the first interim analysis was planned after observing approximately 30% (~87 PFS events) and the second after observing approximately 60% (~174 PFS events), of the targeted number of 290 PFS events (per central radiology review) required for the final statistical analysis. Both interim analyses were to allow for stopping for lack of efficacy (futility) and for outstanding efficacy. Formal testing of the primary PFS endpoint was not performed at the first interim analysis as the main intention had been to investigate futility and nearly all patients had been enrolled by this time. This first interim analysis focused on safety and overall survival only. This was decided prior to the planned analysis and endorsed by the IDMC. As no formal testing of the primary endpoint was performed and no PFS data were available for this first interim analysis, this could be implemented without spending any of the type-I error. The IDMC reviewed the first interim results and recommended that the trial continue as planned without change.

As per protocol, the second interim analysis was conducted after approximately 60% of the targeted 290 PFS events (as per central radiology) required for the final statistical analysis were observed, i.e. after approximately 174 PFS events. The actual number of centrally assessed PFS events observed as of the cut-off date (15 October 2007) and included in the analysis was 191 (or 66% of the targeted 290 events). Four hundred ten patients were randomised to treatment prior to this data cut-off. The efficacy boundary corresponding to this event-based information fraction was 0.0057 on the p-value scale (2.53 on the Z-statistic scale). This predefined efficacy stopping boundary was crossed at the second interim analysis: results from the stratified log-rank test were $p=1.1 \times 10^{-16}$ and Z=8.22. As these values were below the predefined threshold, the null hypothesis was rejected and the primary objective of the trial was met. The IDMC recommended the early termination of the study on 25 February 2008. The IDMC stated that the improvement in PFS was seen across all subsets of patients, including the favourable-, intermediate-, and poor-risk prognostic categories defined by the MSKCC criteria. The Study Steering Committee subsequently endorsed this recommendation, and the trial was unblinded on 28 February 2008.
The assessment is based on the study report from the 2nd interim analysis and the efficacy update from August 2008.

There were two amendments to the study made: the first one on 19 October 2006, before the first patient was included. The second amendment was on 28 February 2007, when 58 patients were included. There were no changes to the planned analyses.

The Safety population was defined as all patients who received at least one dose of study drug and who had at least one valid post-baseline safety assessment.

The open-label period population included only patients who received at least one dose of open-label everolimus and had at least one safety or efficacy assessment during the open-label period.

Baseline data
There were 272 patients assigned to treatment with everolimus and 138 patients were randomised to placebo. The major baseline characteristics are provided in the Table 8, 9, 10.

Table 8 Demographic characteristics in the full analysis set – Study C2240

Demographic characteristic	Everolimus 10 mg N=272	Placebo N=138
Age (years)		
Mean (standard deviation)	60.6 (10.4)	59.3 (9.6)
Median	61.0	60.0

Demographic characteristic	Everolimus 10 mg N=272		Placebo N=138	
Range	27 to 85		29 to 79	
Age group (years) (n [%])				
<65 years	162	(59.6)	97	(70.3)
≥65 years	110	(40.4)	41	(29.7)
Gender (n [%])				
Male	212	(77.9)	105	(76.1)
Female	60	(22.1)	33	(23.9)
Race (n [%])				
Caucasian	246	(90.4)	121	(87.7)
Asian	11	(4.0)	10	(7.2)
Black	2	(0.7)	3	(2.2)
Native American	1	(0.4)	0	
Other	8	(2.9)	3	(2.2)
Missing	4	(1.5)	1	(0.7)
Ethnicity (n [%])				
Other [a]	218	(80.1)	110	(79.7)
Hispanic/Latino	14	(5.1)	3	(2.2)
Japanese	10	(3.7)	8	(5.8)
Indian (Indian subcontinent)	1	(0.4)	1	(0.7)
Mixed	1	(0.4)	1	(0.7)
Missing	28	(10.3)	15	(10.9)

[a] Other includes all individuals who were not assigned to a specific ethnicity category (e.g., Chinese, Hispanic/Latino, Indian, Japanese, Mixed, etc)

Table 9 Previous disease-related in the full analysis set – Study C2240

Previous treatments	Everolimus 10 mg N=272 n (%)		Placebo N=138 n (%)	
Antineoplastic therapy	272	(100.0)	138	(100.0)
Radiotherapy	83	(30.5)	38	(27.5)
Surgery	262	(96.3)	131	(94.9)
Prior medications				
Targeted therapy	272	(100.0)	138	(100.0)
VEGFr-TKI	272	(100.0)	138	(100.0)
Sunitinib only	124	(45.6)	60	(43.5)
Sorafenib only	77	(28.3)	42	(30.4)
Both sunitinib and sorafenib	71	(26.1)	36	(26.1)
EGFR TKI	5	(1.8)	7	(5.1)
Immunotherapy	174	(64.0)	91	(65.9)
Chemotherapy	36	(13.2)	22	(15.9)
Hormonal therapy	5	(1.8)	5	(3.6)
Other	15	(5.5)	4	(2.9)

The majority of patients in both treatment groups had progressed either while still receiving VEGFR-TKI therapy or within 1 week of discontinuing treatment (70.9% versus 79.0% for the everolimus and placebo treatment groups, respectively).

Table 10 Patient characteristics in the full analysis set – Study C2240

Patient characteristic	Everolimus 10 mg N=272 n (%)		Placebo N=138 n (%)	
Karnofsky performance status				
100	75	(27.6)	38	(29.0)
90	98	(36.0)	53	(38.4)
80	70	(25.7)	30	(21.7)
70	28	(10.3)	15	(10.9)
Missing	1	(0.4)	0	
MSKCC prognostic score				
Favorable risk	79	(29.0)	39	(28.3)
Intermediate risk	153	(56.3)	78	(56.5)
Poor risk	40	(14.7)	21	(15.2)
Histologic grade				
Well differentiated	21	(7.7)	10	(7.2)
Moderately differentiated	56	(20.6)	31	(22.5)
Poorly differentiated	83	(30.5)	40	(29.0)
Undifferentiated	17	(6.3)	9	(6.5)
Unknown	95	(34.9)	48	(34.8)
Time from initial diagnosis				
≤6 months	6	(2.2)	3	(2.2)
>6 months to ≤12 months	19	(7.0)	5	(3.6)
>12 months to ≤24 months	67	(24.6)	28	(20.3)
>24 months	180	(66.2)	98	(71.0)
Missing	0		4	(2.9)
Number of organs involved				
1	26	(9.6)	14	(10.1)
2	67	(24.6)	35	(25.4)
3	87	(32.0)	41	(29.7)
4	59	(21.7)	30	(21.7)
>4	29	(10.7)	15	(10.9)
Organ type involved				
Lymph nodes	203	(74.6)	98	(71.0)
Lung	199	(73.2)	112	(81.2)
Bone	100	(36.8)	43	(31.2)
Liver	94	(34.6)	49	(35.5)
Kidney	31	(11.4)	16	(11.6)
CNS	15	(5.5)	11	(8.0)
Other	134	(49.3)	57	(41.3)

Study included: [Study C2240]

The treatment arms were balanced for the relevant demographic factors and disease characteristics and previous treatments. Approximately 37% of the patients were aged ≥65 years and three-quarters of the patients were male, reflecting the higher incidence of RCC among men, and the majority of patients (89.5%) were Caucasian, reflecting the countries that participated in the study. All patients had advanced disease with time from initial diagnosis of 2 years or longer for the majority, most patients presented with 3 or more involved organs. All patients had received at least one prior VEGFR-TKI-based regimen. Approximately 50%, 20%, and 10% of patients from the two treatment groups had also received prior therapy with IFN-α, IL-2, and bevacizumab, respectively.

Numbers analysed

The efficacy analysis is based on all randomised patients. Patients who did not receive everolimus are excluded from the safety analysis. In total, as the cut-off date of October 2007, 277 patients were assigned to everolimus and 139 patients were assigned to placebo.

Table 11 Analysis population by treatment – Study C2240

	RAD001 10mg/day (plus BSC) N=272 n (%)	Placebo (plus BSC) N=138 n (%)	All patients N=410 n (%)
Analysis population			
Full analysis set (FAS)	272 (100)	138 (100)	410 (100)
Safety	269 (98.9)	135 (97.8)	404 (98.5)
Safety (open-label period)*	1 (0.4)	79 (57.2)	80 (19.5)

* used to analyze data from the open-label period only, referred to as Safety population in the open-label reports

Per study protocol, the second interim analysis was conducted after approximately 174 PFS events (approximately 60% of the targeted 290 PFS events) were observed by central radiology as required for the final statistical analysis. The cut-off date for the second interim analysis was determined using a statistical prediction model based on PFS events per the investigator. The actual number of centrally assessed PFS events observed as of the cut-off date (15 October 2007) and included in the analysis was 191 PFS events (or 66% of the targeted 290 PFS events). The efficacy boundary corresponding to this event-based information fraction was 0.0057 on the p-value scale (2.53 on the Z-statistic scale). The updated analysis per central review is based on 266 events (everolimus: 155 events; placebo: 111 events).

Outcomes and estimation

Primary endpoint: Progression-free survival

The primary statistical analysis to compare PFS of everolimus-treated group with placebo-treated group was performed using a one-sided log-rank test stratified by three strata defined by the MSKCC risk criteria. In the interim analysis conducted with a cut-off date of 15 October 2007, the median PFS was 4.01 months in the everolimus group (95% CI 3.71-5.52 months) and 1.87 months in the placebo group (95% CI, 1.81 to 1.94 months) with HR of 0.30 (95% CI 0.22-0.40). In the final analysis with a cut-off date of 28 February 2008, which included 6 patients more than the interim analysis, the median PFS was 4.90 months in the everolimus group (95% CI 3.98- 5.52) and 1.87 months in the placebo group (95% CI 1.84-1.94) with a HR of 0.3 (95% CI 0.25-0.43), resulting in a difference of approximately 3 months (Figure 8). The calculated P-value was $p<0.001$, which was smaller than the required efficacy stopping boundary of $p=0.005747$. The IDMC reviewed the results together with secondary endpoints and recommended early stopping the study after the second interim analysis.

The estimated hazard ratio of the treatment effect of everolimus versus placebo obtained from a stratified Cox proportional hazard model using the same strata as the log-rank test was HR 0.33 (95% CI 0.25-0.43).

Figure 8 **Kaplan-Meier probability of progression-free survival by independent central review in the full analysis set – Study C2240**

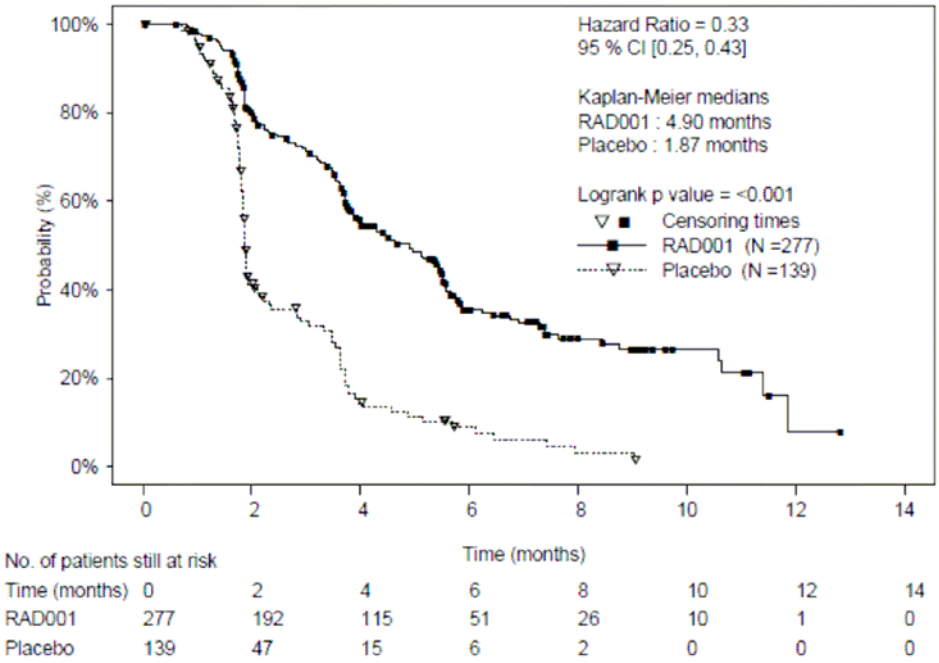


Table 12 **Progression-free survival event categories by independent central review in the full analysis set – Study C2240**

PFS event categories	Everolimus 10 mg N=277 n (%)		Placebo N=139 n (%)	
No of PFS events	155	(56.0)	111	(79.9)
Progression	134	(48.4)	103	(74.1)
Death	21	(7.6)	8	(5.8)
Censored	122	(44.0)	28	(20.1)

As shown in Table 12, the pattern of censoring was not uniform between the arms. As expected, more patients were censored in the everolimus-treatment arm because they were ongoing without event while relatively more patients were censored in the placebo-treatment arm because of new anticancer treatment in the control arm (Table 13). The decision to change therapy was based on the investigator assessment of progress which sometimes was not in concordance with the central radiological review.

Table 13 **Summary of the censoring reasons for PFS based on central radiology review, by treatment – Study C2240.**

Reason for Censoring	Everolimus 10mg/day (plus BSC) N=272 n (%)	Placebo (plus BSC) N=138 n (%)
Total number of censored patients	171 (62.9%)	48 (34.8%)
Ongoing without event	133 (77.8%)	24 (50.0%)
Lost to follow-up	2 (1.2%)	0 (0.0%)
Withdrew consent	6 (3.5%)	0 (0.0%)
Adequate assessment no longer available	8 (4.7%)	4 (8.3%)
New cancer therapy added	22 (12.9%)	20 (41.7%)

Secondary endpoint: Overall survival (OS)

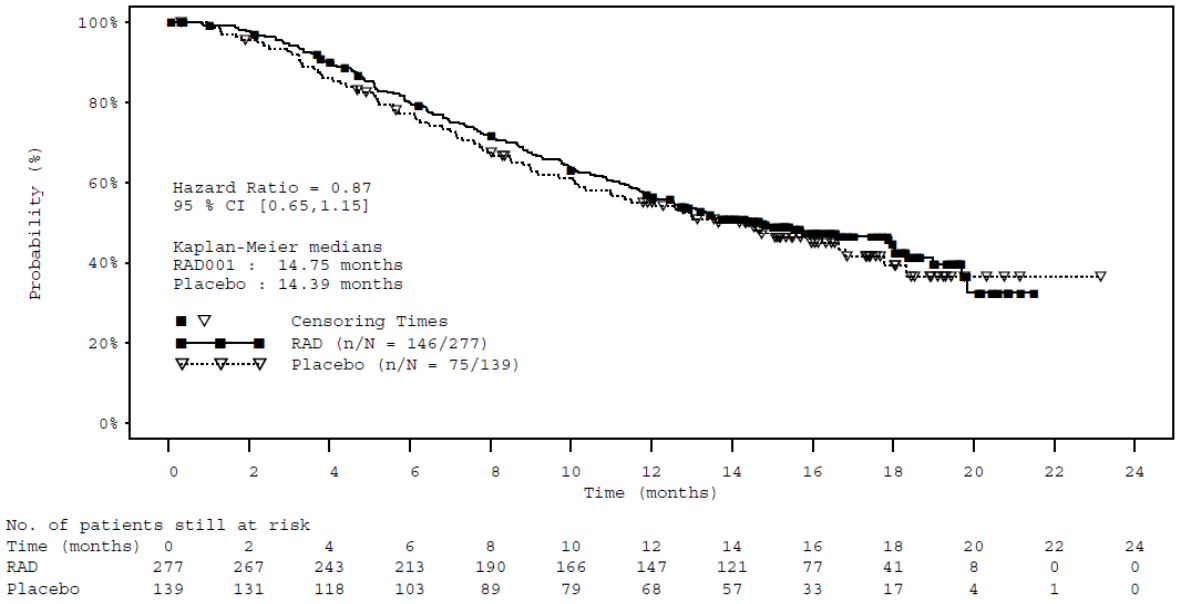
The study design permitted the crossover of patients initially randomised to placebo to everolimus at the time of progression. The study design prevents the study from being powered to detect any difference in terms of OS. No statistically significant difference relative to placebo was evident for OS between the two treatments (p=0.137) (Table 14). A trend in favour of everolimus was observed (HR 0.82; 95% CI 0.57-1.17; p=0.137). The Kaplan-Meier plots for both treatments are in parallel (Figure 9). From the updated results provided with a data cut-off of 15 November 2008, 283 patients out of 416 patients randomised to everolimus were censored for survival analysis. There were 281 patients known to be alive at the time of data cut-off. From the 33 patients that did not crossover to everolimus therapy, 18 patients were known to have died with a median survival of 5.2 months.

Table 14 Comparison of overall survival between everolimus and placebo in pivotal phase III trial for the full analysis set – Study C2240

Overall survival	Number (%) of deaths		Comparison between groups		
	Everolimus N=277	Placebo N=139	Hazard ratio [a]	95% CI [a]	p-value [b]
Primary analysis	85 (30.7)	48 (34.5)	0.82	0.57 to 1.17	0.137

[a] Cox model; [b] One-sided stratified log-rank test

Figure 9 Overall survival probability in the full analysis set – Study C2240



No. of patients still at risk

Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24
RAD	277	267	243	213	190	166	147	121	77	41	8	0	0
Placebo	139	131	118	103	89	79	68	57	33	17	4	1	0

Secondary endpoint: Objective response rate

A very low response rate was observed and no difference in ORR (CR + PR) was apparent between the two treatment arms. Objective response, based on RECIST criteria, was documented in only 5 patients corresponding to 1.8% (95% CI: 0.6-4.2%) of patients receiving everolimus therapy vs 0% for placebo (Table 15).

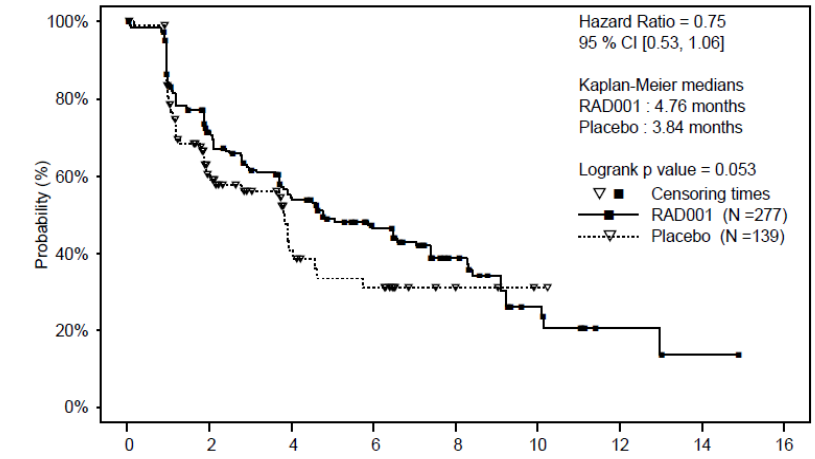
Table 15 Summary of best overall response in the full analysis set – Study C2240

	Everolimus 10 mg N=279 n (%)		Placebo N=139 n (%)	
Objective tumour response rate	5	(1.8)	0	
Complete response	0		0	
Partial response	5	(1.8)	0	
Disease stabilisation	185	(66.8)	45	(32.4)
Progressive disease	57	(20.6)	74	(53.2)
Unknown	30	(10.8)	20	(14.4)

Secondary endpoint: Patient reported outcome

Functional Assessment of Cancer Therapy Kidney Symptom Index – Disease-Related Symptoms (FKSI-DRS)[20] was chosen as the primary endpoint for patients reported outcome. No statistically significant differences were evident between the two treatment groups in the time to definitive deterioration of patient-reported outcomes (where definitive deterioration was determined by pre-established criteria for clinically meaningful changes) (Figure 10). Compliance, with regard to completed questionnaires, was low for the two treatment arms, with a level >60% until the fourth post-baseline assessment window. There was no detrimental effect observed when a second QoL tool was used.

Figure 10 Time to deterioration in FKSI-DRS risk score – Study C2240

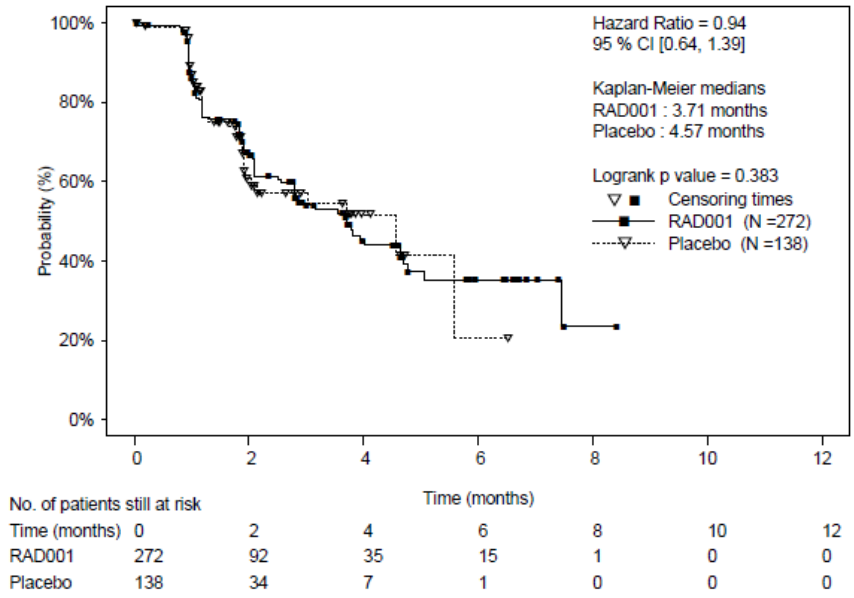


No. of patients still at risk

Time (months)	0	2	4	6	8	10	12	14	16
RAD001	277	120	81	57	27	10	3	1	0
Placebo	139	47	18	12	3	1	0	0	0

[20] Cella D, Yount S, Brucker PS, et al. (2007). Development and validation of a scale to measure disease-related symptoms of kidney cancer. Value Health; 10:285-93.

Figure 11 Definitive deterioration of the physical functioning scale score of the EORTC QLQ-C30 questionnaire – Study C2240



European Organization for the Research and Treatment of Cancer (EORTC) QLQ-30 (Version 3.0) [21] (EORTC QLQ-C30) was chosen to measure QoL as assessed for disease-related symptoms. No significant differences were observed between the two treatment groups in the time to definitive deterioration of the physical functioning or general health status/QoL subscales (Figure 11).

Ancillary analyses

Supportive and sensitivity analyses of PFS

A number of supportive and sensitivity analyses of PFS were presented which are well in line with the primary analysis.

Supportive analyses of PFS were performed to investigate the homogeneity of the treatment effect across prespecified patient subgroups defined by the MSKCC risk factors (i.e. "favourable" corresponds to 1 risk factor, "intermediate" corresponds to 2 risk factors and "poor" corresponds to 3 risk factors). The proportion of patients with a PFS event was lower in the favourable MSKCC risk group treated with everolimus compared with placebo treatment (Table 16).

Table 16 Comparison of PFS between everolimus and placebo by stratum by independent central review in the full analysis set – Study C2240

Category	Number (%) of patients with PFS event		Comparison between groups		
	Everolimus	Placebo	Hazard ratio [a]	95% CI [a]	p-value [b]
MSKCC prognostic score					
Favorable risk (n=120)	**39 (48.1)**	**33 (84.6)**	0.31	0.19 to 0.50	<0.001
Intermediate risk (n=235)	90 (57.7)	61 (77.2)	0.32	0.22 to 0.44	<0.001
Poor risk (n=61)	26 (65.0)	17 (81.0)	0.44	0.22 to 0.85	0.007

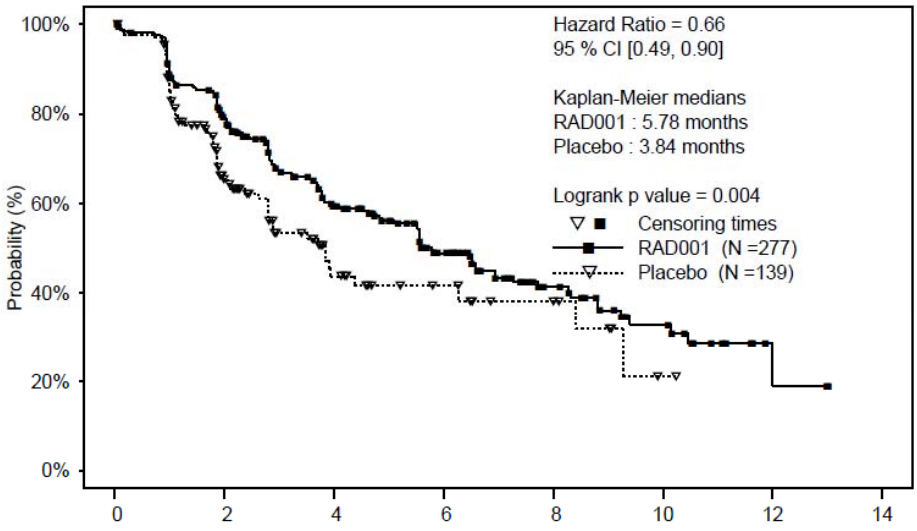
[21] Aaronson NK, Ahmedzai A, Bergman B, et al. (1993). The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst; 85:365-76.

Category	Number (%) of patients with PFS event		Comparison between groups		
	Everolimus	Placebo	Hazard ratio [a]	95% CI [a]	p-value [b]

[a] Cox model; [b] One-sided unstratified log-rank test

Time to deterioration in KPS score was prolonged for patients receiving everolimus therapy with a 34% risk reduction observed, corresponding to a hazard ratio of 0.66 (95% CI: 0.49 to 0.90; p=0.004) (Figure 12). The median time to definitive deterioration of KPS was 5.78 months for the everolimus arm and 3.84 months for placebo. Prolonged time to deterioration in KPS score for patients receiving everolimus may be considered beneficial for the patient although bias due to knowledge about progression cannot be ruled out.

Figure 12 Time to deterioration in KPS score – Study C2240



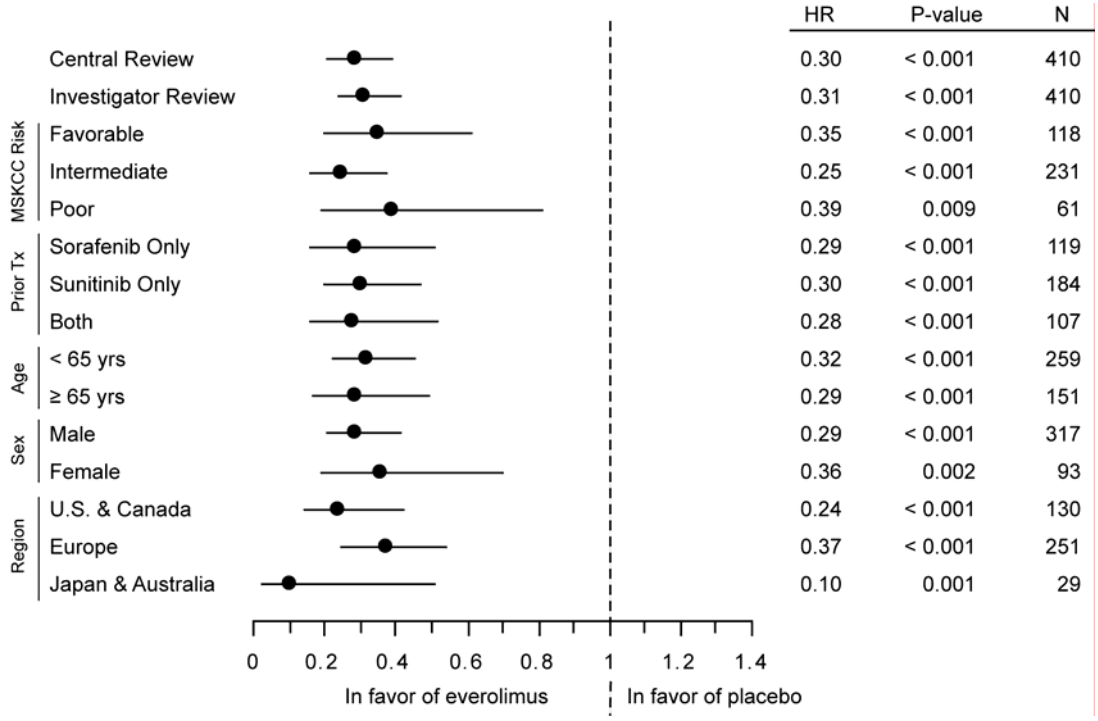
No. of patients still at risk

Time (months)	0	2	4	6	8	10	12	14
RAD001	277	193	119	74	35	18	2	0
Placebo	139	66	25	13	7	1	0	0

Deterioration was determined by pre-established criteria (by ≥1 category, i.e., ≥10-point reduction from baseline). One-sided stratified log-rank test and stratified Cox model using strata defined by MSKCC prognostic score

A subgroup analysis based major demographic subgroups, including age (<65 years, ≥65 years), prior antineoplastic therapy (sunitinib, sorafenib, or both sunitinib and sorafenib), and Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic score categories (favourable-, intermediate-, and poor-risk groups) showed no major differences in HR (Figure 13).

Figure 13 Sensitivity analysis of treatment effect in progression-free survival for patient subgroups – Study C2240



Subgroup analysis results are based on the central radiology review with the exception of the row labelled 'Investigator Review'
The individual dots represent the point estimates for the hazard ratio and the horizontal line the corresponding 95% confidence intervals
Data cut-off: 15 October 2007

Missing tumour assessments

Pre-defined sensitivity analyses of PFS based on central radiology review were performed using "actual event" and "backdating" approach in handling missing tumour assessments.

For the interim analysis, the hazard ratio was 0.30 for the primary analysis and for the "actual event" sensitivity analysis and 0.29 for the "backdating sensitivity" analysis. The mean PFS was 4.01 versus 1.87 months (HR 0.3) in the primary analysis and 3.98 versus 1.87 months (HR 0.29) for the "backdating analysis" for everolimus and placebo, respectively. The difference was statistically significant in each analysis with a p-value <0.001. For the final analysis the hazard ratio was 0.33 for the primary analysis and for the "actual event" sensitivity analysis and 0.32 for the "backdating sensitivity" analysis. The median PFS for the everolimus group was 4.90 months for the primary analysis and the "actual event" sensitivity analysis and 4.30 months for the "backdating sensitivity" analysis. The median PFS was 1.87 months for the placebo group in each of these analyses. The difference was statistically significant in each analysis with a p-value <0.001.

Investigator assessment

Analysis of PFS was also performed using the investigator's assessments. For the interim analysis, the median PFS was 4.57 months in the everolimus group (95% CI, 3.91-5.52) and 1.84 months in the placebo group (95% CI, 1.81-1.94). The calculated p-value of one-sided stratified log-rank test is p < 0.001, and the HR is 0.31 (95% CI 0.24-0.41). For the final analysis, the median PFS was 5.49 months in the everolimus group (95% CI, 4.63-5.82 months) and 1.87 months in the placebo group (95% CI, 1.84-2.23 months). The calculated p-value of one-sided stratified log-rank test is p < 0.001, and the HR is 0.32 (95% CI, 0.25-0.41).

An additional pre-defined sensitivity analysis of PFS was performed by combining events from both central radiology review and investigator.

For the interim analysis the median PFS was 3.61 months in the everolimus group (95% CI, 3.19-3.84) and 1.84 months in the placebo group (95% CI, 1.77-1.87). The calculated p-value of one-sided stratified log-rank test is $p < 0.001$, and the hazard ratio is 0.34 (95% CI 0.26-0.45). For the final analysis, the PFS was 3.75 months in the everolimus group (95% CI, 3.55-4.11 months) and 1.84 months in the placebo group (95% CI, 1.77-1.87 months). The calculated p-value of one-sided stratified log-rank test is $p < 0.001$, and the HR is 0.38 (95% CI, 0.30-0.47).

Exploratory analyses

Prolonged PFS on open-label everolimus is believed to confound the OS result. A retrospective analysis of the 106 placebo patients that crossed-over to everolimus therapy indicated that median PFS while they received placebo was 1.87 months. Following crossover to everolimus, median PFS was 5.09 months for this same cohort (Table 17). This compares to the median PFS of 5.49 for everolimus and 1.87 for placebo as per investigator assessment in the double blind phase.

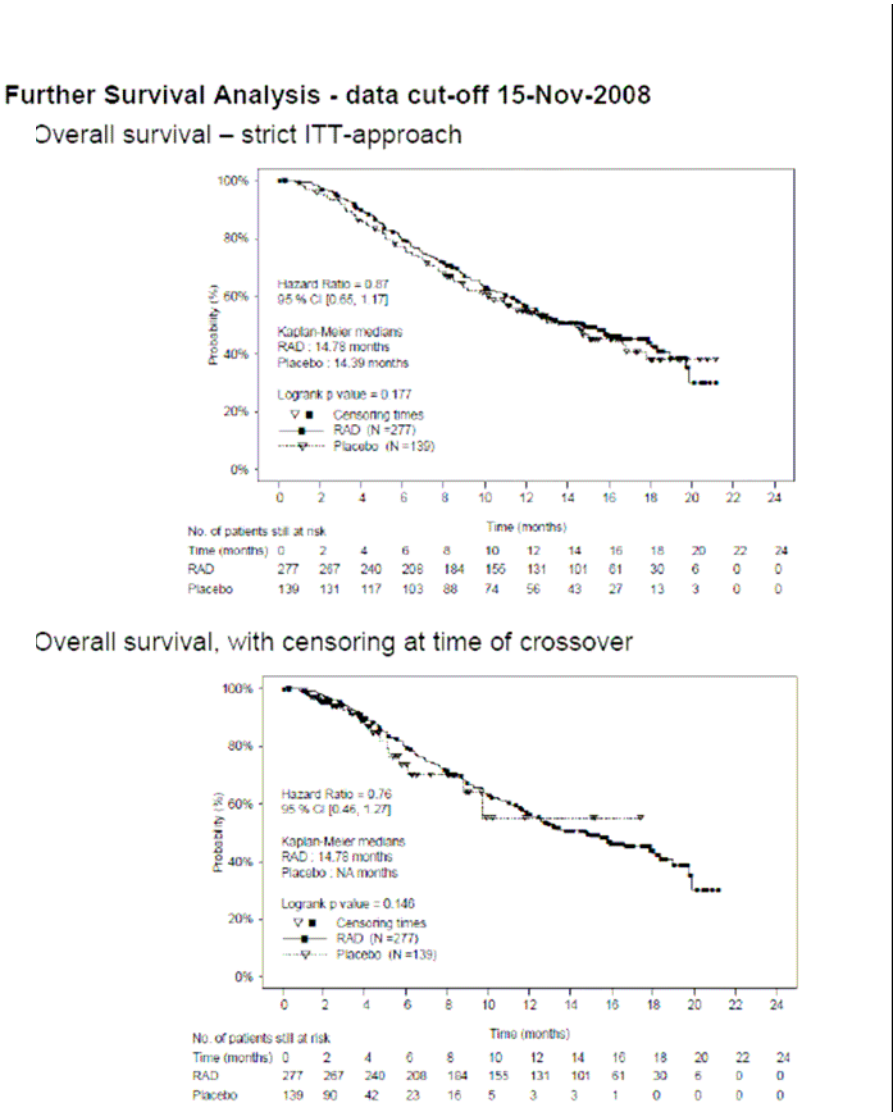
Table 17 Summary of PFS statistics by investigator assessment – Study C2240

Parameter	Double-blind phase		Open-label phase
	Everolimus 10 mg N=277	Placebo N=139	Everolimus 10 mg [a] N=106
Median PFS (months)	5.49	1.87	5.09
95% CI	(4.63 to 5.82)	(1.84 to 2.23)	(3.71 to 7.56)
4-month PFS rate (%)	62.7	19.4	54.3
95% CI	(56.7 to 68.6)	(12.7 to 26.1)	(43.0 to 65.5)
6-month PFS rate (%)	41.8	8.6	46.3
95% CI	(35.4 to 48.2)	(3.6 to 13.6)	(34.2 to 58.3)
12-month PFS rate (%)	17.7	NA	NA
95% CI	(9.9 to 25.6)	-	-

[a] Includes only placebo patients who crossed-over to receive treatment with open-label everolimus

An additional post-hoc exploratory analysis of OS was performed where placebo-treated patients were censored at the time of crossover (Figure 14). The HR was 0.76 (95% CI 0.46-1.27; p=0.146).

Figure 14 Summary of overall survival in the ITT population and censoring at the time of crossover – Study C2240



P-values based on one-sided stratified log-rank test and hazard ratios obtained from stratified Cox model both using data defined by MSKCC prognostic score.

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

There were no pooled analyses performed.

- Clinical studies in special populations

Clinical efficacy was not investigated in patients with hepatic and renal impairment.

- Supportive study (ies)

There are no phase II studies submitted by the applicant for the applied indication. The anti-tumour efficacy of everolimus in the target population was initially demonstrated in 5 of 12 patients with RCC enrolled into two phase-I studies[22].

Two sequential cohorts of patients with mRCC recruited to a phase II investigator-initiated trial subsequently reported response rates or 15-32 %. This information is based on abstracts only.

- Discussion on clinical efficacy

[22] Porter LL, Burris A, Jones SF, et al (2006). Summary of results in patients with metastatic renal cell cancer (RCC) for phase I studies of RAD001 (everolimus). J Clin Oncol; 24(18 Suppl): abstract 14599.

The pharmacokinetics of everolimus, have been investigated as an immunosuppressant medicinal product. The higher dosage of everolimus administered as an anticancer medicinal product (10 mg per day vs. 0.75 bid) does not change the main properties and principles which are already known.

After oral administration, 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. There is a food effect on C_{max} but not AUC suggesting that everolimus can be administered both in the fast and fed state. In healthy subjects, high fat meals reduced systemic exposure to everolimus 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 recommended dose adjustments were aimed at a C_{min} of 10 µg/ml for clinical situations where co-administration of inhibitors/inducers of CYP3A4 or PgP cannot be avoided. The dose recommendation was based on PK modelling. Thus the lack of any "target" C_{min} level for specific therapeutic situations where unavoidable co-administration of moderate to strong inhibitors/inducers of CYP3A4 and/or hepatic impairment for everolimus, was of major concern. This issue was resolved by recommendations in the SPC in section 4.4 and 4.5 and to "contraindicate" the use of everolimus in patients with severe hepatic impairment (Child-Pugh C). Further follow-up measures were introduced to determine reasonable target for means of dose adjustment in case of non-avoidable co-administration of CYP3A4 inhibitors/inducers.

In the absence of an intravenous administration form, lower limits of absolute bioavailability estimates are 5% and 11% which are based on a mass balance trial. As about 60% of the radioactivity absorbed is due to metabolites, and taking into account a) the exclusive metabolic elimination of everolimus, b) the long elimination half-life, and c) the even longer elimination half-life of metabolites, it must be assumed that a relevant part of the metabolites in the circulation are due to absorption of metabolites from the gut. Everolimus should be administered orally once-daily at the same time every day, consistently either with or without food (see SPC section 5.2). Everolimus tablets should be swallowed whole with a glass of water. The tablets should not be chewed or crushed. If a dose is missed, the patient should not take an additional dose, but take the usual prescribed next dose.

The PK is linear in the dose range investigated. After administration of everolimus in patients with advanced solid tumours, steady-state $AUC_{0-\tau}$ 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. t_{max} occurs at 1 to 2 hours post-dose. There was a significant correlation between $AUC_{0-\tau}$ and pre-dose trough concentration at steady-state.

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 everolimus 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. Blood cells are a relevant compartment of everolimus distribution and distribution into blood cells is a saturable process at therapeutic doses as blood cell-to-plasma ratio decrease with increasing concentrations of everolimus.

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 cyclosporin, 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. Thus, everolimus is excreted nearly exclusively by hepatic elimination and in the faeces. There is a negligible amount found in urine.

Everolimus is a substrate of CYP3A4 but no specific interaction studies were reported with CYP3A4 substrates and everolimus other than a clinically relevant interaction with ketoconazole. Since potential interaction is limited primarily to co-administration with CYP3A4 inhibitors, the applicant has committed to submit a follow-up study on the effect of everolimus on orally administered midazolam, a CYP3A4 substrate. 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 of everolimus. A target exposure for therapeutic drug monitoring was discussed and proposed by the CHMP as altered exposure is expected when everolimus is co-administered with interacting agents. As a follow-up measure reasonable target for means of dose adjustment in case of co-administration of CYP3A4/PgP inducers/inhibitors will be identified. Dose recommendations for co-administration of everolimus with potent inhibitors will be provided together with target concentrations and an evaluation of the potential benefit associated with therapeutic drug monitoring. Variability in interaction effects between individuals and difference in interaction effects between different potent inhibitors will be addressed.

A relevant set of sub-populations were investigated. There are no relevant effects of gender on PK. In a population pharmacokinetic evaluation in cancer patients, no significant influence of age (27-85 years) on oral clearance of everolimus was detected. 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. Also, as it can be expected by the elimination kinetics, renal impairment has no effect on PK. 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. However, there is a clear effect of hepatic impairment on elimination with a clear correlation of bilirubin levels and AUC. 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 SPC sections 4.2 and 4.4) and a commitment by the applicant to study hepatic impairment will be included as a follow-up measure.

The assessment of clinical efficacy of everolimus in RCC is based on one pivotal, phase III, double blind, randomised study (n=410) in patients who have progressed after treatment with VEGF-inhibitors (mostly sunitinib and /or sorafenib). Everolimus and BSC were compared (2:1) to placebo and BSC. PFS was chosen as primary endpoint and OS, ORR and QoL were chosen as secondary endpoints. The trial was terminated early by the IRB because the predefined stop criteria were met. At the time of cut-off the HR in the primary analyses (ITT/FAS, centralized radiology review) was 0.30 and statistically very compelling ($p<10^{-16}$). At the last data cut-off, median PFS for everolimus was 4.90 months compared to 1.87 months for placebo control. The majority of patients from the placebo group crossed over to open-label everolimus. These patients had a median PFS of 5.09 months based on investigators assessment of response. Relevant sensitivity and supportive analyses on PFS were performed. Treatment effect across pre-specified patients subgroups defined as favourable-risk, intermediate-risk and poor-risk by the MSKCC showed lower numbers of patients with a PFS event in the everolimus-treated arm compared to placebo-treated arm. In addition, the time to deterioration in KPS score was longer in the everolimus arm compared to placebo arm. There was no difference observed between treatment OS, where as a cut-off date of 15 November 2008, the median OS for everolimus-treated patients was 14.8 months and 14.4 months for placebo (on an intention-to-treat basis i.e., including crossover). This could be related to the design of the study where crossover from placebo to active treatment at the time of progression was allowed and thus confounds the survival result and prevents the detection of a significant difference in OS and also to the fact that the survival time of the patient population is longer than expected with lower numbers of deaths.

The requirements for one "pivotal study" as described in the guideline CPMP/EWF/2330/99 were fulfilled in the pivotal trial. However, there were some aspects which caused concern. There were no supportive phase I/II trials conducted in the sought indication and the evidence in phase II trials in other indications was very weak. The clinical relevance of PFS as the primary endpoint and the benefit of approximately 3 months difference in PFS between treatments were discussed, especially since this was in disagreement with scientific advice from the SAWP, which advocated the use of OS as the preferred endpoint. Moreover, the significance of the primary endpoint was questioned, in particular since there is no additional support for a patient benefit in terms of QoL and PRO data presented.

Clinical safety

The overall evaluation is based upon data from 596 patients who have been exposed to everolimus at the recommended dose (10 mg), and using the proposed treatment regimen (daily monotherapy) in various patient populations (Table 18).

Table 18 Pooled dataset for everolimus 10mg monotherapy – Safety population

Study No	Study design, objectives, and population	No of patients receiving 10-mg daily dose regimen
[C2240]	Double-blind, randomised, placebo-controlled, phase-III study (with open-label extension) Safety and efficacy in patients with mRCC whose disease has progressed despite prior VEGFr-TKI therapy	274 + 137 [a] (open-label phase following crossover from placebo)
[C2101 Part 1/ C2102]	Dose-escalation in patients with advanced solid tumours	33
[C2107]	Phase-Ib study investigating safety, tolerability, and molecular pharmacodynamic effects in patients with advanced solid tumours	12
[C1101]	Open-label, single-arm, dose-escalation study in Japanese patients with advanced solid tumours	3
[C2235]	Open-label, single-arm phase-II study Safety and efficacy in patients with advanced NSCLC previously treated with either chemotherapy (CT) only or with CT and an EGFR-TKI	85
[C2239]	Open-label, stratified phase-II study Safety and efficacy in patients with advanced pNET after the failure of cytotoxic chemotherapy	115 Stratum 1
	Total	**596 [a]**

[a] One patient in Study C2240 was randomised to receive everolimus therapy but was subsequently mistakenly entered into the open-label phase of the study; this patient is counted only once in the total row

- Patient exposure

Overall, exposure to everolimus in the study C2240 is presented in Table 19 and for the total monotherapy pooled dataset in Table 20. In total, 96 patients (35.7%) were exposed to everolimus therapy for a period of ≥ 4 months with a total exposure of 77.8 patient-years. Treatment duration (calculated from the date of the first to the last dose of study drug [including treatment interruptions]) was considerably longer for patients receiving everolimus where the median duration of therapy was 95.0 days (range: 12-315) for patients treated with everolimus compared with 57.0 days for those receiving placebo (range: 21-237).

Table 19 Duration of exposure to study drug after randomisation – Study C2240

Exposure	Everolimus 10 mg N=269		Placebo N=135	
Exposure categories, n (%)				
≥4 weeks	262	(97.4)	127	(94.1)
≥8 weeks	221	(82.2)	85	(63.0)
≥12 weeks	152	(56.5)	44	(32.6)
≥16 weeks	96	(35.7)	32	(23.4)
≥20 weeks	71	(26.4)	14	(10.4)
≥24 weeks	45	(16.7)	6	(4.4)
≥32 weeks	9	(3.3)	1	(0.7)
Duration of exposure (days)				
Mean (standard deviation)	105.7	(58.5)	75.3	(42.6)
Median	95.0		57.0	
Range	12 to 315		21 to 237	

Table 20 Duration of exposure to study drug – Monotherapy Pooled Dataset

Exposure	Study C2240 Everolimus 10 mg N=269		Pooled data Everolimus 10 mg N=596	
Exposure categories, n (%)				
<4 weeks	7	(2.6)	44	(7.4)
4 - <8 weeks	41	(15.2)	98	(16.4)
8 - <12 weeks	69	(25.7)	119	(20.0)
12 - <16 weeks	56	(20.8)	108	(18.1)
16 - <20 weeks	25	(9.3)	49	(8.2)
20 - <24 weeks	26	(9.7)	44	(7.4)
24 - <28 weeks	19	(7.1)	29	(4.9)
28 - <32 weeks	17	(6.3)	28	(4.7)
32 - <36 weeks	4	(1.5)	17	(2.9)
36 - <40 weeks	4	(1.5)	20	(3.4)
40 - <44 weeks	0		8	(1.3)
44 - <48 weeks	1	(0.4)	8	(1.3)
≥48 weeks	0		24	(4.0)
Duration of exposure (days)				
Mean (standard deviation)	105.7	(58.5)	118.6	(92.1)
Median	95.0		91.0	
Range	12 to 315		1 to 615	

Studies included: [Study C2240], [Study C2239], [Study C1101], [Study C2101 monotherapy/C2102], [Study C2107], and [Study C2235]

Dose interruptions and dose reductions in study C2240 are reported for approximately 37% and approximately 15% in the everolimus and placebo treatment groups, respectively. The main reason was adverse events (AEs) (26 % in the everolimus group).

Adverse events

Nearly all patients reported AEs throughout the study. System organ classes with a higher proportion of everolimus-treated patients reporting events (≥ 10% relative to placebo) included:

- gastrointestinal disorders
- general disorders and administration site conditions
- skin and subcutaneous tissue disorders
- respiratory, thoracic and mediastinal disorders; metabolism and nutrition disorders
- blood and lymphatic system disorders
- infections and infestations

- ‘investigations’

The frequency per system organ class is presented for study C2240 (Table 21) and for the pooled dataset (Table 22).

Table 21 Adverse events by system organ class – Study C2240

	Second interim analysis Data cut-off: 15-Oct-2007				Safety Update Data cut-off: 28-Feb-2008			
	Everolimus 10 mg N=269		Placebo N=135		Everolimus 10 mg N=274		Placebo N=137	
	n (%)		n (%)		n (%)		n (%)	
Any primary system organ class	**257**	**(95.5)**	**126**	**(93.3)**	**265**	**(96.7)**	**128**	**(93.4)**
Gastrointestinal disorders	203	(75.5)	62	(45.9)	223	(81.4)	68	(49.6)
General disorders and administration site conditions	196	(72.9)	81	(60.0)	217	(79.2)	84	(61.3)
Skin and subcutaneous tissue disorders	150	(55.8)	25	(18.5)	165	(60.2)	29	(21.2)
Respiratory, thoracic and mediastinal disorders	138	(51.3)	42	(31.1)	176	(64.2)	49	(35.8)
Metabolism and nutrition disorders	128	(47.6)	31	(23.0)	155	(56.6)	37	(27.0)
Blood and lymphatic system disorders	100	(37.2)	26	(19.3)	133	(48.5)	25	(18.2)
Musculoskeletal and connective tissue disorders	90	(33.5)	41	(30.4)	118	(43.1)	47	(34.3)
Nervous system disorders	89	(33.1)	34	(25.2)	106	(38.7)	38	(27.7)
Infections and infestations	67	(24.9)	15	(11.1)	101	(36.9)	25	(18.2)
Investigations	63	(23.4)	18	(13.3)	81	(29.6)	19	(13.9)
Psychiatric disorders	36	(13.4)	14	(10.4)	46	(16.8)	14	(10.2)
Renal and urinary disorders	26	(9.7)	11	(8.1)	42	(15.3)	13	(9.5)
Eye disorders	22	(8.2)	1	(0.7)	31	(11.3)	1	(0.7)
Vascular disorders	19	(7.1)	13	(9.6)	27	(9.9)	11	(8.0)
Injury, poisoning and procedural complications	19	(7.1)	7	(5.2)	25	(9.1)	7	(5.1)
Cardiac disorders	17	(6.3)	4	(3.0)	27	(9.9)	4	(2.9)
Ear and labyrinth disorders	8	(3.0)	3	(2.2)	12	(4.4)	5	(3.6)
Hepatobiliary disorders	7	(2.6)	3	(2.2)	10	(3.6)	3	(2.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7	(2.6)	2	(1.5)	12	(4.4)	3	(2.2)
Endocrine disorders	5	(1.9)	0		5	(1.8)	1	(0.7)
Reproductive system and breast disorders	5	(1.9)	0		12	(4.4)	0	
Surgical and medical procedures	2	(0.7)	1	(0.7)	0		1	(0.7)
Immune system disorders	2	(0.7)	0		2	(0.7)	0	
Congenital, familial and genetic disorders	0		0		1	(0.4)	0	

Patients with multiple AEs within a system organ class are counted only once within that specific organ class

Study included: Study C2240
Source: [Appendix 1, PT-Table 2.1-1a]

Table 22 Adverse events by system organ class – Monotherapy Pooled Dataset

	Study C2240 Everolimus 10 mg N=269 n (%)		Pooled dataset Everolimus 10 mg N=596 n (%)	
Any primary system organ class	**257**	**(95.5)**	**576**	**(96.6)**
Gastrointestinal disorders	203	(75.5)	472	(79.2)
General disorders and administration site conditions	196	(72.9)	446	(74.8)
Skin and subcutaneous tissue disorders	150	(55.8)	343	(57.6)
Respiratory, thoracic and mediastinal disorders	139	(51.7)	315	(52.9)
Metabolism and nutrition disorders	128	(47.6)	308	(51.7)
Blood and lymphatic system disorders	100	(37.2)	215	(36.1)
Musculoskeletal and connective tissue disorders	90	(33.5)	214	(35.9)
Nervous system disorders	89	(33.1)	217	(36.4)
Infections and infestations	67	(24.9)	198	(33.2)
Investigations	63	(23.4)	182	(30.5)
Psychiatric disorders	36	(13.4)	111	(18.6)
Renal and urinary disorders	26	(9.7)	65	(10.9)
Eye disorders	22	(8.2)	43	(7.2)
Vascular disorders	19	(7.1)	56	(9.4)
Injury, poisoning and procedural complications	19	(7.1)	39	(6.5)
Cardiac disorders	17	(6.3)	40	(6.7)
Ear and labyrinth disorders	8	(3.0)	21	(3.5)
Hepatobiliary disorders	7	(2.6)	31	(5.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7	(2.6)	24	(4.0)
Reproductive system and breast disorders	5	(1.9)	21	(3.5)
Endocrine disorders	5	(1.9)	8	(1.3)
Immune system disorders	2	(0.7)	6	(1.0)
Surgical and medical procedures	2	(0.7)	5	(0.8)
Congenital, familial and genetic disorders	0		1	(0.2)

The incidence of stomatitis, anaemia, asthenia, fatigue, and rash were the most common AEs reported with everolimus therapy.

Adverse events occurring more commonly in the everolimus treatment group (with a ≥ 5% difference between treatment arms) are summarized in Table 23 and 24 with the respective grading. It is striking in the pivotal study that the incidence of AEs in the placebo arm (93.3 %) as well as the rate of grade 3 (23.0 %) and 4 (4.4%) AEs are high. As this is likely to be associated to the underlying disease and co-morbidities of the study population, the comparing incidence rates with everolimus to incidence rates with placebo is of major importance.

Other adverse reactions occurring more frequently with everolimus than with placebo, but with an incidence of <5% include:

- Metabolism and nutrition disorders: Common: dehydration (1.5%), exacerbation of pre-existing diabetes mellitus (1.1%); Uncommon: new onset of diabetes mellitus
- Psychiatric disorders: Common: insomnia (3.3%)
- Nervous system disorders: Uncommon: ageusia
- Eye disorders: Common: eyelid oedema (3.3%), conjunctivitis (1.5%)
- Cardiac disorders: Uncommon: congestive cardiac failure
- Vascular disorders: Common: hypertension (1.8%): Not known: haemorrhages
- Respiratory, thoracic and mediastinal disorders: Common: haemoptysis (1.1%)
- Gastrointestinal disorders: Common: abdominal pain (3.6%), dysphagia (2.6%), dyspepsia (2.6%)
- Skin and subcutaneous tissue disorders: Common: hand-foot syndrome (4.7%), nail disorder (4.7%), erythema (3.6%), acneiform dermatitis (3.3%), onychoclasis (2.9%), skin exfoliation (1.8%)
- Renal and urinary disorders: Common: increased daytime urination (1.8%)
- General disorders and administration site conditions: Common: chest pain (1.1%); Uncommon: impaired wound healing

Table 23 Adverse events by preferred term irrespective of relationship to treatment occurring more commonly (by 5% or more) with everolimus therapy in with grading – Study C2240

	Second interim analysis Data cut-off: 15-Oct-2007						Safety Update Data cut-off: 28-Feb-2008					
	Everolimus 10 mg N=269			Placebo N=135			Everolimus 10 mg N=274			Placebo N=137		
	All %	Gr 3 %	Gr 4 %	All %	Gr 3 %	Gr 4 %	All %	Gr 3 %	Gr 4 %	All %	Gr 3 %	Gr 4 %
Patients with ≥1 AE	**95.5**	**45.7**	**8.6**	**93.3**	**23.0**	**4.4**	**96.7**	**51.8**	**13.1**	**93.4**	**23.4**	**5.1**
Stomatitis	35.7	4.1	0.4	7.4	0	0	37.6	4.0	0.4	6.6	0	0
Anemia	28.3	7.1	0.4	14.8	4.4	0.7	37.6	9.5	0.7	14.6	4.4	0.7
Asthenia	27.9	1.9	0.4	20.0	3.7	0	33.2	2.6	0.7	22.6	4.4	0
Fatigue	27.5	4.5	0	25.9	3.0	0	30.7	5.5	0	27.0	2.9	0.7
Rash	25.7	1.1	0	5.9	0	0	29.2	1.1	0	6.6	0	0
Diarrhea	24.5	1.5	0	5.9	0	0	29.6	1.5	0	6.6	0	0
Cough	23.0	0.4	0	14.1	0	0	29.9	0.7	0	16.1	0	0
Anorexia	21.9	1.1	0	12.6	0.7	0	25.2	1.5	0	13.9	0.7	0
Nausea	20.4	1.1	0	17.8	0	0	26.3	1.5	0	19.0	0	0
Dyspnea	19.3	4.5	1.5	10.4	2.2	0	23.7	6.2	1.5	14.6	2.9	0
Edema peripheral	17.8	0.4	0	7.4	0	0	24.8	0.7	0	8.0	0.7	0
Pyrexia	16.0	0.4	0	8.1	0	0	19.7	0.7	0	8.8	0	0
Vomiting	15.6	1.1	0	10.4	0	0	20.4	2.2	0	11.7	0	0
Mucosal inflammation	15.2	1.5	0	2.2	0	0	18.6	1.5	0	1.5	0	0
Hypercholesterolemia	14.9	1.9	0	1.5	0	0	20.1	3.3	0	2.2	0	0
Headache	14.5	0.7	0	8.1	0.7	0	18.6	0.7	0.4	8.8	0.7	0
Epistaxis	13.8	0	0	0	0	0	17.9	0	0	0	0	0
Dry skin	10.8	0.4	0	4.4	0	0	12.8	0.4	0	5.1	0	0
Pruritus	10.0	0.4	0	4.4	0	0	13.5	0.7	0	6.6	0	0
Hypertriglyceridemia	10.0	0.7	0	2.2	0	0	14.6	1.1	0	2.2	0	0
Dysgeusia	8.6	0	0	2.2	0	0	10.2	0	0	2.2	0	0
Hyperglycemia	8.2	4.1	0	2.2	1.5	0	12.0	6.2	0	2.2	1.5	0
Abdominal pain	7.8	2.2	0	3.0	0	0	9.5	3.3	0	4.4	0	0
Blood creatinine increased	7.8	0.4	0	0.7	0	0	9.5	1.1	0	0	0	0
Aphthous stomatitis	7.4	0	0	0	0	0	9.1	0	0	0.7	0	0
Pneumonitis	7.1	2.6	0	0	0	0	9.9	2.6	0	0	0	0
Thrombocytopenia	5.6	1.1	0	0	0	0	6.6	1.5	0	0	0	0
Lymphopenia	5.2	1.5	0	2.2	0	0	7.7	4.4	0	1.5	0	0
Palmar-plantar erythrodysesthesia syndrome	5.2	0.4	0	0	0	0	4.7	0.4	0	0	0	0
Pleural effusion	4.5	1.1	0	0.7	0	0	6.6	1.8	0	0.7	0	0
Nail disorder	2.2	0	0	0	0	0	5.1	0	0	0	0	0

The event with maximum severity is counted for patients who experienced multiple episodes of an event
Study included: Study C2240

Table 24 Grading (severity) of adverse events by preferred term irrespective of relationship to treatment (with grade 3-4 events reported in at least 1% in either group) in pooled dataset – Monotherapy safety population

	Study C2240 Everolimus 10 mg N=269			Pooled data Everolimus 10 mg N=596		
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades N (%)	Grade 3 n (%)	Grade 4 n (%)
Patients with ≥1 AE	257 (95.5)	123 (45.7)	23 (8.6)	576 (96.6)	268 (45.0)	70 (11.7)
Anemia	76 (28.3)	19 (7.1)	1 (0.4)	150 (25.2)	36 (6.0)	6 (1.0)
Dyspnea	52 (19.3)	12 (4.5)	4 (1.5)	127 (21.3)	28 (4.7)	9 (1.5)
Fatigue	74 (27.5)	12 (4.5)	0	198 (33.2)	44 (7.4)	1 (0.2)
Stomatitis	96 (35.7)	11 (4.1)	1 (0.4)	205 (34.4)	23 (3.9)	1 (0.2)
Hyperglycemia	22 (8.2)	11 (4.1)	0	54 (9.1)	25 (4.2)	1 (0.2)
Dehydration	11 (4.1)	8 (3.0)	1 (0.4)	27 (4.5)	10 (1.7)	1 (0.2)
Gamma-glutamyltransferase increased	13 (4.8)	8 (3.0)	0	22 (3.7)	11 (1.8)	0
Pneumonitis	19 (7.1)	7 (2.6)	0	25 (4.2)	9 (1.5)	0
Abdominal pain	21 (7.8)	6 (2.2)	0	77 (12.9)	16 (2.7)	3 (0.5)
Pneumonia	10 (3.7)	6 (2.2)	0	27 (4.5)	15 (2.5)	1 (0.2)
Asthenia	75 (27.9)	5 (1.9)	1 (0.4)	143 (24.0)	25 (4.2)	2 (0.3)
Back pain	26 (9.7)	4 (1.5)	2 (0.7)	67 (11.2)	9 (1.5)	2 (0.3)
Hypercholesterolemia	40 (14.9)	5 (1.9)	0	66 (11.1)	9 (1.5)	0
Lung disorder	8 (3.0)	5 (1.9)	0	16 (2.7)	6 (1.0)	0
General physical health deterioration	6 (2.2)	3 (1.1)	2 (0.7)	13 (2.2)	8 (1.3)	2 (0.3)
Diarrhea	66 (24.5)	4 (1.5)	0	166 (27.9)	13 (2.2)	0
Hypophosphatemia	12 (4.5)	4 (1.5)	0	25 (4.2)	11 (1.8)	0
Lymphopenia	14 (5.2)	4 (1.5)	0	25 (4.2)	8 (1.3)	1 (0.2)
Mucosal inflammation	41 (15.2)	4 (1.5)	0	84 (14.1)	9 (1.5)	0
Anorexia	59 (21.9)	3 (1.1)	0	139 (23.3)	9 (1.5)	0
Diabetes mellitus	4 (1.5)	3 (1.1)	0	13 (2.2)	8 (1.3)	0
Hyperkalemia	5 (1.9)	3 (1.1)	0	9 (1.5)	4 (0.7)	0
Nausea	55 (20.4)	3 (1.1)	0	161 (27.0)	14 (2.3)	1 (0.2)
Pain in extremity	18 (6.7)	3 (1.1)	0	33 (5.5)	3 (0.5)	0
Pleural effusion	12 (4.5)	3 (1.1)	0	28 (4.7)	9 (1.5)	0
Rash	69 (25.7)	3 (1.1)	0	166 (27.9)	4 (0.7)	0
Thrombocytopenia	15 (5.6)	3 (1.1)	0	49 (8.2)	11 (1.8)	3 (0.5)
Vomiting	42 (15.6)	3 (1.1)	0	118 (19.8)	10 (1.7)	1 (0.2)
Pyrexia	43 (16.0)	1 (0.4)	0	113 (19.0)	3 (0.5)	3 (0.5)
Abdominal pain upper	11 (4.1)	1 (0.4)	0	44 (7.4)	6 (1.0)	1 (0.2)
Respiratory failure	4 (1.5)	0	1 (0.4)	9 (1.5)	1 (0.2)	5 (0.8)
Hypokalemia	2 (0.7)	0	0	18 (3.0)	7 (1.2)	1 (0.2)
Hyponatremia	1 (0.4)	0	0	18 (3.0)	8 (1.3)	1 (0.2)

AE preferred terms are listed in descending order of frequency of grade 3 plus grade 4 events in the everolimus treatment group in Study C2240
The event with maximum severity is counted for patients who reported multiple episodes of an event.
Studies included: Study C2240, C2239, C1101, C2101 monotherapy/C2102, C2107, C2235

Potential safety concerns were identified during clinical development, which include eight categories of events that are displayed in Table 25 with the respective rates in the pivotal study:

Table 25 Clinical adverse events irrespective of relationship to treatment – Study C2240

	Second interim analysis Data cut-off: 15-Oct-2007				Safety Update Data cut-off: 28-Feb-2008			
	Everolimus 10 mg N=269		**Placebo N=135**		**Everolimus 10 mg N=274**		**Placebo N=137**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Any clinically notable AE	**221**	**(82.2)**	**53**	**(39.3)**	**237**	**(86.5)**	**53**	**(38.7)**
Stomatitis / oral mucositis / ulcers	112	(41.6)	11	(8.1)	120	(43.8)	11	(8.0)
Hematopoiesis decreased / cytopenias	103	(38.3)	24	(17.8)	136	(49.6)	25	(18.2)
Rash and similar events	84	(31.2)	9	(6.7)	95	(34.7)	9	(6.6)
Metabolic events	71	(26.4)	11	(8.1)	101	(36.9)	13	(9.5)
Renal events	27	(10.0)	4	(3.0)	36	(13.1)	3	(2.2)
Pulmonary events	24	(8.9)	0		36	(13.1)	0	
Bleeding and thromboembolic events	19	(7.1)	6	(4.4)	23	(8.4)	6	(4.4)
Hepatic events	9	(3.3)	1	(0.7)	11	(4.0)	1	(0.7)

Study included: Study C2240
Source: [Appendix 1, PT-Table 2.1-11a]

Non-infectious pneumonitis
Non-infectious pneumonitis is a class effect of rapamycin derivatives. Cases of non-infectious pneumonitis (including interstitial lung disease) have also been described in patients taking everolimus (see SPC section 4.8). The rate of clinical apparent pneumonitis is 13.1 % for everolimus, cough and dyspnea are reported with approximately 23 % and 19 %, respectively. Some of these have been 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.

Infections
In the study C2240, infections were diagnosed in 67 patients (24.9%) in the everolimus treatment group and in 15 patients (11.1%) in the placebo arm. There was a 16-fold grade 3 and 4-fold grade 4 infections in the everolimus arm. Specific grade 3 or 4 infections occurring in ≥1 patient were: pneumonia (grade 3 [n=6]), septic shock (grade 3 [n=1]; grade 4 [n=1]), and urinary tract infection (grade 3 [n=2]). Four grade 3 fungal infections (of various types) were also reported: aspergillosis, bronchopulmonary aspergillosis, Candida, and fungal infection (not specified). One of the patients with a pulmonary aspergillosis also had a staphylococci septicaemia.

- Serious adverse event/deaths/other significant events

A summary table for SAEs, death, AEs leading to discontinuation, and other significant AEs is displayed in Table 26. Serious adverse events 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 were dyspnea (7.3 %), pyrexia (4.4 %), pleural effusion (3.3 %), pneumonitis (3.6 %), anaemia (3.3%) and dehydration (2.9 %). Deaths 'on-treatment' including the initial 28 days of discontinuing therapy were recorded for 28 patients (6.8 %) by the data cut-off date of 28 February 2008. Of the 28 patients who died, 21 (7.7%) had received treatment with everolimus and 7 (5.1%) with placebo. Two deaths, both in patients receiving everolimus therapy, were suspected as being causally related to treatment. One patient died from overwhelming candidal sepsis, complicated by acute respiratory failure, while the second patient also died from sepsis. A third patient for whom the principal cause of death was progressive renal cancer experienced acute respiratory failure concurrently, with ongoing grade 3 interstitial lung disease (that was suspected to be drug-related). This observation led to an update to the Label to indicate that non-infectious pneumonitis has on occasion been associated with a fatal outcome.

Across the broader development program reported in the pooled dataset, 6 patients (1.0%) have died where the primary cause of death was reported to be an AE within the "respiratory, thoracic, and mediastinal disorders" system organ class.

Table 26 On-treatment deaths by system organ class and preferred term in pooled dataset – Monotherapy safety population

	Study C2240 Everolimus 10 mg N=269 n (%)		Pooled data Everolimus 10 mg N=596 n (%)	
Patients with AE as primary cause of on-treatment death	14	(5.2)	42	(7.0)
General disorders and administration site conditions	6	(2.2)	10	(1.7)
Disease progression	6	(2.2)	9	(1.5)
Adverse event	0		1	(0.2)
Study indication	3	(1.1)	13	(2.2)
Disease progression	3	(1.1)	13	(2.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	(1.1)	10	(1.7)
Renal cell carcinoma	1	(0.4)	3	(0.5)
Renal cancer	1	(0.4)	2	(0.3)
Metastatic renal cell carcinoma	1	(0.4)	1	(0.2)
Neoplasm	0		3	(0.5)
Pancreatic neuroendocrine tumor	0		1	(0.2)
Respiratory, thoracic and mediastinal disorders	1	(0.4)	6	(1.0)
Acute respiratory failure	1	(0.4)	1	(0.2)
Acute pulmonary edema	0		1	(0.2)
Acute respiratory distress syndrome	0		1	(0.2)
Aspiration	0		1	(0.2)
Hydropneumothorax	0		1	(0.2)
Respiratory failure	0		1	(0.2)
Renal and urinary disorders	1	(0.4)	1	(0.2)
Renal failure acute	1	(0.4)	1	(0.2)
Infections and infestations	0		1	(0.2)
Pneumonia	0		1	(0.2)
Metabolism and nutrition disorders	0		1	(0.2)
Cachexia	0		1	(0.2)

System organ classes are listed in descending order of frequency in the everolimus treatment group in study C2240; AE preferred terms are sorted within organ class also by descending order of frequency with everolimus in study C2240.
Studies included: C2240, C2239, C1101, C2101 monotherapy/C2102, C2107 and C2235.

- Laboratory findings

Clinical chemistry abnormalities were reported in the majority of patients receiving everolimus therapy, with increases in cholesterol, triglycerides, gamma glutamyltransferase, glucose, creatinine, and alkaline phosphatase, and decreases in phosphate being seen in >30% of patients. The majority of grade 3 abnormalities were increased glucose, increased gamma glutamyltransferase, decreased phosphate, and increased cholesterol.
Haematologic abnormalities were common with decreases in red cells, white cells, and platelets being noted in >10% of patients.

- Safety in special populations

Adverse events were evaluated according to demographic subgroups (gender, age, race, and ethnicity). No dose adjustment is required for elderly patients. No dose adjustment is required for renal impaired patients. For patients with moderate hepatic impairment (Child-Pugh class B), the dose should be reduced to 5 mg daily. 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 (see SPC sections 4.4 and 5.2).

Everolimus is not recommended for use in children due to lack of data on safety and efficacy.

Everolimus is contraindicated for patients with hypersensitivity to everolimus or to any of the excipients.

Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
Based on non-clinical findings, male fertility may be reversibly compromised by treatment with everolimus (see SPC section 5.3). Women of childbearing potential must use an effective method of contraception while receiving everolimus. There are no or limited amount of data from the use of everolimus in pregnant women. Studies in animals have shown reproductive toxicity effects (see SPC section 5.3). 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 passes into the milk. Women taking everolimus should therefore not breast-feed.

- Safety related to drug-drug interactions and other interactions

Concurrent treatment with strong inhibitors of CYP3A4 or PgP (including but not limited to ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin and telythromycin) should be avoided (see section 4.5). 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 co-administered with ketoconazole (a strong CYP3A4 inhibitor and PgP inhibitor).

Concomitant treatment with moderate inhibitors of CYP3A4 and PgP requires caution.
There was an increase in exposure to everolimus in healthy subjects when everolimus was co-administered with:

– 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).

– cyclosporin (a CYP3A4 substrate and a PgP inhibitor; C_{max} and AUC increased by 1.8- and 2.7-fold, respectively).

Use caution when administering everolimus in combination with moderate CYP3A4 inhibitors or PgP inhibitors. If patients require co-administration of a moderate CYP3A4 or PgP inhibitor, reduce the dose to 5 mg daily. Further dose reduction to 5 mg every other day may be required to manage adverse reactions.

Other moderate inhibitors of CYP3A4 and PgP that may increase everolimus blood concentrations include certain antifungal agents (e.g. fluconazole) and calcium channel blockers (e.g. diltiazem).

Substances that are inducers of CYP3A4 or PgP may decrease everolimus blood concentrations by increasing metabolism or the efflux of everolimus from intestinal cells. Concurrent treatment with strong inducers of CYP3A4 or PgP should be avoided where possible (see SPC section 4.5). 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%. Other inducers of CYP3A4 that may increase the metabolism of everolimus and decrease everolimus blood levels include St. John's wort (*Hypericum perforatum)*, anticonvulsants (e.g. carbamazepine, phenobarbital, phenytoin) and anti-HIV agents (e.g. efavirenz, nevirapine). Concomitant treatment with moderate inducers of CYP3A4 or PgP requires caution.

If patients require co-administration of a strong CYP3A4 inducer, an everolimus dose increase from 10 mg daily up to 20 mg daily should be considered (based on pharmacokinetic data), using 5 mg increments. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers.

- Discontinuation due to adverse events

Discontinuation due to adverse events occurred 3 times more often with everolimus than with placebo (10.4 and 3.7 %, respectively.).

- Post marketing experience

Not applicable

- Discussion on clinical safety

Stomatitis, anaemia, asthenia, fatigue, and rash were the most common AEs reported with everolimus therapy. These events are consistent with the known safety profile of everolimus and other rapamycin derivatives. Everolimus has immunosuppressive properties and may predispose patients to infections, especially infections with opportunistic pathogens.

Management of severe and/or intolerable suspected adverse reactions may require dose alterations. Everolimus may be dose reduced or temporarily withheld (e.g. for one week) followed by reintroduction at 5 mg daily. If dose reduction is required, the suggested dose is 5 mg daily (see SPC section 4.4).

Everolimus is contraindicated for patients with hypersensitivity to the active substance, to other rapamycin derivatives or to any of the excipients. 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 SPC section 4.3).

For non-infectious pneumonitis, patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue everolimus 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. Everolimus may be re-initiated at 5 mg daily (see SPC section 4.4 and 4.8).

For cases where symptoms of non-infectious pneumonitis are severe, everolimus therapy should be discontinued and the use of corticosteroids may be indicated until clinical symptoms resolve. Therapy with everolimus may be re-initiated at 5 mg daily depending on the individual clinical circumstances.

Everolimus has immunosuppressive properties and may predispose patients to infections, especially infections with opportunistic pathogens (see SPC section 4.8). Localised and systemic infections, including pneumonia, other bacterial infections and invasive fungal infections, such as aspergillosis or candidiasis, have been described in patients taking everolimus. Some of these infections have been severe (e.g. leading to respiratory failure) and occasionally have had a fatal outcome. Physicians and patients should be aware of the increased risk of infection with everolimus, be vigilant for symptoms and signs of infection, and institute appropriate treatment promptly. Patients with pre-existing infections should have them appropriately treated and fully resolved before starting treatment with everolimus. If a diagnosis of invasive systemic fungal infection is made during everolimus treatment, everolimus should be promptly and permanently discontinued and the patient treated with appropriate antifungal therapy.

The use of live vaccines should be avoided during treatment with everolimus (see SPC section 4.5).

Mouth ulcers, stomatitis and oral mucositis have been seen in patients treated with everolimus (see SPC 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 SPC section 4.5).

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

Everolimus should not be used in patients with severe hepatic impairment (Child-Pugh class C) (see SPC sections 4.2 and 5.2).

Hyperglycaemia has been reported in clinical trials (see SPC section 4.8). The majority of cases occurred in patients who had an abnormal fasting glucose level before taking everolimus. Monitoring of fasting serum glucose is recommended prior to the start of everolimus therapy and periodically thereafter. Optimal glycaemic control should be achieved before starting a patient on everolimus.

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

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of the multidrug efflux pump P-glycoprotein (PgP). Absorption and subsequent elimination of everolimus may therefore 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. Co-administration with strong inhibitors of CYP3A4 or P-glycoprotein (PgP) should be avoided (see SPC section 4.5). If no alternative treatment is available and co-administration with strong inhibitors of CYP3A4 is crucial, the patient should be carefully monitored for safety. If necessary, dose reduction may be considered for management of adverse drug reactions.

Grapefruit, grapefruit juice and other foods that are known to affect cytochrome P450 and PgP activity should be avoided during treatment.

Use caution when administering everolimus in combination with moderate CYP3A4 inhibitors or PgP inhibitors (see SPC section 4.5). If patients require co-administration of a moderate CYP3A4 or PgP inhibitor, reduce the dose to 5 mg daily. Further dose reduction to 5 mg every other day may be required to manage adverse reactions.

Co-administration with strong inducers of CYP3A4 or PgP should be avoided (see SPC section 4.5). If patients require co-administration of a strong CYP3A4 inducer, based on pharmacokinetic studies, an everolimus dose increase from 10 mg/day up to 20 mg/day should be considered, using 5 mg increments. This dose of everolimus is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued, the everolimus dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer.

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 drugs which are CYP3A4 and/or PgP substrates.

The response to vaccination may be affected and vaccination may therefore be less effective during treatment with everolimus. The use of live vaccines should be avoided during treatment with everolimus (see SPC section 4.4). Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG (Bacillus Calmette-Guérin), yellow fever, varicella, and TY21a typhoid vaccines.

There are no or limited amount of data from the use of everolimus in pregnant women. Studies in animals have shown reproductive toxicity effects (see SPC section 5.3). 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 passes into the milk. Women taking everolimus should therefore 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 everolimus.

Reported experience with overdose in humans is very limited. Single doses of up to 70 mg have been given with acceptable acute tolerability. General supportive measures should be initiated in all cases of overdose.

2.5 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 MAA submitted a risk management plan

Table 27 is a summary of the risk management plan

Table 27 Summary of the risk management plan version 2.3

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

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		daily. For cases where symptoms of non-infectious pneumonitis are severe, Afinitor therapy should be discontinued and the use of corticosteroids may be indicated until clinical symptoms resolve. Therapy with Afinitor may be re-initiated at 5 mg daily depending on the individual clinical circumstances. Section 4.8: Pneumonitis – Very common (Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar haemorrhage, pulmonary toxicity, and alveolitis).
Infections	Routine pharmacovigilance Active follow-up of all serious spontaneous post-marketing reports, and all clinical trial SAE reports, using a targeted questionnaire / checklist	Risk is included in EU-SPC Sections 4.4 and 4.8. Section 4.4: Afinitor has immunosuppressive properties and may predispose patients to infections, especially infections with opportunistic pathogens (see section 4.8). Localised and systemic infections, including pneumonia, other bacterial infections and invasive fungal infections, such as aspergillosis or candidiasis, have been described in patients taking Afinitor. Some of these infections have been severe (e.g. leading to respiratory failure) and occasionally fatal. Physicians and patients should be aware of the increased risk of infection with Afinitor, be vigilant for symptoms and signs of infection, and institute appropriate treatment promptly. Pre-existing infections should be treated appropriately and have resolved fully before starting treatment with Afinitor. If a diagnosis of invasive systemic fungal infection is made, Afinitor treatment should be promptly and permanently discontinued and the patient treated with appropriate antifungal therapy. Decreased […] lymphocytes, neutrophils […] have been reported in clinical trials. Monitoring of complete blood count is recommended prior to the start of Afinitor therapy and periodically thereafter. Section 4.8: Infections – Very common

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		(Includes all events within the 'infections and infestations' system organ class (such as pneumonia, sepsis, and opportunistic infections (eg, aspergillosis and candidiasis))
Hypersensitivity reactions	Routine pharmacovigilance Active follow-up of all serious spontaneous post-marketing reports, and all clinical trial SAE reports, using a targeted questionnaire / checklist	Risk is included in EU-SPC Sections 4.3 and 4.4. Section 4.3: Hypersensitivity to the active substance, to other rapamycin derivatives, or to any of the excipients. Section 4.4: Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, 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).
Stomatitis	Routine pharmacovigilance	Risk is included in EU-SPC Sections 4.4 and 4.8. Section 4.4: Mouth ulcers, stomatitis and oral mucositis have been observed in patients treated with Afinitor (see section 4.8). In such cases topical treatments are recommended, but alcohol- or peroxide-containing mouthwashes should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless fungal infection has been diagnosed (see section 4.5). Section 4.8: Stomatitis – Very common (Includes stomatitis and aphthous stomatitis, and mouth and tongue ulceration)
Increased creatinine	Routine pharmacovigilance Active follow-up of all serious spontaneous post-marketing reports, and all clinical trial SAE reports, using a targeted	Risk is included in Sections 4.4 and 4.8 of the EU-SPC. Section 4.4: Elevations of serum creatinine, usually mild, have been

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
	questionnaire / checklist	reported in clinical trials (see section 4.8). Monitoring of renal function, including measurement of blood urea nitrogen (BUN) or serum creatinine, is recommended prior to the start of Afinitor therapy and periodically thereafter. Section 4.8: Creatinine increased – Very common
Hyperglycaemia/ new onset diabetes	Routine pharmacovigilance	Risk is included in EU-SPC Sections 4.4 and 4.8. Section 4.4: Hyperglycaemia, […] have been reported in clinical trials (see section 4.8). The majority of cases of hyperglycaemia occurred in patients who had an abnormal fasting glucose level before taking Afinitor. Monitoring of fasting serum glucose is recommended prior to the start of Afinitor therapy and periodically thereafter. When possible optimal glycaemic control should be achieved before starting a patient on Afinitor. Section 4.8: Glucose increased – Very common New-onset diabetes mellitus - Uncommon
Drug interactions	Routine pharmacovigilance To address drugs eliminated by CYP3A4, and PgP substrates: Study: *In vivo* investigation of the effect of everolimus on orally administered midazolam Meta-analyses to evaluate the relationships between safety/efficacy and everolimus exposure (e.g. C_{min}, C_{1h}, and C_{2h}) using data of PK blood samples that are being collected in ongoing clinical studies. Identification of a reasonable target for means of dose	Risk is communicated in EU-SPC Sections 4.4 and 4.5. Section 4.4: Co-administration with inhibitors and inducers of CYP3A4 and/or the multidrug efflux pump P-glycoprotein (PgP) should be avoided. If co-administration of a ***moderate*** CYP3A4 and/or PgP inhibitor or inducer cannot be avoided, dose adjustments of Afinitor can be taken into consideration based on predicted AUC (see section 4.5). Concomitant treatment with

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
	adjustment in case of co-administration of CYP3A4/PgP inducers/inhibitors. Provision of dose recommendations for co-administration of everolimus with potent inhibitors together with target concentrations and an evaluation of the potential benefit associated with therapeutic drug monitoring. Address variability in interaction effects between individuals and difference in interaction effects between different potent inhibitors.	***potent*** CYP3A4 inhibitors result in dramatically increased plasma concentrations of everolimus (see section 4.5). There are currently not sufficient data to allow dosing recommendations in this situation. Hence, concomitant treatment of Afinitor and ***potent*** inhibitors is not recommended. Section 4.5: Dedicated section includes comprehensive drug interaction information for: • CYP3A4 and PgP inhibitors increasing everolimus concentrations • CYP3A4 and PgP inducers decreasing everolimus concentrations • Agents whose plasma concentration may be altered by everolimus
Important potential risks		
Cardiac failure	Routine pharmacovigilance Active follow-up of all serious spontaneous post-marketing reports, and all clinical trial SAE reports, using a targeted questionnaire / checklist	Risk is included in EU-SPC Section 4.8. Congestive cardiac failure - Uncommon
Wound healing complications	Routine pharmacovigilance	Risk is included in EU-SPC Sections 4.4 and 4.8. Section 4.4: Impaired wound healing is a class effect of rapamycin derivatives, including Afinitor. Caution should therefore be exercised with the use of Afinitor in the peri-surgical period. Section 4.8: Impaired wound healing - Uncommon
Lymphopaenia	Routine pharmacovigilance	Risk is included in EU-SPC Sections 4.4 and 4.8. Section 4.4: Decreased […], lymphocytes, neutrophils […] have been reported in clinical trials (see section 4.8). Monitoring of complete blood count is

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		recommended prior to the start of Afinitor therapy and periodically thereafter. Section 4.8: Lymphocytes decreased, neutrophils decreased - Very common
Hypophosphataemia	Routine pharmacovigilance	Risk is included in EU-SPC Sections 4.8. Section 4.8: Phosphate decreased – Very common
Dyslipidaemia	Routine pharmacovigilance	Risk is included in EU-SPC Sections 4.4 and 4.8: Section 4.4: […] hyperlipidaemia and hypertriglyceridaemia have been reported in clinical trials (see section 4.8). Section 4.8: Cholesterol increased, triglycerides increased – Very common
Important missing information		
Paediatric patients	Routine pharmacovigilance Safety review of clinical trial experience in ongoing study protocols RAD001-C2244 and M2301	Information provided in EU-SPC Section 4.2: Paediatric patients (<18 years) Afinitor is not recommended for use in children and adolescents due to lack of data on safety and efficacy.
Pregnancy and lactating women Hormonal contraceptive use	Routine pharmacovigilance	Information provided in EU-SPC section 4.6. Based on non clinical findings, male fertility may be compromised by treatment with everolimus (see section 5.3). Women of childbearing potential must use an effective method of contraception while receiving everolimus. There are no or limited amount of data from the use of everolimus in pregnant women. Studies in animals have shown reproductive toxicity effects (see section

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		5.3). 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.
Patients with renal impairment	Routine pharmacovigilance	Information provided in EU-SPC Sections 4.2 and 5.2. Section 4.2: No dose adjustment is required (see section 5.2). Section 5.2: 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.
Patients with severe hepatic impairment	Routine pharmacovigilance Study CRAD001X2102: Investigation of everolimus in patients with hepatic impairment Child-Pugh class C	Information provided in EU-SPC Sections 4.2, 4.4, and 5.2. Section 4.2: For patients with moderate hepatic impairment (Child-Pugh class B), the dose should be reduced to 5 mg daily. 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 (see sections 4.4 and 5.2). Section 4.4: Afinitor should not be used in patients with severe hepatic impairment (Child-Pugh class

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		C) (see sections 4.2 and 5.2). Section 5.2: The impact of severe hepatic impairment (Child-Pugh class C) on the pharmacokinetics of everolimus has not been assessed (see sections 4.2 and 4.4).
Patients with other morbidities: 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 Patients with coagulation disorders Patients with severe cardiac disease Patients with impairment of gastrointestinal function Patients undergoing chronic treatment with steroids or another immunosuppressive agent Patients who have undergone surgery within 2 weeks prior to treatment Long-term safety Race other than Caucasian	Routine pharmacovigilance	None

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality
The quality of the medicinal product Afinitor containing the active substance everolimus is considered satisfactory when used in accordance with the conditions defined in the SPC.
Physicochemical and biological aspects relevant to the uniform clinical performance have been investigated and controlled in a satisfactory manner.

Non-clinical pharmacology and toxicology
The preclinical 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.

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.

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.

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.

Efficacy
The C2240 study, a phase III, international, multicentre, randomised, double-blind study comparing everolimus 10 mg/day and placebo, both in conjunction with best supportive care, was conducted in patients with metastatic renal cell carcinoma whose disease had progressed despite prior treatment with VEGFR-TKI therapy (sunitinib, sorafenib, or both sunitinib and sorafenib). Prior therapy with bevacizumab and interferon-α was also permitted. Patients were stratified according to MSKCC prognostic score (favourable- *vs.* intermediate- *vs.* poor-risk groups) and prior anticancer therapy (1 *vs.* 2 prior VEGFR-TKIs).

Progression-free survival (PFS), documented using RECIST (Response Evaluation Criteria in Solid Tumours) and assessed via a blinded, independent central review, was the primary endpoint. Secondary endpoints included safety, objective tumour response rate (ORR), overall survival (OS), disease-related symptoms (DRS), and quality of life (QoL). After documented radiological progression, patients could be unblinded by the investigator: those randomised to placebo were then able to receive open-label everolimus 10 mg/day. The Independent Data Monitoring Committee recommended termination of this trial at the time of the second interim analysis as the primary endpoint had been met.

In total, 416 patients were randomised 2:1 to receive everolimus (n=277) or placebo (n=139). Demographics were well balanced (pooled median age [61 years; range 27-85], 77% male, 88% Caucasian, number of prior VEGFR-TKI therapies [1-74%, 2-26%]). In the final analysis with a cut-off date of 28 February 2008, which included 6 patients more than the interim analysis with a total of 277 patients, the median PFS was 4.90 months in the everolimus group (95% CI 3.98- 5.52) and 1.87 months in the placebo group (95% CI 1.84-1.94) with a HR of 0.33 (95% CI 0.25-0.43), resulting in a difference of approximately 3 months. Everolimus was superior to placebo for the primary endpoint of PFS, with a statistically significant 67% reduction in the risk of progression or death. Six-month PFS rates were 36% for everolimus therapy compared with 9% for placebo. Confirmed objective tumour responses were observed in 5 patients (2%) receiving everolimus, while none were observed in patients receiving placebo. Therefore, the PFS advantage primarily reflects the population with disease stabilisation. No statistically significant treatment-related difference in OS was noted (HR 0.87; 95%CI 0.65-1.17; p=0.177). It is possible that crossover to open-label everolimus following disease progression for patients allocated to placebo confounded the detection of any treatment-related difference in overall survival.

Safety

The main toxicities are not unexpected given the known class effects of mTOR inhibitors. The safety data described in study C2240 reflects exposure to everolimus (n=274) and placebo (n=137) in a randomised phase III study for the treatment of metastatic renal cell carcinoma. In total, 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 toxicological profile of everolimus 10 mg monotherapy was described as being mainly:

- gastrointestinal (stomatitis, aphthous stomatitis, mucosal inflammation, dry mouth, nausea, vomiting, diarrhoea, anorexia)
- respiratory (cough, dyspnea, pneumonitis epistaxis)
- infection-related
- affecting the body as a whole (peripheral oedema, headache, pyrexia, asthenia)
- skin-related (rash, pruritus, dry skin, palmar-plantar erythrodysesthesia syndrome)
- metabolic (hypertriglyceridemia, hyperglycemia, hypercholesteremia)
- haematologic (anaemia, thrombocytopenia).

Moreover, AEs related to investigations, eye disorders and nervous system were reported at least 5 % more often as in the placebo arm as an indicator of causality. Most of the reported toxicity was mild to moderate.

The rates of adverse reactions resulting in permanent discontinuation were 7% and 0% for the everolimus and placebo treatment groups, respectively. Most adverse reactions were grade 1 or 2 in severity. Grade 3 or 4 adverse reactions were reported in 39% versus 7% of patients receiving everolimus and placebo, respectively. Adverse events have been specifically addressed: stomatitis /mucositis, infections, cytopenias, rash and similar events, metabolic events, renal events, pulmonary events, bleeding and thromboembolic events, hepatic events. The incidence of severe adverse events, serious adverse events and events leading to treatment discontinuation are higher compared to placebo.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these concerns.

- User consultation

User testing of the PL was performed in English. The user testing of the PL was judged as acceptable.

Risk-benefit assessment

The results for the study C2240 for the primary endpoint PFS was considered statistically significant: the median PFS for everolimus was 4.90 months compared to 1.87 months for placebo control. In addition, the majority of patients from the placebo group crossed over to open label everolimus. These patients had a median PFS of 5.09 months based on investigators assessment of response. However, the CHMP commented that a gain in PFS may not be clinically relevant since it was not accompanied by supportive benefit in terms of OS, ORR, QoL and PRO data. Most importantly, there was no effect on OS where everolimus-treated patients had a median OS of 14.75 months compared to 14.39 months for placebo in the ITT population (HR 0.87; 95%CI 0.65-1.1) (data cut off 15 November 2008).

The CHMP requested the advice of the Scientific Advisory Group in Oncology (SAG-O) on the issue of the relevance of a gain of approximately of 3 months PFS in relation to a lack of additional support from OS, QoL and PRO. The SAG agreed that PFS can be an appropriate endpoint for the demonstration of benefit in this setting, although this was dependent on the magnitude of the effect and on any associated benefits in terms of other relevant clinical endpoints. The SAG members agreed

that the observed difference of about 3 months in median PFS for everolimus compared to placebo constitutes a clear sign of anti-tumour activity. The SAG discussed whether this could constitute a clinically significant benefit on its own. Most SAG members agreed that although the benefit cannot be considered as established based on the observed effect on PFS alone, in this disease setting it is reasonable to assume that this effect should also be associated with relevant effects in terms of OS, and QoL, although this assumption remains to be proven. Supportive exploratory data, particularly in terms of deterioration of performance status provided some support for this assumption. Exploratory analyses of OS aiming to correct for the crossover were not considered to provide substantial supportive information. The majority of the SAG-O concluded that based on the data provided and reasonable assumptions, a clinical benefit could be considered as reasonably likely.

The CHMP noted that the trial design chosen by the applicant as a crossover study of placebo-treated patients after evidence of progression was of concern as this would preclude a reliable analysis of the true effect of everolimus on OS. To respond to the CHMP concerns, the applicant provided results from exploratory analyses showing that censoring of placebo at the time of crossover to everolimus did not affect the PFS in favour of everolimus (HR 0.79; 95%CI 0.48-1.29; p=0.171) in addition to providing a model for correcting for bias introduced by crossover. The CHMP also requested the advice of the SAG-O on whether the trial design of placebo as a comparator and a crossover to everolimus at the time of progression was appropriate, given that patients had fewer options when the trial was originally designed. The SAG-O agreed that a trial without crossover after progression would have been difficult to conduct. A trial using other comparators or crossover to other salvage treatment was also not considered a viable option. The SAG-O regretted that insufficient effort had been made to collect biopsies from tumours (primaries and metastatic lesions), or in some cases normal tissues, that are needed to obtain data on target saturation or downstream events, in accordance to the EMEA guideline on The Evaluation Of Anticancer Medicinal Products In Man. Nevertheless, a number of SAG-O members acknowledged the difficulties of obtaining biopsy material in this particular setting. The SAG-O advised that additional studies should be conducted in order to determine the optimal dosing of everolimus in the applied indication.

Although everolimus showed a statistical significance for PFS in the pre-treated RCC population, the CHMP had concerns over the lack of randomised controlled trials for OS in support of the applied indication and appropriate dosing. Given that everolimus is metabolised almost exclusively by CYP3A4, there is a risk of under dosing or overdosing when co-administration of inducers or inhibitors of CYP3A4. Since potential interaction is limited primarily to co-administration with CYP3A4 inhibitors, the applicant has committed to submit a follow-up study on the effect of everolimus on orally administered midazolam, a CYP3A4 substrate, as a post-authorisation commitment. The CHMP also recommended that the applicant commits to an adjustment of the dose by identifying reasonable target for means of dose adjustment in case of co-administration of CYP3A4/PgP inducers/inhibitors. The applicant also committed to conduct meta-analyses to evaluate the relationships between safety/efficacy and everolimus exposure (e.g. C_{min}, C_{1h}, and C_{2h}) using data of PK blood samples that are being collected in ongoing clinical studies. Dose recommendations for co-administration of everolimus with potent inhibitors will be provided together with target concentrations and an evaluation of the potential benefit associated with therapeutic drug monitoring. Variability in interaction effects between individuals and difference in interaction effects between different potent inhibitors will also be addressed by applicant. As everolimus has not been evaluated in patients with severe hepatic impairment, the CHMP does not recommend the use of everolimus in this patient's population. The applicant has committed to perform a study on the effect of hepatic impairment (Child Pugh A-C), and dose modifications according to grade, on PK as a follow-up measure recommended by the CHMP.

The CHMP also noted that the effect of food could influence absorption of everolimus and therefore, a recommendation to take everolimus consistently with or without food at the same time each day to ensure consistency of dosing interval was emphasised in the SPC.

The CHMP noted that close monitoring for adverse event reports concerning renal toxicity, cardiac failure, severe infections, exacerbation of background diseases (e.g. myocarditis), non-infectious pneumonitis, and missing information should be discussed in detail in future PSUR submissions. In

addition, a special attention should be given in future PSURs regarding off-label use and off-label use in children. The applicant has provided a commitment to discuss these issues in future PSURs.

The CHMP, taking into consideration the views of the SAG-O and the applicant's responses to the concerns raised during the procedure, is of the opinion that the robust analysis of the PFS results and the treatment effect of approximately 3 months difference for PFS is considered clinically relevant for this indication. The CHMP also considers that the toxicity profile of everolimus is mild to moderate and that the efficacy demonstrated with everolimus outweighs any safety concerns in the target patient population.

Treatment with everolimus should be initiated and supervised by a physician experienced in the use of anticancer therapies.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Afinitor (everolimus) is not similar to Nexavar (sorafenib) and Torisel (temsirolimus) within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of everolimus in the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy was favourable and therefore recommended the granting of the marketing authorisation.

And

In addition, the CHMP, with reference to Article 8 of Regulation EC No 141/2000, considers everolimus not to be similar (as defined in Article 3 of Commission Regulation EC No. 847/2000) to Sutent, Nexavar and Torisel for the same therapeutic indication.