2 September 2011

EMA/723893/2011

Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Afinitor

everolimus

Procedure No.: EMEA/H/C/001038/II/0008

Note

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

21 July 2011
EMA/723893/2011
Committee for Medicinal Products for Human Use (CHMP)

CHMP variation assessment report

Type II variation EMEA/H/C/001038/II/0008

1. Scientific discussion

1.1. Introduction

Neuroendocrine tumours (NETs) comprise a group of neoplasms derived from peptide- and amine-producing cells of the neuroendocrine system. They are characterised histologically by the intracellular presence of markers of endocrine tissue, such as chromogranin A (CgA), synaptophysin, and neuron-specific enolase. NETs may be classified according to their embryological origin, as arising from the foregut (e.g., bronchial or gastric carcinoid), midgut (e.g., small intestine or appendiceal carcinoid), or hindgut (e.g., colon or rectal carcinoid). NETs are broadly subcategorised into functional and nonfunctional tumours and are usually subclassified as carcinoid tumours (NETs with carcinoid syndrome) or pancreatic NETs. The term 'carcinoid' is typically used to describe a well- to moderately-differentiated NET arising outside the pancreas. The number of persons affected by the condition in the Community was estimated to be approximately 1.8 in 10,000.

The main primary sites of origin for NETs are the gastrointestinal tract (62% to 67%) and the lung (22% to 27%). Those arising from the pancreas are recognized to have a different genetic profile, more aggressive clinical course, and different pattern of response to cytotoxic chemotherapy. Midgut tumours are considered the classic tumour associated with carcinoid syndrome and are more commonly symptomatic. In contrast, the majority of pancreatic NETs are nonfunctional tumours. Overall, 40% to 60% of patients with NET are asymptomatic at presentation. Approximately 40% of patients have advanced disease at initial presentation, with up to 75% with liver metastases at the time of diagnosis.

Advanced NETs are considered incurable. Stage of disease significantly influences the prognosis, with the best 5-year survival rate in localized disease (93%) and a poor 5-year survival rate in distant metastatic disease. Median overall survival (OS) from the date of initial diagnosis among patients with metastatic well- to moderately-differentiated NETs of the small bowel, cecum, appendix, rectum, lung, and colon are 65, 55, 31, 26, 17, and 7 months, respectively[1]. Median OS for metastatic pancreatic NET has been reported to be 17 months[2].

Management of NETs is generally guided by histology. High-grade or poorly-differentiated NETs have an aggressive course, and their management parallels that of small-cell lung cancer. Well- to moderately-differentiated NETs are considered to be more indolent but are resistant to most cytotoxic agents. For advanced NETs, therapeutic options focus on controlling the hormonal syndrome and

[1] Yao JC, Hassan M, Phan A, et al (2008) One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumours in 35,825 cases in the United States. J Clin Oncol; 26: 3063-72.
[2] Halfdanarson TR, Rabe KG, Rubin J, et al (2008)] Pancreatic neuroendocrine tumours (PNETs): incidence, prognosis and recent trend toward improved survival. Ann Oncol; 19: 1727-33.

inhibiting tumour growth. Recently, sunitinib has been approved in the EU for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults. Other treatments include somatostatin analogues (SSAs), angiogenesis inhibitors, chemotherapy, and radiotherapy, interferon (IFN), surgical resection and embolisation of hepatic metastases. Peptide receptor radiotherapy (radiolabeled therapy) represents an additional option available in a limited number of medical centres. At present, surgery is the only curative treatment for NETs.

Everolimus, a derivative of rapamycin, acts as a signal transduction inhibitor, selectively inhibiting the mammalian target of rapamycin (mTOR), a key serine-threonine kinase regulating protein synthesis and ultimately cell growth, cell proliferation, angiogenesis, and survival. mTOR is a component in the PI3K/AKT /mTOR pathway known to be deregulated in numerous human cancers. A role for everolimus has been suggested by the regulatory role of mTOR in cell growth, metabolism and protein translation, coupled with the observation that the PI3K/mTOR pathway is activated by insulin-like growth factor-1 (IGF-1) in NETs. Everolimus may play a role in inhibiting hormonal hypersecretion, cell growth, and NET proliferation by interrupting the IGF-1/PI3K/mTOR signalling cascade.

On 05/06/2007 and 14/11/2007, orphan designations EU/3/07/449 and EU/3/07/488 were granted by the European Commission for everolimus for the conditions of renal cell carcinoma and gastro-entero-pancreatic neuroendocrine tumours, respectively. Further to request of the applicant, these orphan designations were withdrawn from the Community Register on 18/07/11.

Everolimus is approved in Europe since 2003 under the trade name of Certican for the prophylaxis of organ rejection in adult patients following allogeneic renal or cardiac transplant.

Afinitor (everolimus) was approved on 3 August 2009 for the "treatment of patients with advanced renal cell carcinoma (RCC) whose disease has progressed on or after treatment with VEGF-targeted treatment".

In this type II variation (C.I.6.a), the Marketing Authorisation Holder (MAH) of Afinitor applied for a new indication in the treatment of patients with advanced gastro-entero-pancreatic neuroendocrine tumours.

Further to the assessment as discussed below, the approved indication was the following: Afinitor is indicated for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease. Consequently, sections 4.1, 4.4, 4.5, 4.8 and 5.1 of the Summary of Product Characteristics and the Package Leaflet have been updated. Annex II has been updated to the new template. The MAH also took the opportunity to update the product information in line with the QRD template (version 7.3.1) and minor corrections.

No orphan medicinal product is authorised for the same therapeutic indication.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) N° 1901/2006 as amended, the application included EMA decisions (P/2/2007 and P/67/2008) on the granting of product specific waivers.

1.2. Non-Clinical aspects

No new non-clinical study reports have been submitted by the MAH to support the application. The MAH provided an addendum to the non-clinical overview containing bibliographical references based on published literature.

Ecotoxicity / environmental risk assessment

Due to absence of local, national or international databases in EU, the MAH has performed a calculation of PEC based on prevalence data of NETs in white populations in US. Assuming a maximum prevalence of malignant and benign NETs in the EU population of 4.7 per 10000 persons, the calculated PECsurface water was 0.00235 µg/L which is below the trigger value of 0.01 µg/L for a Phase II Tier A assessment. Considering that everolimus has previously been approved for an orphan indication (renal cell carcinoma, prevalence 1.04 in 10000) the resulting PEC values have been added, resulting in an overall PEC of 0.00461 µg/L. The environmental risk assessment report was updated to include the predicted maximum annual amount of everolimus in the transplantation setting (Certican) for the next five years. The resulting overall PECsurface water was 0.00474, which was below the trigger for a Phase II – Tier A assessment. Therefore, a Phase II assessment is not considered necessary.

Discussion and conclusion on non-clinical aspects

No new non-clinical study reports have been submitted by the MAH. This is considered acceptable for the proposed new indication. The non-clinical review performed by the MAH contains recent publications on the pharmacology of everolimus. The anti-angiogenic properties of everolimus are well-known. In addition, a number of studies showing *in vitro* activity of everolimus with neuroendocrine cell lines have been presented. However, other data have shown a poor correlation between *in vitro* and *in vivo* sensitivities to everolimus.

With regards to the environmental risk assessment, the predicted environmental concentration of everolimus is below the trigger value for a phase II assessment (10 ng/l) when considering the prevalence of renal cell carcinoma and advanced pancreatic neuroendocrine tumours in the EU population. Referring to the logKow of 4, PBT assessment is not necessary. The medicinal product Afinitor is unlikely to represent a risk for the environment when considering the prevalence of renal cell carcinoma and advanced pancreatic neuroendocrine tumours (Afinitor was designated as orphan drug in each of the indication, the orphan designations were subsequently withdrawn) and that the trigger PEC surface value including the transplantation indication was below the trigger for a Phase II –Tier A assessment.

In conclusion, the available non-clinical information is considered sufficient for the new indication and the current information provided in the SmPC is considered adequate.

1.3. Clinical aspects

The application is based on the clinical development program of everolimus in advanced neuroendocrine tumours CNETs that consists in three studies:

Source of data	Details
Controlled trials	2 phase III trials: • C2324, a pivotal confirmatory phase-III study in patients with advanced pancreatic NET (pNET) • C2325, a pivotal confirmatory phase-III study in patients with advanced NET with a history of carcinoid tumour
Uncontrolled trials	• C2239, a supportive phase-II study in patients with advanced pNET

Long-term data	Open-label extensions to the controlled phase III trials and uncontrolled trial
Other sources of efficacy	Publication on an uncontrolled, investigator-initiated study

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

According to the MAH, all trials in the everolimus NET clinical development program were conducted in full compliance with Good Clinical Practice (GCP).

The CHMP were consulted on the clinical development of everolimus for the treatment of patients with advanced NET. The CHMP issued a scientific advice and considered the extent of the program to be acceptable, and agreed to the study design of the pivotal phase-III trials. For the pivotal study C2324 the clinical endpoints, and their methods of assessment are considered appropriate.

1.3.1. Clinical Pharmacology

Pharmacokinetics

To support the current application for the treatment of advanced NET, pharmacokinetic data were obtained from the two pivotal phase-III studies, C2324 and C2325 (Table 1). Additional predose everolimus pharmacokinetic samples were collected in the supportive phase-II study (C2239).

Table 1: Summary of studies with clinical pharmacology component

Study No.	Study objectives, population	No of patients	Treatment duration	Everolimus dose / day
[C2324]	PK and exposure-response relationship in patients with advanced pancreatic NET	Total: 410 E: 207 Placebo: 203	Until disease progression, unacceptable toxicity, or death, or discontinuation for any other reason	10 mg once daily
[C2325]	PK and exposure-response relationship in patients with advanced carcinoid tumour Effects of everolimus on octreotide exposure	Total: 429 E: 216 [a] Placebo: 213 [a]	Until disease progression, unacceptable toxicity, or death, or discontinuation for any other reason	10 mg once daily
[C2239 Update]	PK and exposure-response relationship in patients with advanced pancreatic NET	Total: 160 Stratum 1: 115 Stratum 2: 45 [a]	Until disease progression, unacceptable toxicity, or death, or discontinuation for any other reason	10 mg once daily

E Everolimus; NET Neuroendocrine tumour; PK Pharmacokinetics
[a] Patients were also administered depot octreotide (Sandostatin LAR)

Pharmacokinetics in Target population

Everolimus 5 mg tablets were used in the two phase III studies C2324 and C2325. These 5-mg tablets were quantitatively and qualitatively equivalent to the approved Afinitor formulation.

Patients in study C2324 received everolimus 10 mg/day plus best supportive care. The everolimus dose could be reduced to 5 mg/day. Full PK profiles were obtained from a small subset of patients. Predose (C_{min}) samples were drawn in other patients.

The pharmacokinetic results from the patients with full PK profiles are shown in Table 2.

Table 2: Summary statistics of everolimus PK parameters at steady state after 10 mg daily doses – Study C2324

Regimen	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}t\ last}$ (ng.h/mL)	CL/F (L/h)	C_{min} (ng/mL)
10 mg QD (n=7)	62.4 ± 18.5 (29.6%)	1.17 (0.5-24.0)	594 ± 313 (52.8%)	20.2 ± 7.7 (38.2%)	9.80 ± 4.95 (50.5%)
10 mg QD [a] (n=5)	56.3 ± 11.8 (20.9%)	1.17 (0.5-2.0)	430 ± 79 (18.3%)	24.0 ± 4.9 (20.3%)	8.80 ± 3.78 (42.9%)

Values are mean ± standard deviation (coefficient of variation %) with the exception of t_{max} where median (range) is summarized

[a] Excluding data from the 2 patients with atypically high concentrations at 24-hours postdose

The mean and median everolimus C_{min} values over the 10 first cycles in this study are shown in Table 3 for Study C2324. Inter-subject variability in C_{min} ranged from 39.6% to 127%.

Table 3: Mean +/- SD and median everolimus C_{min} (ng/ml) at steady state in the first 10 study cycles after 10 mg or 5 mg daily doses – C2324

	10 mg daily dose (n=175)				5 mg daily dose (n=41)			
Cycle	n	Mean	SD	Median	n	Mean	SD	Median
1	120	14.8	11.2	11.9	1			
2	114	13.3	9.6	11.7	1			
3	108	12.7	8.9	9.9	12	8.5	4.654	6.72
4	88	13.3	9.2	11.3	15	7.82	4.854	6.36
5	85	13.6	11.8	10.0	18	7.07	4.022	5.92
6	78	13.4	10.7	10.5	17	8.54	4.309	6.42
7	67	13.6	8.9	10.9	19	7.37	5.071	5.69
8	64	13.3	7.8	11.2	19	6.54	3.158	5.71
9	65	13.1	8.1	10.7	20	8.59	4.921	7.48
10	55	13.7	10.4	11.0	17	7.52	4.274	6.23

Summary statistics of the PK parameters of the patients with full PK profiles at steady-state for Study C2325 are summarized in Table 4.

Table 4: Everolimus PK parameters at steady state in patients with pancreatic NET – Study C2325

Regimen	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}\tau}$ (ng.h/mL)	CL/F (L/h)	C_{min} (ng/mL)
10 mg QD (n=5)[a]	74.8 ± 33.6 (44.9%)	0.50 (0.50-5.0)	578 ± 243 (42.1%)	19.5 ± 6.8 (35.0%)	9.47 ± 2.59 (27.3%)

Values are mean ± standard deviation (coefficient of variation %) with the exception of t_{max} where median (range) is summarized

[a] n = 9 for C_{max}, C_{min}, and t_{max}

Inter-subject variability (CV%) of C_{min} after the 10 mg daily dose ranged from 32.9% (n=7 in Cycle 33) to 130% (n=19 in Cycle 21). Dose reduction to 5 mg/day was required for a number of patients. Mean and median C_{min} after the 10 and 5 mg doses are shown in Table 5.

Table 5: Mean +/- SD and median everolimus C_{min} (ng/ml) at steady state in the first 10 study cycles after daily doses of 10 mg or 5 mg – Study C2325

	10 mg daily dose (N=170)				5 mg daily dose (N=63)			
Cycle	n	Mean	SD	Median	n	Mean	SD	Median
1	114	17.9	14.2	12.3				
2	106	16.5	16.3	11.3	1			
3	104	15.8	13.3	11.4	13	7.88	5.09	6.00
4	73	19.2	20.5	11.1	19	6.59	3.69	4.79
5	73	16.9	18.4	11.7	23	6.42	4.28	4.83
6	59	15.6	10.7	12.7	23	6.72	4.57	5.20
7	55	17.0	12.5	12.9	25	6.15	3.56	4.81
8	55	18.3	21.1	11.7	22	7.23	6.48	5.24
9	45	19.2	18.5	11.7	24	7.38	5.91	5.05
10	40	16.0	11.6	12.2	21	7.88	6.06	5.45

Pharmacokinetic interaction studies

- Effects of co-administration of somatostatin analogues on everolimus exposure

Octreotide is a synthetic octapeptide analogue of somatostatin. The potential of octreotide at different concentrations to inhibit human CYP enzyme activity was assessed in pooled human liver microsomes *in vitro*. Low to no inhibition by octreotide (up to 20 µM) and no time-dependent inhibition of all CYP enzymes tested was observed.

The effect of somatostatin or somatostatin analogue therapy on everolimus pharmacokinetics *in vivo* was evaluated in the Phase III Study C2324 and the Phase II study C2239, by comparing everolimus C_{min} levels from patients with and without concomitant somatostatin therapy.

Patients in study C2239 received everolimus 10 mg/day as monotherapy (Stratum 1) or with octreotide every 28th day (Stratum 2). The normal dose was 20 mg every 28th day, but it could be reduced to 10 mg or increased to 30 mg every 28th day. Serial blood samples for steady-state full everolimus PK profile were collected from 11 patients at pre-dose, 0.5, 1, 2, 5 and 24 hours post-dose. Pre-dose blood sample for concentration determination of octreotide in plasma were collected for all patients on Day 1 of every cycle at predose and on Day 15 of Cycle 1. The effect of octreotide on the C_{min} of everolimus was assessed by comparing the log-transformed C_{min} of everolimus in Stratum 1 and Stratum 2 at Cycle 1 Day 15 by using an ANOVA model adjusted for the stratum as a fixed effect (Table 6).

Table 6: Summary statistics of everolimus C_{min} in stratum 1 and statum 2 on cycle 1 Day 15 (full analysis) and cycle day 15 (sensitivity analysis) – Study C2239

Cycle 1 – Day 15 (full analysis)

	Stratum 1	Stratum 2
N	92	30
Mean ± SD (CV%)	15.7 ± 15.82 (100.6%)	17.3 ± 18.08 (104.5%)
Geometric mean	11.3	13.1
Geometric mean and 90% CI of C_{min} ratio (Stratum 2/Stratum 1)	1.16 [0.88;1.54]	

Cycle Day 15 (sensitivity analysis)

	Stratum 1	Stratum 2
N	36	4
Mean ± sd (CV%)	14.3 ± 17.57 (123.0%)	13.7 ± 4.16 (30.3%)
Geometric mean	9.6	13.3
Geometric mean ratio and 90% CI (Stratum 2/Stratum 1)	1.38 [0.63;3.03]	

- Effect of co-administration of everolimus on octreotide exposure

Coadministration of everolimus and depot octreotide in Study C2325 increased octreotide C_{min} with a geometric mean ratio (everolimus/placebo) of 1.47 (90% CI: 1.32, 1.64).

Special populations

Race

In study C2324, it appeared that mean C_{min} values after the 5 mg and 10 mg daily dose were slightly higher in Japanese patients (8.87 ng/ml, 95%CI 6.93-11.3; 17.0 ng/ml, 95%CI 14.1-20.5) than in non-Japanese patients (5.45 ng/ml, 95%CI 4.95-5.98; 10.8 ng/ml, 95%CI 10.0-11.5).

Pharmacodynamics

Pharmacodynamic data were derived from Studies C2324 and C2325.

Exposure-response relationship

Results of the Cox regression of the relationship between risk ratio for PFS and time-normalised everolimus Cmin suggested a trend of longer PFS with higher everolimus C_{min} values for studies C2324 (risk ratio = 0.73 [95% CI: 0.50-1.08]) and C2325 (risk ratio 0.66; 95% CI: 0.40 to 1.08).

The relationship between clinically notable adverse events and everolimus Cmin was explored using Kaplan-Meier methodology. Time-normalised everolimus C_{min} was divided into three categories, corresponding to trough concentrations of < 10 ng/mL, 10-30 ng/mL, and > 30 ng/mL. The relationship between everolimus Cmin and time to first clinically notable AE was also investigated by a Cox regression model including the log-transformed time-normalised everolimus C_{min} as a covariate. For study C2324, the Kaplan-Meier and Cox regression analyses of everolimus C_{min} and safety variables showed a trend for stomatitis/oral mucositis/ulcers and renal events. However, for study C2325, no notable adverse events were observed.

Exposure-response relationship - Co-administration of everolimus and octreotide

The correlation between tumour size reduction and octreotide C_{min} values was evaluated using a marginal generalised linear mixed model. The analysis showed a probability of tumour size reduction with odds ratios of 0.992 and 0.999, for a 1.5 fold increase in octreotide Cmin in the everolimus and placebo arm, respectively.

The relationship between octreotide exposure and PFS was investigated by a Cox regression model. In the everolimus plus octreotide treatment arm, the overall impact of octreotide log-C_{min} on PFS was not statistically significant (p=0.17). In the placebo arm, where octreotide was administered alone, the impact of octreotide exposure on PFS was not statistically significant (HR = 0.89; 95% CI: 0.76 - 1.03, p=0.13). In addition, the HRs for PFS when increasing the octreotide concentration by 1.5-fold in the

octreotide resistant patients and in patients who were octreotide-naive or responding to octreotide compared to the total patient population is shown in Table 7.

Table 7: Cox regression analysis of the impact of a 1.5-fold increase in octreotide C_{min} on PFS (placebo and octreotide arm) – Study C2325

	Hazard ratio (95% CI)		
Fold increase in C_{min}	**Total population**	**Excluding octreotide resistant patients[a]**	**Octreotide resistant patients[b]**
1.5 X octreotide C_{min}	0.89 (0.76, 1.03)	0.83 (0.68, 1.02)	0.94 (0.75, 1.19)

(a) PFS events = 80; censored events = 66
(b) PFS events = 28; censored events = 22

The hazard ratios on PFS for a 1.5-fold increase (4 ng/mL to 6 ng/mL) in octreotide C_{min} at the everolimus C_{min} of 2.5, 5, and 10 ng/mL and a 2-fold increase (5 ng/mL to 10 ng/mL) in everolimus C_{min} at the octreotide C_{min} of 4 and 6 ng/mL are summarized in Table 8.

Table 8: Cox regression analysis of the impact of a 1.5-fold increase in octreotide C_{min} and a 2-fold increase in everolimus C_{min} on PFS – Study 2325

Fold increase in C_{min}	Hazard ratio	95% CI	At C_{min} of octreotide or everolimus
1.5 X octreotide C_{min}	1.29	1.00 - 1.65	At everolimus C_{min} of 10 ng/mL
1.5 X octreotide C_{min}	0.95	0.64 - 1.40	At everolimus C_{min} of 5 ng/mL
1.5 X octreotide C_{min}	0.70	0.35 - 1.37	At everolimus C_{min} of 2.5 ng/mL
2 X everolimus C_{min}	0.74	0.46 - 1.18	At octreotide C_{min} of 6 ng/mL
2 X everolimus C_{min}	0.54	0.32 - 0.92	At octreotide C_{min} of 4 ng/mL

Discussion and Conclusion on clinical pharmacology

The MAH has provided pharmacokinetic data in support of the applied indication obtained from the two pivotal phase-III studies (C2324 and C2325) and data from additional predose pharmacokinetic samples that were collected from the supportive phase-II study (C2239). No new information has been provided on the absorption, distribution, metabolism, excretion of everolimus. The recommendation in the SmPC to take everolimus consistently either with or without food remained the same. In study C2324, the recommendation was to take everolimus at the same time as or immediately after a meal. This was not expected to have led to a clinically relevant difference in overall exposure to everolimus and outcome in the trial. With regards to pharmacokinetic in special population, the recommendation remained the same as in the currently approved indication. Everolimus dose should be reduced to 5 mg in patients with moderate hepatic impairment (Child-Pugh class B) and is not recommended for use in patients with severe hepatic impairment (Child-Pugh class C).

The MAH presented data on pharmacokinetic interactions. In studies C2324 and C2325, C_{min} values were analysed separately for patients with or without co-administration of CYP3A4/PgP substrates, inhibitors, or inducers. In general, there were no apparent differences between the groups for CYP3A4 substrates, inhibitors and inducers. These results suggest that octreotide is not expected to inhibit the metabolic clearance of co-medications metabolized by CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. However, due to small sample sizes, especially for inhibitors of CYP3A4 or Pgp, data should be interpreted with caution. The current SmPC warnings and interactions for CYP3A4 and Pgp are considered appropriate for the NET indication.

The data from study C2325 indicate no expected effect of octreotide on CYP-mediated clearance of everolimus as mean steady state levels of octreotide were reported to be around 5 ng/ml or approximately 0.005 µM. In study C2324, the minor increase seen in everolimus C_{min} at concomitant

octreotide administration is not considered clinically relevant. A new sentence in section 4.5 of the SmPC has been included to highlight the lack of significant effect of octreotide on the efficacy response to everolimus patients with advanced NETs "Co-administration of everolimus and depot octreotide increased octreotide C_{min} with a geometric mean ratio (everolimus/placebo) of 1.47. A clinically significant effect on the efficacy response to everolimus in patients with advanced neuroendocrine tumours could not be established."

In a Cox regression model, relationship between HR for PFS and everolimus C_{min} suggested an increase in PFS with higher C_{min} values. The impact of octreotide and everolimus exposure on HR of PFS was analogous to one another when the drugs were coadministered. The risk for progression was consistently reduced for a 2-fold increase in everolimus exposure at both octreotide C_{min} of 4 and 6 ng/mL, suggesting that everolimus maintained a positive impact on PFS irrespective of octreotide exposure.

The relationship between log-transformed everolimus C_{min} and biomarkers CgA and 5-HIAA were investigated by fitting a linear mixed model to CgA and 5-HIAA values separately. There was no apparent relationship between log-transformed C_{min} and the biomarkers CgA.

1.3.2. Clinical Efficacy

Dose response study

There were no study reports submitted on dose response.

Main study

Study C2324: A randomized double-blind phase III study of RAD001 10 mg/d plus best supportive care versus placebo plus best supportive care in the treatment of patients with advanced pancreatic neuroendocrine tumor (NET)

The study C2324 was a phase-III, international, multicenter, double-blind, randomised, placebo-controlled study.

Methods

Study Participants

The key inclusion criteria were:

- Advanced (unresectable or metastatic) biopsy-proven pancreatic NET
- Radiological documentation of progression of disease within 12 months prior to randomisation. If the patient received anti-tumour therapy during the past 12 months, he/she must have radiological documentation of progression of disease while on or after receiving the therapy.
- Confirmed low-grade or intermediate-grade neuroendocrine carcinoma
- Measurable disease per RECIST using triphasic computed tomography (CT) scan or multiphase MRI for radiologic assessment

The key exclusion criteria were:

- Poorly-differentiated neuroendocrine carcinoma, high-grade neuroendocrine carcinoma, adenocarcinoid, goblet cell carcinoid, or small-cell carcinoma
- Cytotoxic chemotherapy, immunotherapy, or radiotherapy within 4 weeks prior to randomisation
- Hepatic artery embolization within the last 6 months (1 month if there were other sites of measurable disease), or cryoablation/radiofrequency ablation of hepatic metastasis within 2 months of enrolment
- Prior therapy with mTOR inhibitors (sirolimus, temsirolimus, everolimus)

Treatments

A 10 mg dose of everolimus or matching placebo was given by continuous oral daily dosing of two 5 mg tablets.

Concomitant treatments

Best supportive care deemed necessary for patients by the treating physician included the use of somatostatin analogs; proton-pump inhibitors (PPI) for gastrinoma; diazoxide, or feeding tube for insulinoma; pancrealipase (lipase, protease, and amylase) for patients with pancreatic exocrine insufficiency; and non-specific anti-diarrheals (loperamide); opiates; etc.

Treatment duration and cross-over

Patients were treated with blinded study treatment (everolimus or matching placebo) until objective tumour progression was documented per RECIST (by the investigator) or until any other protocol-specified reason for treatment discontinuation was determined. During the double-blind phase of the study, tumour assessments were performed by the local radiologist and sent for central review until the patient started a new anti-tumour therapy.

Once radiological disease progression was documented by the local radiologist, the treating oncologist could unmask the treatment. Patients in the placebo group could be offered treatment with everolimus. For the open-label phase of the study, tumour assessments were required to be assessed locally and were not sent for central review. All patients who received open-label treatment with everolimus continued to have safety and efficacy assessments as in the double-blind phase of the trial.

Patients who had not progressed at the time of discontinuation of study treatment were to be followed with tumour assessments. The study site was to continue to send radiological assessments for central review. In addition, radiological assessments were to be sent for central review for patients with disease progression (as assessed by the local investigator) who had not started on new anti-tumour therapy (including open label everolimus).

In addition, patients were followed for safety until at least 28 days after study treatment discontinuation and for survival until the final survival analysis.

Objectives

Primary objective

- To determine whether treatment with everolimus 10 mg/d plus BSC prolongs PFS compared to treatment with placebo plus BSC in patients with advanced pancreatic NET.

Secondary objectives

- To evaluate the effect of everolimus on other tumour endpoints: objective response rate (ORR) (complete response [CR] or partial response [PR]), response duration

- To compare overall survival (OS) between the study arms
- To determine the safety and tolerability of everolimus (10 mg/d) in patients with advanced pancreatic NET
- To characterize the pharmacokinetics (PK) of everolimus in pancreatic NET indications
- Changes from baseline in chromogranin A (CgA), neuron specific enolase (NSE), pancreatic polypeptide, gastrin, glucagon, and vasoactive intestinal peptide (VIP); and insulin, proinsulin, and c-peptide in patients with insulinomas
- To characterize pre-treatment tumour samples by immunohistochemical and genetic analyses indicating activation of the mTOR pathway
- To assess the relationship between everolimus steady state levels, tumour response, and chromogranin A (CgA) response (50% decrease from baseline)
- To determine the effects of everolimus on plasma anti-angiogenic molecules e.g. , vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), placental growth factor (PLGF), soluble vascular endothelial growth factor receptor 1(VEGFR1), and soluble vascular endothelial growth factor receptor 2 (VEGFR2)

Outcomes/endpoints

The primary efficacy variable of this study was **progression-free survival** (PFS) defined as the time from the date of randomisation to the date of first documented disease progression or death due to any cause. If a patient had not progressed or had died at the date of the analysis cut-off or when he/she received any further anti-cancer therapy, PFS was censored at the time of the last tumour assessment before the cut-off date or the other anti-cancer therapy date. For the primary analysis, PFS was based on data from the local investigator assessment in accordance with RECIST.

The secondary efficacy endpoints were **overall survival** (OS) and **objective response rate** (ORR). Overall survival was defined as the time from date of randomisation to the date of death due to any cause. If a patient was not known to have died, survival was censored at the date of last contact. Safety assessments consisted of monitoring and collecting all AEs, SAEs with their severity and relationship to study drug, and pregnancies. They included the regular monitoring of hematology, blood chemistry and urine and regular assessments of vital signs, and physical examination.

In order to monitor for non-infectious pneumonitis, chest X-Rays or chest CT were performed at screening, at regular intervals during efficacy assessments and as clinically indicated, and at the end of the study. Additional workup included pulmonary function tests and bronchoscopy with bronchoalveolar lavage (BAL) and/or biopsy was performed per the discretion of the investigator if there was evidence of non-infectious pneumonitis.

Efficacy assessments - Radiologic tumour assessment

Tumours evaluations were done at baseline and every 12 weeks while on study. Investigators were required to use the same methods for assessment and technique.

All patients at baseline were to have at least one measurable disease lesion by triphasic CT or multiphase MRI. The multiphase CT scan consisted of 3 specific timepoints: pre-contrast, arterial, and finally portal venous phase; multiphase MRI was acceptable for patients in whom contrast was contraindicated. Measurable disease lesions were to have at least one dimension with the longest diameter 20 mm using conventional techniques or 10 mm with spiral CT scan (with minimum lesion

size no less than double the slice thickness). All baseline, evaluations were performed as closely as possible to initiating study treatment, never more than 28 days before treatment began.

Each centre had a designated radiologist or other physician who was responsible for the interpretation of radiological evaluations, i.e., the same radiologist/physician performed the evaluation.

Response and progression evaluation were performed according to RECIST and were based exclusively on radiological findings obtained at tumour evaluations.

If there was clinical suspicion of disease progression at any time, a physical examination and radiological confirmation were required to be performed promptly rather than waiting for the next scheduled radiological assessment. Initially, radiological evaluations were performed by a local radiologist or responsible physician and all were reviewed by an Independent Central Radiology Review as specified within the Independent Review Charter.

Sample size

Using an unstratified log-rank test at the one-sided 2.5% significance level, a total of 282 events was needed to allow for at least 92.6% power to demonstrate a 33% risk reduction (HR for everolimus/placebo of about 0.67, as calculated from an anticipated 50% increase in median PFS, from 6 to 9 months in the everolimus group compared to the placebo group).

It was planned that a uniform accrual of approximately 23 patients per month over 74 weeks with a minimum follow-up of 39 weeks for a total of 352 patients would be required to obtain 282 PFS events. It was estimated that 10% of patients would be lost to follow-up; thus, a total sample size of 392 patients were to be randomised.

Randomisation

Randomisation was stratified by whether or not patients received prior cytotoxic chemotherapy and by WHO performance status (0 versus 1 or 2) at baseline.

Blinding (masking)

Randomisation data were kept strictly confidential until the time of unblinding at progression of disease and at time of final analyses, and were not accessible to anyone involved in the conduct of the study with the exception of the Independent Data Monitoring Committee who performed an ongoing safety review; and the identity of the treatments was concealed by use of study drugs (everolimus and matching placebo) that were all identical in packaging, labelling, appearance, and schedule of administration.

Statistical methods

The primary analysis was performed in the FAS population and based on the local investigator assessments. The primary analysis was analysed using a stratified one-sided log-rank test. The test was stratified by whether or not patients had received prior cytotoxic chemotherapy and by WHO performance status (0 versus 1 or 2) at baseline.

PFS was censored at the last adequate tumour assessment if one of the following occurred:

(a) absence of an event; (b) the event occurred after a new anticancer therapy (including open-label everolimus) was given; or (c) the event occurred after two or more missing tumour assessments. PFS was not censored for any other reason; and in particular, not for a discontinuation from the study medication (for any reason).

The treatment effect estimate, i.e., hazard ratio (HR) with the 95% CI, for the primary analysis based on local investigator assessments of PFS, was obtained from a stratified Cox proportional hazard model (unadjusted for any other covariates) using the same stratification factors as the log-rank test.

By default, if disease progression or death was documented after one single missing tumour assessment, the actual event date of disease progression/death was used for the PFS event date. If disease progression was documented after two or more missing tumour assessments, the PFS time of these patients was censored at the date of the last tumour assessment with overall lesion response of CR, PR, or stable disease.

Results

Participant flow

Patient disposition for the full analysis set is presented in Table 9.

Table 9: Patient disposition in the Full Analysis Set (FAS) – Study C2324

Patient disposition	Everolimus 10 mg N=207 n (%)	Placebo N=203 n (%)	Total N=410 N (%)
Ongoing	**66 (31.9)**	**26 (12.8)**	**92 (22.4)**
Discontinued	**141 (68.1)**	**177 (87.2)**	**318 (77.6)**
Main cause of discontinuation			
Disease progression	92 (44.4)	163 (80.3)	255 (62.2)
Adverse event(s)	36 (17.4)	7 (3.4)	43 (10.5)
Patient withdrew consent	4 (1.9)	4 (2.0)	8 (2.0)
Death	4 (1.9)	3 (1.5)	7 (1.7)
Protocol deviation	4 (1.9)	0	4 (1.0)
Lost to follow-up	1 (0.5)	0	1 (0.2)

Recruitment

Patients were enrolled from 82 sites worldwide in the US, Canada, Brazil, EU (Germany, Spain, Belgium, France, Greece, Italy, Netherlands, Slovakia (Slovak Republic), Sweden, United Kingdom), Switzerland and Asia (Japan, Republic of Korea, Taiwan and Thailand).

Conduct of the study

The study protocol was amended once (on 22 January 2010). The primary efficacy analysis in Study C2324, which was originally planned as PFS as per independent central radiology review (IRC), was formally amended to PFS as per the local investigator assessment (INV) following a blinded review of the number of PFS events.

Independent Central Radiology Review included radiology assessment by an Independent Review Committee (IRC) and - following amendment 1 - as needed, by an Independent Adjudication Committee (IAC).

- The IRC was constituted by teams of two board-certified independent radiologists who reviewed radiological images from investigational sites on an ongoing basis. Discrepancies between the two central readers were adjudicated.

- The IAC was constituted by a board certified radiologist and oncologist both with experience in NET. Adjudication was performed in a blinded manner so that committee members had no knowledge of study treatment assignment or origin of RECIST evaluations (i.e., local or central).

Major protocol violations concerned the lack of documented progression or lack of documentation of well to moderately differentiated histology (Table 10).

Table 10: Summary of major protocol deviations (FAS) – Study C2324

Protocol deviation type	Everolimus 10 mg N=207 n (%)	Placebo N=203 n (%)	Total N=410 N (%)
Total no. of patients	6 (2.9)	7 (3.4)	13 (3.2)
Inclusion/exclusion criterion			
No documented evidence of PD within 12 months	1 (0.5)	6 (3.0)	7 (1.7)
Poorly differentiated carcinoma	3 (1.4)	1 (0.5)	4 (1.0)
Incomplete documentation of pancreatic NET	1 (0.5)	0	1 (0.2)
No measurable lesion	1 (0.5)	0	1 (0.2)

PD = Disease progression; NET = Advanced neuroendocrine tumor

Baseline data

Demographic characteristics are shown in Table 11.

Table 11: Demographic characteristics (FAS) – Study C2324

Demographic characteristic	Everolimus 10 mg N=207 n (%)	Placebo N=203 n (%)	Total N=410 N (%)
Age (years)			
Mean (standard deviation)	57.1 (12.2)	56.2 (11.4)	56.6 (11.8)
Median	58.0	57.0	58.0
Range	23 – 87	20 – 82	20 – 87
Age group			
< 65 years	146 (70.5)	153 (75.4)	299 (72.9)
≥ 65 years	61 (29.5)	50 (24.6)	111 (27.1)
Gender			
Male	110 (53.1)	117 (57.6)	227 (55.4)
Female	97 (46.9)	86 (42.4)	183 (44.6)
Race			
Caucasian	156 (75.4)	166 (81.8)	322 (78.5)
Asian	40 (19.3)	34 (16.7)	74 (18.0)
Black	9 (4.3)	2 (1.0)	11 (2.7)
Other	2 (1.0)	1 (0.5)	3 (0.7)
Ethnicity			
Other	160 (77.3)	163 (80.3)	323 (78.8)
Japanese	23 (11.1)	19 (9.4)	42 (10.2)
Chinese	12 (5.8)	7 (3.4)	19 (4.6)
Hispanic/Latino	8 (3.9)	11 (5.4)	19 (4.6)
Mixed	4 (1.9)	1 (0.5)	5 (1.2)
Indian (Indian subcontinent)	0	2 (1.0)	2 (0.5)

Disease characteristics at baseline are shown in Tables 12 and 13.

Table 12: Disease characteristics (FAS) – Study C2324

Patient or disease characteristic	Study C2324 N=410			
	Everolimus N=207 n (%)		Placebo N=203 n (%)	
Primary site of cancer				
Pancreas	201	(97.1)	200	(98.5)
Other	6	(2.9)	3	(1.5)
Histology				
Neuroendocrine carcinoma	145	(70.0)	149	(73.4)
Pancreatic islet cell tumor	60	(29.0)	51	(25.1)
Carcinoid	2	(1.0)	2	(1.0)
Other	0		1	(0.5)
Histologic grade				
Well differentiated	170	(82.1)	171	(84.2)
Moderately differentiated	35	(16.9)	30	(14.8)
Unknown	2	(1.0)	2	(1.0)
Time from initial diagnosis				
≤ 6 months	24	(11.6)	33	(16.3)
> 6 months to ≤ 2 years	65	(31.4)	43	(21.2)
> 2 years to ≤ 5 years	54	(26.1)	81	(39.9)
> 5 years	64	(30.9)	46	(22.7)
Time between disease progression and randomization				
≤ 1 month	73	(35.3)	61	(30.0)
> 1 month to ≤ 2 months	43	(20.8)	53	(26.1)
> 2 months to ≤ 3 months	30	(14.5)	29	(14.3)
> 3 months to ≤ 12 months	58	(28.0)	54	(26.6)
> 12 months	3	(1.4)	1	(0.5)
Missing	0		5	(2.5)
WHO performance status				
0	139	(67.1)	133	(65.5)
1	62	(30.0)	64	(31.5)
2	6	(2.9)	6	(3.0)

WHO World Health Organization

Table 13: RECIST tumour-specific characteristics (FAS) – Study C2324

Tumor-specific characteristic	Study C2324 N=410			
	Everolimus N=207 n (%)		Placebo N=203 n (%)	
Number of organs involved				
1	51	(24.6)	62	(30.5)
2	85	(41.1)	64	(31.5)
≥ 3	70	(33.8)	77	(37.9)
Organ type involved				
Liver	190	(91.8)	187	(92.1)
Pancreas	92	(44.4)	84	(41.4)
Lymph nodes	68	(32.9)	73	(36.0)
Lung	28	(13.5)	30	(14.8)
Bone	13	(6.3)	29	(14.3)
Other	53	(25.6)	56	(27.6)

Prior antineoplastic therapy at baseline is shown in Table 14.

Table 14: Prior antineoplastic therapy (FAS) – Study C2324

Prior therapy	Study C2324 N=410			
	Everolimus N=207 n (%)		Placebo N=203 n (%)	
Any prior antineoplastic therapy [a]	**207**	**(100.0)**	**203**	**(100.0)**
Any prior surgery [b]	**207**	**(100.0)**	**203**	**(100.0)**
Biopsy	154	(74.4)	146	(71.9)
Other	121	(58.5)	119	(58.6)
Any prior medications [c]	**119**	**(57.5)**	**118**	**(58.1)**
Chemotherapy	104	(50.2)	102	(50.2)
Targeted therapy	10	(4.8)	14	(6.9)
Immunotherapy	7	(3.4)	9	(4.4)
Hormonal therapy	2	(1.0)	2	(1.0)
Other	20	(9.7)	26	(12.8)
Any prior radiotherapy	**47**	**(22.7)**	**41**	**(20.2)**

[a] Any prior antineoplastic therapy includes patients who have had medication, radiotherapy, or surgery
[b] A patient with multiple surgery types is counted only once within 'Any prior surgery'
[b] A patient with multiple therapy types is counted only once within 'Any prior medications'

Numbers analysed

Four hundred ten (410) patients were randomised and constituted the Full Analysis Set (FAS); 207 patients were assigned to treatment with everolimus and 203 patients were randomised to placebo. Out of 410 patients, 407 (99.3%) patients received at least one dose of study medication and had at least one post-baseline safety assessment and thus, constituted the Safety Set. The other 3 patients either withdrew informed consent or were randomised incorrectly and did not receive study medication. The analysis sets (FAS, Safety, per-protocol set [PP], open label set [OL]) are described in Table 15.

Table 15: Analysis Sets – Study C2324

Analysis population	Everolimus 10 mg n (%)	Placebo n (%)	Total N (%)
Full Analysis Set (FAS)	207 (100.0)	203 (100.0)	410 (100.0)
Safety Set (Safety)	204 (98.6)	203 (100.0)	407 (99.3)
Per-protocol Set (PP)	182 (87.9)	189 (93.1)	371 (90.5)
Open-label Set (OL)	1 (0.5)	148 (72.9)	149 (36.3)

Within the FAS, 39 patients were excluded from the PP Set due to: insufficient everolimus exposure (n=18), unknown overall response based on investigator review (n=17), or major protocol deviations (n=13). An additional 26 patients who were not major protocol deviators were also excluded from the PP Set.

There were 149 (36.3%) patients who entered the open-label phase and thus constituted the OL; all but one of these patients received placebo during the double-blind phase.

Outcomes and estimation

The primary efficacy analysis was conducted when 274 PFS events had occurred in the double-blind treatment phase of the study (corresponding to a data cut-off date of 28-Feb-2010). Median study follow-up was 17.0 months.

- **Primary endpoint**

The results for the analyses of PFS per local investigator assessment, adjudicated central radiology and central radiology review are presented in the Table 16.

Table 16: Comparison of PFS between everolimus and placebo (FAS) – Study C2324

Progression-free survival	Study C2324 N=410					
	Local (INV)		Adjudicated (IAC)		Central (IRC)	
	E n=207	Placebo n=203	E n=207	Placebo n=203	E n=207	Placebo n=203
No of PFS events (n [%])	109 (52.7)	165 (81.3)	95 (45.9)	142 (70.0)	87 (42.0)	112 (55.2)
Progression	95 (45.9)	158 (77.8)	84 (40.6)	132 (65.0)	76 (36.7)	102 (50.2)
Death	14 (6.8)	7 (3.4)	11 (5.3)	10 (4.9)	11 (5.3)	10 (4.9)
Censored (n [%])	98 (47.3)	38 (18.7)	112 (54.1)	61 (30.0)	120 (58.0)	91 (44.8)
Median PFS (months)	11.04	4.60	11.40	5.39	13.67	5.68
Improvement in median PFS (months)	6.44		6.01		7.99	
Hazard ratio	0.35		0.34		0.38	
95% confidence interval	0.27, 0.45		0.26, 0.44		0.28, 0.51	
p-value	<0.001 ($1.2x10^{-17}$)		<0.001 ($2.9x10^{-16}$)		<0.001 ($2.6x10^{-11}$)	

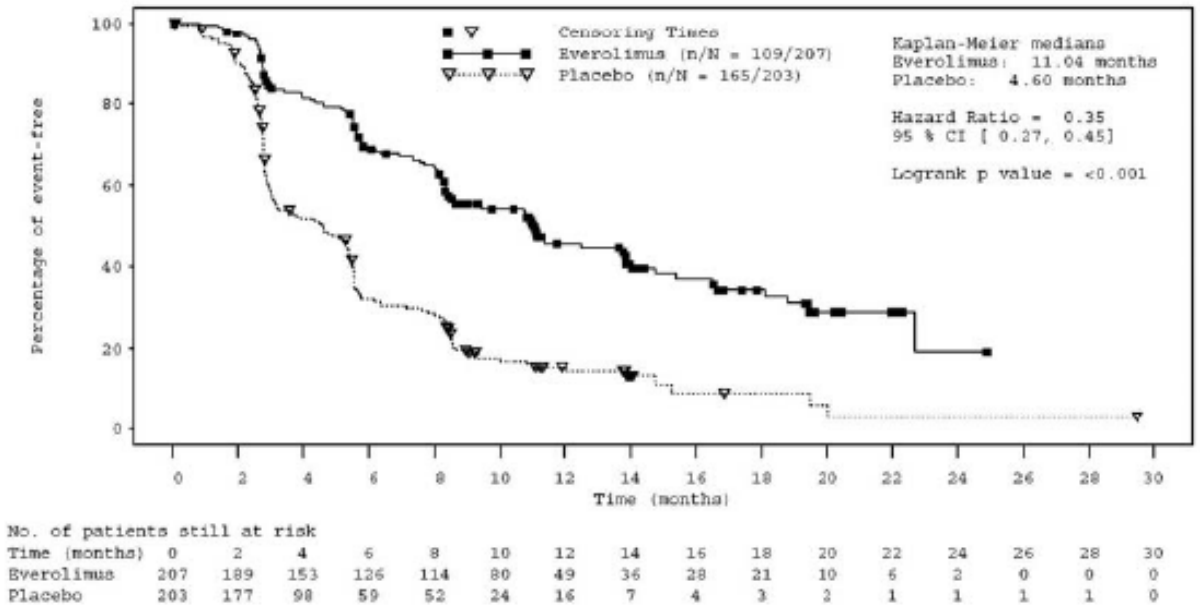
Adjudicated - Independent adjudicated central assessment; Central - Independent central radiology review; E - Everolimus; Local - Local investigator assessment; PFS - Time from randomization to disease progression or death

Hazard ratios of < 1.00 show everolimus has a favorable outcome compared with placebo. Hazard ratios are obtained from a stratified unadjusted Cox model.
P-values are obtained from a stratified one-sided log-rank test

The Kaplan-Meier plots for the primary analysis is presented in Figure 1.

Figure 1: Kaplan-Meier plot of PFS for local investigator assessment, independent adjudicated central assessment and central radiology review (FAS) – Study C2324

Local investigator assessment (INV)



No. of patients still at risk

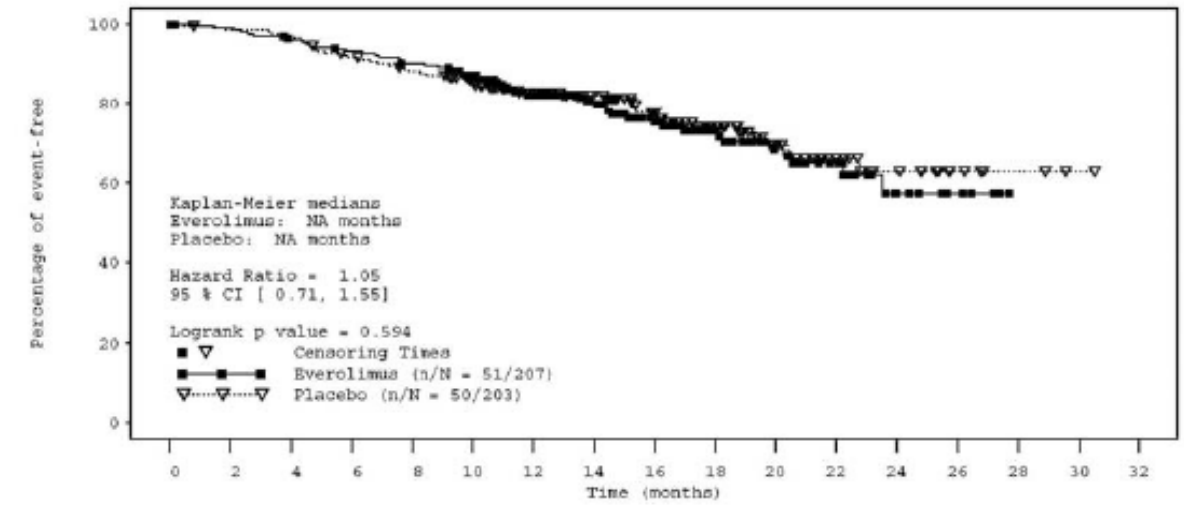
Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
Everolimus	207	189	153	126	114	80	49	36	28	21	10	6	2	0	0	0
Placebo	203	177	98	59	52	24	16	7	4	3	2	1	1	1	1	0

- **Secondary endpoints**

Overall survival

No statistically significant difference was observed between the two treatment groups in terms of OS (Figure 2 and Table 17). Crossover occurred for 148 of the 203 patients (72.9%) initially randomised to placebo prior to the data cut-off (and for 148 of 163 patients receiving placebo therapy who had disease progression and were thus eligible for crossover).

Figure 2: Kaplan-Meier plot of overall survival (FAS) – Study C2324



No. of patients still at risk

Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32
Everolimus	207	203	195	188	181	162	122	97	74	53	38	26	9	5	0	0	0
Placebo	203	199	195	183	174	160	129	109	87	63	42	23	16	7	3	1	0

An updated overview of overall survival at different cut-off dates is presented in Table 17.

Table 17: Overview of overall survival (FAS) – Study C2324

Endpoint	Hazard ratio (95% confidence interval)	1-sided p-value
Overall survival – (data cutoff 28-Feb-2010)		
Primary analysis	1.05 (0.71, 1.55)	0.594
Cox model adjusting for prespecified baseline covariates	1.03 (0.70, 1.53)	
Overall survival 90-Day Safety Update (data cutoff 03-Jun-2011)		
Primary analysis	0.99 (0.68, 1.43)	--
Cox model adjusting for prespecified baseline covariates	0.97 (0.66, 1.41)	--
Overall survival CHMP requested update (data cutoff 23-Feb-2011)		
Primary analysis	0.89 (0.64, 1.23)	--
Cox model adjusting for prespecified baseline covariates	0.87 (0.62, 1.21)	--

Overall response rate

A summary of the overall responses for INV, IAC and IRC are presented in Table 18.

Table 18: Summary of the objective response rate and best overall response categories by treatment group for INV, IAC, IRC (FAS) – Study C2324

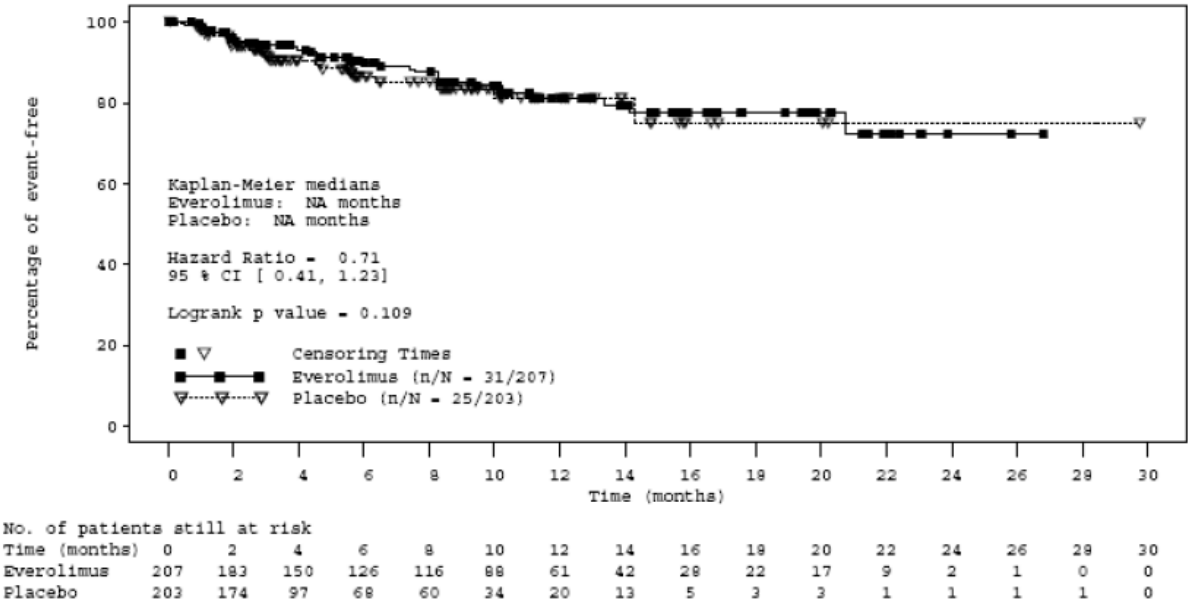
Objective response	Study C2324 N=410					
	Local (INV)		Adjudicated (IAC)		Central (IRC)	
	E n=207	Placebo n=203	E n=207	Placebo n=203	E n=207	Placebo n=203
Objective response rate (n [%])	10 (4.8)	4 (2.0)	6 (2.9)	1 (0.5)	5 (2.4)	1 (0.5)
Complete response	0	0	0	0	0	0
Partial response	10 (4.8)	4 (2.0)	6 (2.9)	1 (0.5)	5 (2.4)	1 (0.5)
Stable disease (n [%])	151 (72.9)	103 (50.7)	163 (78.7)	120 (59.1)	167 (80.7)	135 (66.5)
Progressive disease (n [%])	29 (14.0)	85 (41.9)	23 (11.1)	72 (35.5)	20 (9.7)	56 (27.6)
Unknown (n [%])	17 (8.2)	11 (5.4)	15 (7.2)	10 (4.9)	15 (7.2)	11 (5.4)
95% CI ORR	2.3, 8.7	0.5, 5.0	1.1, 6.2	0.0, 2.7	0.8, 5.5	0.0, 2.7
p-value	0.091		0.065		0.114	

Adjudicated - Independent adjudicated central assessment; Central - Independent central radiology review; E - Everolimus; Local - Local investigator assessment; ORR = CR + PR

Performance status

There were relatively few events of WHO performance status deterioration as of the data cut-off date (Figure 3). Medians were not reached for either treatment group. The resultant HR estimate was 0.71 (95% CI: 0.41-1.23) although the difference was not statistically significant (p=0.109).

Figure 3: Kaplan-Meier plot of time to deterioration of WHO performance status (PS) by treatment group – Study C2324



No. of patients still at risk

Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
Everolimus	207	183	150	126	116	88	61	42	28	22	17	9	2	1	0	0
Placebo	203	174	97	68	60	34	20	13	5	3	3	1	1	1	1	0

Biomarkers

Baseline levels of CgA and NSE were characterized relative to the ULN. 'Elevated' CgA was defined as levels exceeding 2 x ULN.

CgA levels at baseline

- Patients with elevated baseline CgA: HR 0.31; 95% CI: 0.21-0.46; p<0.001 (n=187)
- Patients without elevated baseline CgA: HR 0.38; 95% CI: 0.27-0.53; p<0.001 (n=218)

NSE levels at baseline

- Patients with elevated baseline NSE: HR 0.35; 95% CI: 0.21-0.59; p<0.001 (n=104)
- Patients without elevated baseline NSE: HR 0.34; 95% CI: 0.25-0.47; p<0.001 (n=293)

Five biomarkers (bFGF, VEGF, PLGF, sVEGFR1, and sVEGFR2) related to the angiogenesis pathway were analyzed. Results indicated a decrease of sVEGFR2 levels in everolimus-treated patients relative to placebo at Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 4, Day 1.

Ki 67

Everolimus-treated patients presented a trend towards longer PFS as per local investigator assessment relative to placebo-treated patients in all three subgroups. HR estimates were 0.36 (95% CI: 0.10-1.33), 0.59 (95% CI: 0.24-1.44), and 0.36 (95% CI: 0.16-0.82) in the Ki 67 < 2%, Ki 67 > 2% to < 5%, and Ki 67 > 5% subgroups, respectively.

Ancillary analyses

Several sensitivity analyses were performed and are shown in Table 19.

Table 19: Subgroup analysis for PFS based on local investigator assessment by treatment arm (FAS) – Study C2324

Subgroup variable	Total no. patients (n)	Everolimus 10 mg N=207 Median PFS (months) 95% CI	Placebo N=203 Median PFS (months) 95% CI	P value [1]	Hazard ratio [2] [95% CI]
Age group					
< 65 years	299	11.04 [8.34, 13.86]	4.47 [2.96, 5.39]	<0.001	0.39 [0.29, 0.53]
≥ 65 years	111	11.14 [8.02, NA]	4.90 [2.92, 5.55]	<0.001	0.36 [0.22, 0.58]
Gender					
Male	227	11.04 [8.31, 14.00]	4.60 [3.12, 5.52]	<0.001	0.41 [0.30, 0.58]
Female	183	11.01 [8.18, 16.49]	3.25 [2.79, 5.39]	<0.001	0.33 [0.23, 0.48]
Race					
Caucasian	322	10.84 [8.31, 11.40]	4.60 [3.12, 5.42]	<0.001	0.41 [0.31, 0.53]
Asian	74	19.45 [8.31, NA]	3.81 [2.69, 8.31]	<0.001	0.29 [0.15, 0.56]
Black	11	NA [2.33, NA]	NA [2.79, NA]	0.325	0.58 [0.05, 6.38]
Other	3	NA [2.60, NA]	2.10 [NA, NA]	0.079	0 [0.00, NA]
WHO performance status					
0	279	13.80 [10.78, 16.59]	5.39 [3.19, 5.68]	<0.001	0.39 [0.28, 0.53]
1 or 2	131	8.31 [6.90, 11.17]	3.02 [2.79, 4.76]	<0.001	0.30 [0.20, 0.47]
Geographic region					
Europe	156	10.81 [7.98, 12.52]	4.60 [2.92, 5.55]	<0.001	0.47 [0.32, 0.69]
America	185	11.01 [8.11, 14.75]	4.63 [3.02, 5.49]	<0.001	0.36 [0.25, 0.52]
Asia	69	19.45 [8.31, NA]	2.86 [2.69, 8.34]	<0.001	0.29 [0.14, 0.56]
Liver involvement at baseline					
Yes	377	10.94 [8.31, 13.80]	3.78 [2.96, 5.36]	<0.001	0.37 [0.28, 0.47]
No	33	NA [5.62, NA]	7.79 [2.83, 8.49]	0.025	0.36 [0.13, 1.05]
Tumor grade [3]					
Well differentiated	341	10.94 [8.31, 13.67]	4.60 [3.06, 5.49]	<0.001	0.41 [0.31, 0.53]
Moderately differentiated	65	16.59 [6.34, NA]	3.02 [2.50, 5.36]	<0.001	0.21 [0.11, 0.42]
Prior chemotherapy					
Yes	189	11.01 [7.69, 14.75]	3.02 [2.83, 4.57]	<0.001	0.34 [0.24, 0.49]
No	221	11.10 [8.41, 15.38]	5.49 [3.65, 5.72]	<0.001	0.41 [0.29, 0.58]
Prior long-acting somatostatin analog					
Yes	203	11.17 [8.34, 13.86]	3.65 [2.83, 5.45]	<0.001	0.40 [0.28, 0.57]
No	207	10.81 [8.18, 15.38]	4.90 [2.99, 5.49]	<0.001	0.36 [0.25, 0.51]

CI = Confidence interval; NA = Not applicable; PFS = Progression-free survival
[1] P value is obtained from the stratified one-sided log-rank test.
[2] Hazard ratio is obtained from stratified unadjusted Cox model.
[3] For tumor grade, n=170 for well-differentiated and n=35 for moderately-differentiated.

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

The MAH did not submit data from analysis across trials.

Clinical studies in special populations

The MAH did not submit clinical study reports in special populations.

Supportive studies

C2325: A randomized, double-blind, placebo-controlled, multicenter phase III study in patients with advanced carcinoid tumour receiving Sandostatin LAR Depot and RAD001 10 mg/d or Sandostatin LAR Depot and placebo

The study C2325 was a randomised, double-blind, Phase III study in patients with advanced NETs with a history of carcinoid tumours (advanced [unresectable or metastatic] biopsy-proven carcinoid tumour). Participants in the study were receiving everolimus or placebo with concomitant octreotide depot 30 mg intramuscularly (i.m.) every 28 days. After documented radiological progression, patients could be unblinded by the investigator: placebo randomised patients were able to cross over to receive open-label everolimus plus depot octreotide. The inclusion/exclusion criteria for the study participants, and the study design were similar to those of study C2324. The treatment regimen included the mandatory concomitant octreotide treatment. The planned primary endpoint was PFS as assessed by IRC, key secondary endpoints were PFS as assessed by the local investigator, overall survival and overall response rate and safety.

A sample size of 390 randomised patients was originally planned. As a consequence of a marked slowing in PFS events and issues with informative censoring affecting the central radiology PFS, the final analysis was performed at a predefined fixed calendar time-point (02 April 2010 cut-off) irrespective of the number of PFS events observed and based on a the assessment of the IAC. Four hundred ten (429) patients were randomised and constituted the FAS. Of these, 216 patients were assigned to treatment with everolimus + octreotide and 213 patients were randomised to placebo + octreotide. Of these, 426 (99.3%) patients received at least one dose of study medication and had at least one post-baseline safety assessment and thus, constituted the Safety Set.

In general, demographic and disease characteristics were relatively well-balanced between the two treatment groups, with the exception of important baseline prognostic factors such as WHO performance status 1 and lung carcinoids which were more frequently enrolled in the everolimus arm compared to the placebo arm (Table 20).

Table 20: Disease baseline characteristics – Study C2325

Disease characteristic	Everolimus plus depot octreotide N=216 n (%)		Placebo plus depot octreotide N=213 n (%)		All patients N=429 n (%)	
Primary site of cancer						
Small intestine	111	(51.4)	113	(53.1)	224	(52.2)
Lung	33	(15.3)	11	(5.2)	44	(10.3)
Colon	14	(6.5)	14	(6.6)	28	(6.5)
Pancreas	11	(5.1)	15	(7.0)	26	(6.1)
Liver	7	(3.2)	11	(5.2)	18	(4.2)
Rectum	5	(2.3)	6	(2.8)	11	(2.6)
Stomach	4	(1.9)	6	(2.8)	10	(2.3)
Head and neck	1	(0.5)	0		1	(0.2)
Peritoneum	0		2	(0.9)	2	(0.5)
Kidney	0		1	(0.5)	1	(0.2)
Spinal cord	0		1	(0.5)	1	(0.2)
Other	30	(13.9)	32	(15.0)	62	(14.5)
Missing	0		1	(0.5)	1	(0.2)
Histology/cytology						
Carcinoid	216	(100.0)	213	(100.0)	429	(100.0)
Histologic grade						
Well differentiated	166	(76.9)	175	(82.2)	341	(79.5)
Moderately differentiated	38	(17.6)	30	(14.1)	68	(15.9)
Poorly differentiated	1	(0.5)	1	(0.5)	2	(0.5)
Unknown	11	(5.1)	6	(2.8)	17	(4.0)
Missing	0		1	(0.5)	1	(0.2)
Time since initial diagnosis						
≤ 6 months	15	(6.9)	23	(10.8)	38	(8.9)
> 6 months to ≤ 2 years	45	(20.8)	53	(24.9)	98	(22.8)
> 2 years to ≤ 5 years	68	(31.5)	51	(23.9)	119	(27.7)
> 5 years to ≤ 10 years	60	(27.8)	61	(28.6)	121	(28.2)
> 10 years	27	(12.5)	23	(10.8)	50	(11.7)
Missing	1	(0.5)	2	(0.9)	3	(0.7)
Time between disease progression and randomization						
≤ 1 month	80	(37.0)	84	(39.4)	164	(38.2)
> 1 month to ≤ 2 months	38	(17.6)	38	(17.8)	76	(17.7)
> 2 months to ≤ 3 months	33	(15.3)	36	(16.9)	69	(16.1)
> 3 months to ≤ 12 months	60	(27.8)	53	(24.9)	113	(26.3)
> 12 months	4	(1.9)	1	(0.5)	5	(1.2)
Missing	1	(0.5)	1	(0.5)	2	(0.5)
WHO performance status *						
0	118	(54.6)	140	(65.7)	258	(60.1)
1	84	(38.9)	62	(29.1)	146	(34.0)
2	14	(6.5)	10	(4.7)	24	(5.6)
Missing	0		1	(0.5)	1	(0.2)

* Value reported at pre-treatment visit. If no value was reported, the Cycle 1 Day 1 value was used

There were some imbalances in the proportion of patients offered subsequent somatostatin analogues therapy post-disease progression. There were 59.6% and 42.1% of patients randomised to placebo and everolimus, respectively that received depot octreotide.

Outcomes and estimation

The primary endpoint PFS (as per IAC assessment) required the boundary for statistical significance of p=0.0246 due to changes in the analyses plan. The primary analysis did not meet this primary endpoint with one-sided p=0.026. The results of the primary and secondary efficacy endpoints (PFS by IAC, PFS by INV and PFS by IRC, OS and ORR) for both treatment arms are presented in Figure 4, 5, and Table 21 and 22.

Figure 4: Kaplan-Meier plot for progression-free survival for everolimus and placebo (FAS) – Study C2325

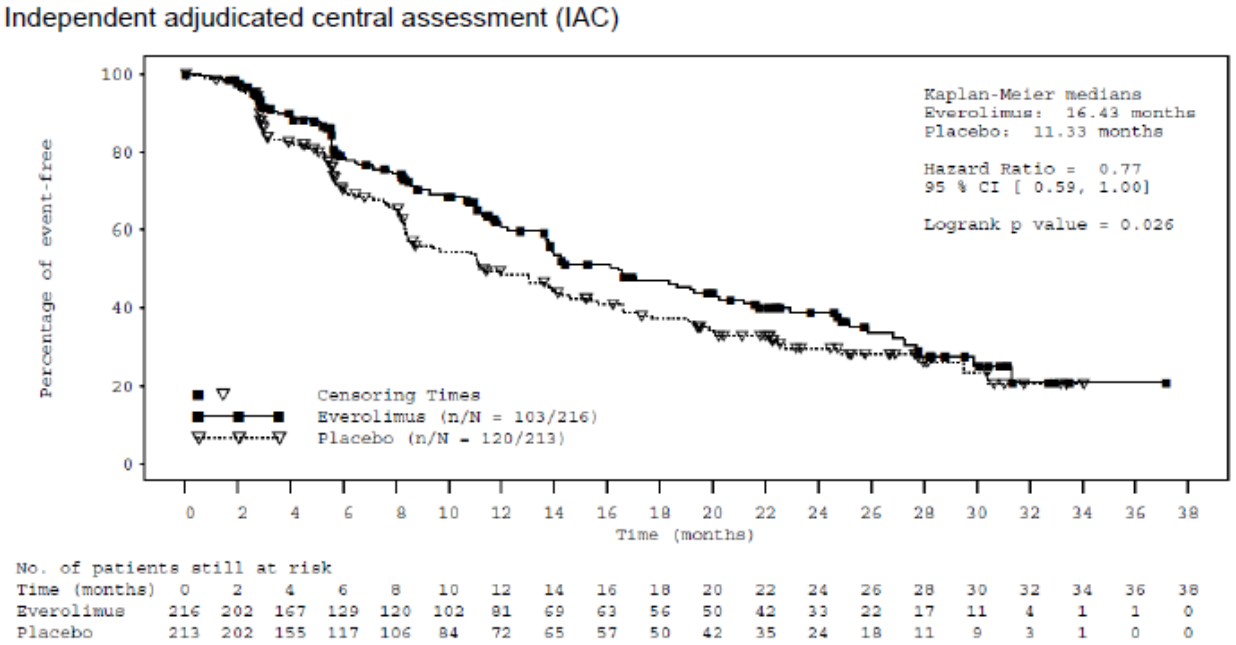


Table 21: Comparison of PFS between everolimus and placebo (Full Analysis Set) – Study C2325

Progression-free survival	Study C2325 N=429					
	Adjudicated (IAC)		Local (INV)		Central (IRC)	
	E n=216	Placebo n=213	E n=216	Placebo n=213	E n=216	Placebo n=213
No of PFS events (n [%])	103 (47.7)	120 (56.3)	128 (59.3)	156 (73.2)	105 (48.6)	103 (48.4)
Progression	69 (31.9)	101 (47.4)	103 (47.7)	136 (63.8)	72 (33.3)	87 (40.8)
Death	34 (15.7)	19 (8.9)	25 (11.6)	20 (9.4)	33 (15.3)	16 (7.5)
Censored (n [%])	113 (52.3)	93 (43.7)	88 (40.7)	57 (26.8)	111 (51.4)	110 (51.6)
Median PFS (months)	16.43	11.33	11.99	8.61	14.88	13.90
Improvement in median PFS (months)	5.10		3.38		0.98	
Hazard ratio	0.77		0.78		0.93	
95% confidence interval	0.59, 1.00		0.62, 0.98		0.71, 1.22	
p-value	0.026		0.018		0.298	

Adjudicated - Independent adjudicated central assessment; Central - Independent central radiology review; E - Everolimus plus depot octreotide; Local - Local investigator assessment; PFS - Time from randomization to disease progression or death; Placebo - Placebo plus depot octreotide

Hazard ratios of < 1.00 show everolimus has a favorable outcome compared with placebo. Hazard ratios are obtained from an unstratified unadjusted Cox model.
P-values are obtained from an unstratified one-sided log-rank test.

Figure 5: Overall survival for everolimus and placebo (FAS) – Study C2325

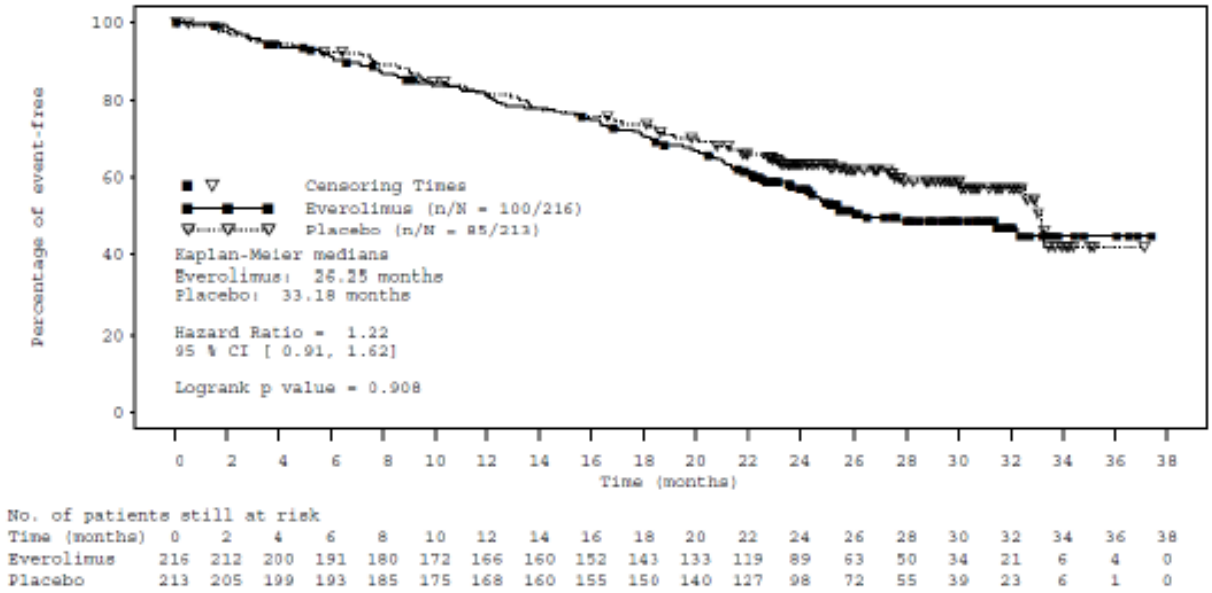


Table 22: Objective response rate for everolimus and placebo (FAS) – Study C2325

Objective response	Study C2325 N=429					
	Adjudicated (IAC)		Local (INV)		Central (IRC)	
	E n=216	Placebo n=213	E n=216	Placebo n=213	E n=216	Placebo n=213
Objective response rate (n [%])	5 (2.3)	4 (1.9)	7 (3.2)	5 (2.3)	4 (1.9)	3 (1.4)
Complete response	0	0	0	0	0	0
Partial response	5 (2.3)	4 (1.9)	7 (3.2)	5 (2.3)	4 (1.9)	3 (1.4)
Stable disease (n [%])	182 (84.3)	172 (80.8)	172 (79.6)	160 (75.1)	182 (84.3)	175 (82.2)
Progressive disease (n [%])	9 (4.2)	26 (12.2)	17 (7.9)	36 (16.9)	10 (4.6)	23 (10.8)
Unknown (n [%])	20 (9.3)	11 (5.2)	20 (9.3)	12 (5.6)	20 (9.3)	12 (5.6)
95% CI ORR	0.8, 5.3	0.5, 4.7	1.3, 6.6	0.8, 5.4	0.5, 4.7	0.3, 4.1
p-value	0.509		0.395		0.508	

Adjudicated - Independent adjudicated central assessment; Central - Independent central radiology review; E - Everolimus plus depot octreotide; Local - Local investigator assessment; ORR = CR + PR; Placebo - Placebo plus depot octreotide

Open-label phase of C2324

A retrospective analysis of patients who crossed-over to everolimus therapy indicated that median PFS following crossover was 11.43 months. These results are similar to the 11.04 months for patients initially randomised to everolimus in the C2324 initial randomised, controlled phase of the study (INV).

Study C2239

Study C2239 is a phase-II, international, multicenter, open-label trial that was designed to valuate the efficacy and safety of everolimus 10 mg in patients with pancreatic NET whose disease had progressed (by RECIST) after failure of prior treatment with cytotoxic chemotherapy.

Stratum 1 consisted of 115 patients receiving everolimus 10 mg. Stratum 2 constituted 45 patients whose disease had progressed during treatment with depot octreotide and who continued with their entry dose of depot octreotide in addition to everolimus 10 mg daily. Objective response rate in Stratum 1 was the primary endpoint. Secondary endpoints were response duration, PFS, and OS. Objective tumour response as per independent central review, based on RECIST, was documented in 9.6% of patients (95% CI: 4.9% –16.5%) from Stratum 1 and 4.4% (95% CI: 0.5% – 15.1%) in Stratum 2, while disease control (corresponding to the proportion of patients with either an objective response or evidence of disease stabilisation) was reported for 77.4% and 84.4% of patients in Stratum 1 and 2, respectively (Table 23).

Table 23: Summary of best overall response as per independent central review (FAS) – Study C2239

Category	Everolimus Stratum 1 N=115				Everolimus plus depot octreotide Stratum 2 N=45			
	Independent central review n (%)		Local investigator n (%)		Independent central review n (%)		Local investigator n (%)	
Objective tumor response rate	11	(9.6)	12	(10.4)	2	(4.4)	5	(11.1)
Complete response	0		0		0		0	
Partial response	11	(9.6)	12	(10.4)	2	(4.4)	5	(11.1)
Stable disease	78	(67.8)	71	(61.7)	36	(80.0)	31	(68.9)
Progressive disease	16	(13.9)	21	(18.3)	0		5	(11.1)
Unknown	10	(8.7)	11	(9.6)	7	(15.6)	4	(8.9)

Median PFS for patients in Stratum 1 was 9.69 months; this was associated with an estimated 2-month PFS rate of 41.7%. Corresponding data for Stratum 2 were 16.7 months and 57.0%, respectively.

Median OS was 24.9 months for Stratum 1 and has yet to be reached for Stratum 2. The estimated 24-month OS rates were 51.1% for Stratum 1 and 54.7% for Stratum 2.

1.3.3. Discussion on clinical efficacy

The pivotal study C2324 was designed to investigate treatment of advanced neuroendocrine tumours with everolimus in patients with well-moderately differenciated tumours. The overall design, inclusion/exclusion criteria and choice of endpoints were considered adequate. The study met the primary endpoint of PFS per local investigator assessment (INV) with a median PFS of 11.4 months (95%CI:8.41-13.86) with everolimus compared with 4.60 months (95%CI:3.06-5.39) for placebo and a HR 0.35 (95%CI 0.27-0.45; p-value <0.001). This was supported by the independent review committee (IRC) analysis of median PFS of 13.67 months with everolimus compared with 5.68 months with placebo (HR 0.38; 95%CI: 0.28-0.51; p<0.001) and independent adjudicated committee (IAC) analyses of median PFS of 11.40 months for everolimus compared with 5.39 months for placebo (HR: 0.34; 95%CI: 0.26-0.44; p<0.001). The ORR was low with everolimus compared with placebo and no difference in overall survival was observed as of the latest cut-off date of 23 February 2011. The subgroup analyses supported the data from the primary endpoint, where PFS in different subgroups was in favour of everolimus treatment. Exploratory investigation of biomarker levels considered as prognostic factors (CgA, NSE, Ki67) in pNET did not reveal any relevant differences or to be predictive of response.

The CHMP expressed a concern for study C2324 over the rationale for the amendment to switch the primary endpoint of PFS from IRC to INV. The CHMP noted that the results for the analysis by INV and the IRC were consistent with the primary analysis and the Kaplan-Meier plots for PFS for all three analyses diverged early, the curves appearing more or less parallel. Furthermore, the HRs for IRC, IAC and INV were all similar. Thus, the CHMP considered that although changing the analysis of the primary endpoint should have been avoided, the effect on PFS was nevertheless reliable and clinically relevant.

Carcinoid and pancreatic neuroendocrine tumours were investigated in separate randomised placebo-controlled trials. The treatment of carcinoid tumours with everolimus was investigated in the prospective study C2325. The study did not show any improvement in PFS (as the increase in PFS was not statistically significant), OS or ORR. There were serious concerns over the discordant results between the INV, IRC, IAC for PFS and the relative decrease in OS in the everolimus treatment arm (difference in median OS of 6.93 months in favour of placebo [HR 1.22; 95% CI: 0.91-1.62; p=0.908]). It is likely that the crossover design of the study has impacted the overall survival results. Imbalances in baseline prognostic factors and subsequent somatostatin analogue therapy after disease progression in favour of the placebo group may have confounded the OS data. Thus, the CHMP was of the opinion that a positive benefit-risk in the carcinoid indication could not be established. A warning in section 4.4 of the SmPC has been included with regards to the safety and efficacy in carcinoid tumours.

1.3.4. Conclusions on the clinical efficacy

The CHMP considered that the results of study C2324, were robust and clinically relevant in the patient population of advanced neuroendocrine tumours.

In the CHMP's view, the efficacy results of study C2325, in a pNET patient population with carcinoid tumours, treated with everolimus in combination with octreotide, did not show a convincing effect on PFS, since analysis by IAC (16.43 months versus 11.33 months in everolimus and placebo treatment, respectively, p=0.026) did not reach statistical significance. In addition, the secondary efficacy endpoints (OS, ORR) did not show differences between the treatment arms and thus, were not considered supportive. Therefore, the results of study C2325 were judged insufficient to support the indication of everolimus treatment in carcinoid cancers.

1.3.5. Clinical Safety

The safety evaluation was based upon data from 850 patients from studies C2239, C2324 and C2325 who were exposed to everolimus at the recommended 10-mg dose, and using the proposed daily treatment regimen (Table 24). Studies C2324 (cut-off date 28 February 2010) and C2325 (cut-off date 02 April 2010) form the basis for safety analyses as these trials were specifically conducted in the indication being applied. Beyond both pivotal phase-III trials, the pooled safety dataset included patients crossed-over to everolimus open-label phase after placebo treatment, as well as patients from supportive study C2239 (cut-off date 01 November 2008).

Table 24: Pooled dataset to support advanced NET indication

Study	Study design, objectives, and population	No of patients receiving 10-mg daily dose regimen
[C2324]	Double-blind, randomized, placebo-controlled, phase-III study (with open-label extension) Safety and efficacy in patients with advanced pancreatic NET	204 + 149 (open-label phase following crossover from placebo)
[C2325]	Double-blind, randomized, placebo-controlled, phase-III study (with open-label extension) Safety and efficacy in patients with advanced carcinoid tumour	215 + 124 (open-label phase following crossover from placebo)
[C2239 Update]	Open-label phase-II study Safety and efficacy in patients with advanced pancreatic NET after the failure of cytotoxic chemotherapy	Stratum 1: 115 Stratum 2: 45
	Total	**850** [a]

[a] Total includes unique patients only – excludes the double-counting of 2 patients who were initially randomized to everolimus but who were subsequently mistakenly entered into the open-label phase of the pivotal studies

Patient exposure

In study C2324, treatment duration was 37.8 weeks for patients receiving everolimus compared with 16.1 weeks for those receiving placebo. In contrast, no difference was evident in treatment duration in Study C2325. From the 271 patients included in the open-label phase, median duration of exposure to everolimus was 28.9 weeks and 26.3 weeks for Studies C2324 and C2325, respectively and 37.8 weeks and 37.0 weeks during the blinded treatment phases. Exposure times of study C2239 were approximately 36 weeks in stratum 1 and 44 weeks in stratum 2.

From the pooled dataset, 312 patients (36.7%) were exposed to everolimus therapy for a period of ≥ 48 weeks with an overall exposure of 693.7 patient-years.

Median dose intensities were 9.8 mg/day and 9.5 mg/day for the everolimus treatment groups in Studies C2324 and C2325, respectively. Exposure and dose intensities were consistent between the Study C2324 and Study C2325 data and the pooled dataset. Exposure information is summarised in Table 25.

Table 25: Exposure to study drug

Exposure	Study C2324		Study C2325		Pooled data
	Everolimus N=204	Placebo N=203	Everolimus N=215	Placebo N=211	Everolimus N=850
Duration of exposure (weeks)					
Mean (standard deviation)	40.9 (27.9)	25.4 (20.3)	53.2 (43.8)	52.1 (41.3)	42.6 (33.6)
Median	37.8	16.1	37.0	36.6	34.8
Range	1.1 to 118.1	0.4 to 132.4	0.6 to 162.6	0.4 to 152.1	0.1 to 162.6
Total patient-year exposure	**159.9**	**98.6**	**219.1**	**210.7**	**693.7**
Cumulative dose (mg)					
Mean (standard deviation)	2394 (1726)	1727 (1401)	3017 (2692)	3542 (2843)	2498 (2087)
Median	2087.5	1130.0	2105.0	2510.0	1842.5
Range	80 to 7420	30 to 9230	40 to 11230	30 to 10650	10 to 11230
Dose intensity (mg/day)					
Mean (standard deviation)	8.6 (2.02)	9.7 (0.79)	8.3 (2.09)	9.7 (0.97)	8.6 (1.97)
Median	9.8	10.0	9.5	10.0	9.7
Range	2.4 to 10.0	5.0 to 10.0	2.8 to 10.0	2.3 to 10.0	2.4 to 10.0

Dose interruptions and dose reductions were more frequent among patients receiving everolimus therapy than for the placebo group. These dose adjustments were primarily attributable to AEs (interruptions: C2324: 52.0% and C2325: 55.3%; reductions: C2324: 27.0% and C2325: 37.7%).

Adverse events

Overall, 99.0% of everolimus-treated patients and 97.5% of the placebo group in Study C2324 and 100.0% of everolimus-treated patients and 96.2% of the placebo group in Study C2325 experienced AEs.

All-causality AEs

System organ classes where there was a higher proportion of everolimus-treated patients reporting events (≥ 10% difference relative to placebo) in either study included:

- skin and subcutaneous tissue disorders
- respiratory, thoracic and mediastinal disorders
- metabolism and nutrition disorders
- blood and lymphatic system disorders
- infections and infestations
- nervous system disorders
- general disorders and administration site conditions
- investigations
- gastrointestinal disorders
- renal and urinary disorders
- injury, poisoning and procedural complications.

Stomatitis, diarrhoea, rash, and fatigue were the most common AEs reported with everolimus therapy (for the pooled dataset) irrespective of relationship (Table 26). Results for the pooled dataset tended to be consistent with those of the studies C2324 and C2325 and are consistent with the known safety profile of everolimus derived from earlier studies in an oncology setting.

Table 26: All-causality adverse events occurring more commonly (by 5% or more) with everolimus

MedDRA preferred term	Study C2324				Study C2325				Pooled data	
	Everolimus N=204		Placebo N=203		Everolimus N=215		Placebo N=211		Everolimus N=850	
	n (%)		n (%)		n (%)		n (%)		n (%)	
Any AE	**202**	**(99.0)**	**198**	**(97.5)**	**215**	**(100.0)**	**203**	**(96.2)**	**844**	**(99.3)**
Stomatitis	110	(53.9)	25	(12.3)	109	(50.7)	24	(11.4)	421	(49.5)
Rash	107	(52.5)	32	(15.8)	88	(40.9)	37	(17.5)	377	(44.4)
Diarrhoea	95	(46.6)	48	(23.6)	114	(53.0)	77	(36.5)	405	(47.6)
Fatigue	89	(43.6)	54	(26.6)	104	(48.4)	91	(43.1)	347	(40.8)
Oedema peripheral	73	(35.8)	24	(11.8)	91	(42.3)	46	(21.8)	277	(32.6)
Nausea	65	(31.9)	66	(32.5)	90	(41.9)	64	(30.3)	314	(36.9)
Headache	61	(29.9)	30	(14.8)	65	(30.2)	48	(22.7)	221	(26.0)
Pyrexia	60	(29.4)	25	(12.3)	43	(20.0)	23	(10.9)	226	(26.6)
Decreased appetite	59	(28.9)	36	(17.7)	64	(29.8)	37	(17.5)	232	(27.3)
Vomiting	58	(28.4)	42	(20.7)	70	(32.6)	43	(20.4)	241	(28.4)
Weight decreased	57	(27.9)	23	(11.3)	59	(27.4)	29	(13.7)	227	(26.7)
Anaemia	45	(22.1)	18	(8.9)	60	(27.9)	22	(10.4)	195	(22.9)
Cough	44	(21.6)	22	(10.8)	60	(27.9)	31	(14.7)	187	(22.0)
Epistaxis	43	(21.1)	3	(1.5)	33	(15.3)	4	(1.9)	143	(16.8)
Pruritus	39	(19.1)	26	(12.8)	41	(19.1)	12	(5.7)	148	(17.4)
Hyperglycaemia	39	(19.1)	20	(9.9)	40	(18.6)	9	(4.3)	161	(18.9)
Dysgeusia	38	(18.6)	10	(4.9)	42	(19.5)	12	(5.7)	154	(18.1)
Asthenia	36	(17.6)	40	(19.7)	51	(23.7)	31	(14.7)	185	(21.8)

MedDRA preferred term	Study C2324				Study C2325				Pooled data	
	Everolimus N=204		Placebo N=203		Everolimus N=215		Placebo N=211		Everolimus N=850	
	n (%)		n (%)		n (%)		n (%)		n (%)	
Dyspnoea	34	(16.7)	15	(7.4)	62	(28.8)	19	(9.0)	167	(19.6)
Abdominal pain upper	32	(15.7)	15	(7.4)	23	(10.7)	28	(13.3)	112	(13.2)
Nasopharyngitis	31	(15.2)	14	(6.9)	19	(8.8)	26	(12.3)	100	(11.8)
Pain in extremity	29	(14.2)	12	(5.9)	32	(14.9)	25	(11.8)	93	(10.9)
Thrombocytopenia	29	(14.2)	2	(1.0)	33	(15.3)	1	(0.5)	107	(12.6)
Nail disorder	27	(13.2)	2	(1.0)	7	(3.3)	0		66	(7.8)
Pneumonitis	27	(13.2)	0		18	(8.4)	2	(0.9)	64	(7.5)
Dry skin	26	(12.7)	12	(5.9)	23	(10.7)	5	(2.4)	99	(11.6)
Arthralgia	25	(12.3)	14	(6.9)	38	(17.7)	28	(13.3)	119	(14.0)
Aphthous stomatitis	25	(12.3)	8	(3.9)	27	(12.6)	3	(1.4)	112	(13.2)
Oropharyngeal pain	22	(10.8)	13	(6.4)	20	(9.3)	6	(2.8)	80	(9.4)
Urinary tract infection	22	(10.8)	11	(5.4)	26	(12.1)	17	(8.1)	87	(10.2)
Dry mouth	22	(10.8)	9	(4.4)	21	(9.8)	6	(2.8)	60	(7.1)
Hypertension	21	(10.3)	9	(4.4)	25	(11.6)	20	(9.5)	82	(9.6)
Hypophosphataemia	20	(9.8)	3	(1.5)	11	(5.1)	5	(2.4)	65	(7.6)
Hypercholesterolaemia	20	(9.8)	1	(0.5)	15	(7.0)	6	(2.8)	61	(7.2)
Diabetes mellitus	20	(9.8)	0		5	(2.3)	5	(2.4)	49	(5.8)
Hypokalaemia	16	(7.8)	5	(2.5)	51	(23.7)	7	(3.3)	107	(12.6)
Ascites	15	(7.4)	4	(2.0)	16	(7.4)	11	(5.2)	49	(5.8)
Neutropenia	14	(6.9)	4	(2.0)	18	(8.4)	3	(1.4)	73	(8.6)
Mouth ulceration	14	(6.9)	4	(2.0)	17	(7.9)	6	(2.8)	51	(6.0)
Pleural effusion	14	(6.9)	3	(1.5)	14	(6.5)	5	(2.4)	47	(5.5)
Haemoglobin decreased	14	(6.9)	2	(1.0)	2	(0.9)	2	(0.9)	28	(3.3)
Hyperlipidaemia	13	(6.4)	2	(1.0)	14	(6.5)	2	(0.9)	38	(4.5)
Upper respiratory tract infection	12	(5.9)	7	(3.4)	27	(12.6)	10	(4.7)	72	(8.5)
Leukopenia	12	(5.9)	4	(2.0)	16	(7.4)	2	(0.9)	49	(5.8)
Chills	12	(5.9)	1	(0.5)	15	(7.0)	8	(3.8)	50	(5.9)
Erythema	11	(5.4)	3	(1.5)	17	(7.9)	4	(1.9)	42	(4.9)
Pneumonia	11	(5.4)	2	(1.0)	16	(7.4)	3	(1.4)	55	(6.5)
Hypocalcaemia	9	(4.4)	6	(3.0)	19	(8.8)	3	(1.4)	48	(5.6)
Hypomagnesaemia	6	(2.9)	0		16	(7.4)	4	(1.9)	28	(3.3)

The most common grade 3 or 4 events in the everolimus treatment groups were hyperglycemia (7.6%), diarrhea (7.4%), abdominal pain (6.9%), anemia (6.8%), and fatigue (6.8%). In comparing the incidence of grade 3 and 4 AEs between everolimus- and placebo-treated patients, events where the respective incidences differed most between the two treatment groups were anemia (Study C2324: +6.3%; Study C2325: +3.7%), stomatitis (+4.9% and +3.7%), hyperglycemia (+4.4% and +6.5%), hypophosphatemia (+4.4% and +2.8%), thrombocytopenia (+3.9% and +4.2%), diarrhea (+2.9% and +5.9%), dyspnea (+2.0% and +5.6%), hypokalemia (+1.5% and +10.7%), and fatigue (+0.4% and +7.9%).

Treatment-related adverse events

The most common adverse events suspected as being drug-related by the investigator where incidence > 20% difference relative to placebo were stomatitis and rash in both studies, and diarrhea in study C2324. ADRs occurring with an incidence ≥ 10% (in the pooled dataset) were stomatitis, rash, diarrhea, fatigue, nausea, decreased appetite, dysgeusia, anemia, weight decreased, peripheral edema, headache, aphthous stomatitis, hyperglycemia, asthenia, vomiting, pruritus, thrombocytopenia, and epistaxis.

The most common grade 3-4 adverse drug reactions, with an incidence ≥ 2%, were hyperglycemia, stomatitis, diarrhea, fatigue, thrombocytopenia, anemia, neutropenia, hypophosphatemia, and asthenia. These events were managable with concomittant medications, non-drug therapies, or dietary interventions.

A summary of treatment-related AEs is presented in Table 27.

Table 27: Treatment-related AEs reported in at least 5% of patients and with a higher rate in everolimus arm (including selected laboratory abnormalities)

System organ class/ MedDRA preferred term	Study C2324						Study C2325					
	Everolimus N=204			Placebo N=203			Everolimus N=215			Placebo N=211		
	All %	Gr 3 %	Gr 4 %	All %	Gr 3 %	Gr 4 %	All %	Gr 3 %	Gr 4 %	All %	Gr 3 %	Gr 4 %
Gastrointestinal disorders												
Stomatitis [a]	64.2	6.9	0	16.7	0	0	61.9	6.5	0	13.7	0	0
Diarrhoea	33.8	3.4	0	9.9	0	0	27.4	6.0	0	15.6	2.4	0
Nausea	20.1	1.5	0	18.2	0	0	19.5	0.5	0	16.1	0.9	0
Vomiting	15.2	0	0	6.4	0	0	10.7	0	0.5	5.2	0.5	0
Dry mouth	7.4	0	0	3.0	0	0	4.7	0	0	1.9	0	0
Abdominal pain	5.4	1.0	0	4.4	0.5	0	4.2	0.9	0	5.7	0.9	0
Skin and subcutaneous tissue disorders												
Rash	48.5	0.5	0	10.3	0	0	37.2	0.9	0	12.3	0	0
Pruritus	14.7	0	0	8.9	0	0	10.7	0	0	3.8	0	0
Nail disorder	11.8	0.5	0	1.0	0	0	2.8	0	0	0	0	0
Dry skin	10.3	0	0	4.4	0	0	7.9	0	0	2.4	0	0
Acne	5.9	0	0	2.0	0	0	2.8	0	0	0.9	0	0
General disorders and administration site conditions												
Fatigue	31.4	1.5	0	14.3	0.5	0	31.2	6.5	0	23.2	2.8	0
Oedema peripheral	20.1	0.5	0	3.4	0	0	13.0	0	0	3.3	0	0
Asthenia	12.7	1.0	0	8.4	1.0	0	10.2	0.9	0	6.6	0.5	0
Pyrexia	10.8	0	0	0	0	0	3.7	0	0	1.9	0	0
Infections and infestations												
Infections [b]	22.5	1.5	1.0	5.9	0.5	0	19.5	4.7	0.5	6.2	0.5	0
Metabolism and nutrition disorders												
Decreased appetite	19.6	0	0	6.9	1.0	0	13.5	0	0	6.2	0	0
Diabetes mellitus	8.3	2.5	0	0	0	0	1.9	0	0	0	0	0
Nervous system disorders												
Headache	19.1	0	0	6.4	0	0	8.8	0	0	8.5	0.5	0
Dysgeusia	17.2	0	0	3.9	0	0	16.7	0.5	0	3.3	0	0
Respiratory, thoracic and mediastinal disorders												
Epistaxis	17.2	0	0	0	0	0	5.6	0	0	0.9	0	0
Pneumonitis [c]	16.7	2.5	0	0	0	0	11.6	2.3	0	0	0	0
Cough	10.8	0	0	1.5	0	0	7.4	0	0	1.9	0	0
Dyspnoea	7.4	1.5	0	3.0	0	0	12.1	1.9	0	1.4	0	0
Investigations												
Weight decreased	15.7	0	0	4.4	0	0	14.9	0.5	0	3.3	0	0
Vascular disorders												
Hypertension	4.9	0.5	0	2.0	0.5	0	5.1	0.9	0	1.9	0.9	0
Clinical chemistry												

System organ class/ MedDRA preferred term	Study C2324						Study C2325					
	Everolimus N=204			Placebo N=203			Everolimus N=215			Placebo N=211		
	All %	Gr 3 %	Gr 4 %	All %	Gr 3 %	Gr 4 %	All %	Gr 3 %	Gr 4 %	All %	Gr 3 %	Gr 4 %
Glucose increased	69.1	16.2	0	36.5	3.9	0.5	61.4	7.9	0	32.2	0.9	0
Cholesterol increased	51.0	0.5	0	6.9	0	0	51.6	1.9	0	11.8	0	0
AST increased	46.1	3.4	0.5	29.1	3.9	0.5	43.7	1.4	0.5	29.9	0.9	0.5
Phosphate decreased	38.2	9.8	0	9.4	3.0	0	52.6	11.2	0.5	14.7	3.8	0
ALT increased	37.3	2.0	0	22.2	1.5	0.5	33.5	1.4	0	28.4	1.4	0
Triglycerides increased	34.8	0	0	4.9	0	0	47.9	0	0	11.8	0	0
Potassium decreased	22.1	2.5	1.5	5.4	0	0	45.6	7.9	0.9	14.2	0.5	0.5
Creatinine increased	16.2	1.0	1.0	9.4	0	0	30.2	2.3	0	12.3	0.5	0
Haematology												
Haemoglobin decreased	64.2	12.3	1.5	27.1	1.5	0.5	74.0	5.1	0.9	32.7	1.4	0.5
Platelets decreased	43.6	2.5	0.5	7.4	0	0	45.6	2.8	0.9	10.9	0.5	0.5
WBC decreased	39.2	2.5	0	6.9	0	0	51.6	2.8	0	16.1	0	0.5
Lymphocytes decreased	38.2	11.8	0.5	16.3	3.9	0	50.2	17.7	0.5	24.2	5.2	0
Neutrophils decreased	27.9	3.4	0.5	14.3	2.0	0	40.0	3.7	0.9	12.8	0	0

[a] Includes stomatitis, aphthous stomatitis, mouth ulceration, and tongue ulceration
[b] Includes all preferred terms within the 'infections and infestations' system organ class
[c] Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary fibrosis, and restrictive pulmonary disease

AST=aspartate aminotransferase; ALT=alanine aminotransferase; WBC=white blood cells

Clinically notable AEs

As a result of signals observed during the conduct of the development program, several AEs requiring close follow-up were identified (Table 28).

Table 28: Clinically notable adverse events irrespective of relationship to treatment

Clinically notable category	Study C2324				Study C2325				Pooled data	
	Everolimus N=204		Placebo N=203		Everolimus N=215		Placebo N=211		Everolimus N=850	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any clinically notable AE	193	(94.6)	144	(70.9)	208	(96.7)	144	(68.2)	801	(94.2)
Stomatitis / oral mucositis / ulcers	138	(67.6)	37	(18.2)	140	(65.1)	31	(14.7)	535	(62.9)
Rash and similar events	119	(58.3)	36	(17.7)	100	(46.5)	40	(19.0)	411	(48.4)
Infections	114	(55.9)	69	(34.0)	139	(64.7)	95	(45.0)	502	(59.1)
Hematopoiesis decreased / cytopenias	86	(42.2)	36	(17.7)	98	(45.6)	32	(15.2)	355	(41.8)
Metabolic events	84	(41.2)	29	(14.3)	68	(31.6)	23	(10.9)	286	(33.6)
Pulmonary events	38	(18.6)	0		25	(11.6)	2	(0.9)	95	(11.2)
Renal events	26	(12.7)	11	(5.4)	33	(15.3)	9	(4.3)	108	(12.7)
Bleeding and thromboembolic events	23	(11.3)	20	(9.9)	49	(22.8)	37	(17.5)	140	(16.5)
Hepatic events	15	(7.4)	15	(7.4)	17	(7.9)	12	(5.7)	64	(7.5)
Intestinal obstruction and/or ileus [a]	6	(2.9)	2	(1.0)	20	(9.3)	14	(6.6)	46	(5.4)

[a] Category not considered in the overall incidence of clinically notable AEs
Studies included: C2324, C2325, and C2239

All categories were reported in a higher proportion in everolimus-treated patients, with the exception of hepatic events which were reported with similar rates. Flushing was found to be uncommon adverse reaction in the safety population with a rate of 3% and 17.4% in everolimus compared to 6.6% and 14.9% in the placebo for studies C2324 and C2325, respectively.

- Non-infectious pneumonitis

Pulmonary events (including pneumonitis and similar events) were diagnosed in 38 and 25 everolimus-treated patients (18.6% and 11.6%) in Studies C2324 and C2325, respectively, and in only 2 patients (0.9%) from the placebo arm of Study C2325. During the course of the study, new or worsening CT/X-ray changes were observed in 30.4% and 11.3% of everolimus- and placebo-treated patients in Study C2324 and in 40.9% and 12.8% in Study C2325, respectively. There was no evidence of progression from grade 2 to grade 3.

Maximum grading (severity) of pulmonary events (pneumonitis and similar) was as follows for the everolimus-treatment groups of the two phase-III pivotal studies:

- grade 1 – 22 patients (5.3%)
- grade 2 – 28 patients (6.7%)
- grade 3 – 12 patients (2.9%)
- grade 4 – 1 patient (0.2%)

Steroid therapy was initiated in 9 of 28 patients with a grade 2 pulmonary event, 11 of 12 with a grade 3 event, and for the single patient with a grade 4 event. Dose adjustments were implemented for 18 patients with grade 2 and 7 patients with a grade 3 event. Resolution was evident for 17 of the 28 patients with grade 2 pulmonary events and for 7 of 12 patients with grade 3 events. Treatment with everolimus was discontinued for 11 patients with a grade 2 pulmonary event and for 3 patients with a grade 3 event.

A summary of pulmonary events is presented in Table 29.

Table 29: Summary of pulmonary events – Studies C2324 and C2325

	Study C2324		Study C2325		Pooled data
	Everolimus N=204 n (%)	Placebo N=203 n (%)	Everolimus N=215 n (%)	Placebo N=211 n (%)	Everolimus N=850 n (%)
AE suspected to be drug related	**34 (16.7)**	**0**	**25 (11.6)**	**0**	**88 (10.4)**
Grade 3	5 (2.5)	0	5 (2.3)	0	12 (1.4)
Grade 4	0	0	0	0	1 (0.1)
AE leading to discontinuation					
Pneumonitis	6 (2.9)	0	3 (1.4)	0	12 (1.4)
Interstitial lung disease	2 (1.0)	0	4 (1.9)	0	7 (0.8)
Lung infiltration	1 (0.5)	0	1 (0.5)	0	2 (0.2)
AE requiring dose adjustment/interruption					
Pneumonitis	14 (6.9)	0	10 (4.7)	0	35 (4.1)
Interstitial lung disease	2 (1.0)	0	2 (0.9)	0	5 (0.6)
Lung infiltration	1 (0.5)	0	0	0	1 (0.1)
Pulmonary fibrosis	1 (0.5)	0	0	0	1 (0.1)

Studies included: C2324, C2325, and C2239

- Infections

Infections were diagnosed in 114 and 139 patients (55.9% and 64.7%) in the everolimus treatment groups of Studies C2324 and C2325 and in 69 and 95 patients (34.0% and 45.0%) from the corresponding placebo arms.

Seven patients from the everolimus treatment arms of Studies C2324 and C2325 reported a total of 9 grade 4 infections (two cases of pneumonia plus single cases of bacterial infection, Enterococcal

bacteremia, Escherichia sepsis, herpes zoster, infection, septic shock, and Staphylococcal sepsis). Grade 3 infections occurred in 38 patients receiving everolimus; those occurring in > 1 patient were pneumonia (n=7), cellulitis (n=5), urinary tract infection (n=4), bacteremia (n=2), gastroenteritis (n=2), and lung infection (n=2). In comparison, 16 placebo-treated patients were diagnosed with grade 3 infections.

Atypical infections including aspergillosis (grade 1 [n=1]) and bronchopulmonary aspergillosis (grade 2 [n=1]; grade 3 [n=2]), pulmonary tuberculosis (grade 2 [n=1]; grade 3 [n=1]), mycobacterium avium complex (grade 1 [n=1]), and reactivation of hepatitis B (n=1; reported 2 months following discontinuation of study drug) were also observed in association with everolimus therapy.

Of the 253 patients receiving everolimus therapy in Studies C2324 and C2325 who were diagnosed with an infection, dose interruption or adjustment was implemented for 46 (11.0%); this was evident most commonly for patients with pneumonia (n=7).

- Stomatitis/oral mucositis

Results from the pooled safety dataset indicate that these events typically subside without dose modification, and 6 patients (0.7%) discontinued therapy as a result of stomatitis with a further 2 (0.2%) discontinuing due to mouth ulcers. Most cases were suspected by the investigator to be treatment-related. Grade 3-4 mucositis-related events were relatively uncommon although they were reported more frequently in the everolimus arm (Table 30).

Table 30: Grading (severity) of stomatitis / oral mucositis / ulcer events irrespective of relationship to treatment

MedDRA preferred term	Study C2324						Study C2325						Pooled data		
	Everolimus N=204			Placebo N=203			Everolimus N=215			Placebo N=211			Everolimus N=850		
	All %	Gr 3 %	Gr 4 %	All %	Gr 3 %	Gr 4 %	All %	Gr 3 %	Gr 4 %	All %	Gr 3 %	Gr 4 %	All %	Gr 3 %	Gr 4 %
Any AE	**67.6**	**6.9**	**0**	**18.2**	**0**	**0**	**65.1**	**6.5**	**0**	**14.7**	**0**	**0**	**62.9**	**5.8**	**0.1**
Stomatitis	53.9	4.9	0	12.3	0	0	50.7	3.7	0	11.4	0	0	49.5	4.0	0.1
Aphthous stomatitis	12.3	0.5	0	3.9	0	0	12.6	0.9	0	1.4	0	0	13.2	0.6	0
Mouth ulceration	6.9	1.5	0	2.0	0	0	7.9	1.4	0	2.8	0	0	6.0	1.1	0
Tongue ulceration	3.9	0	0	0.5	0	0	2.8	0.5	0	0.5	0	0	2.0	0.1	0

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

Studies included: C2324. C2325. and C2239

- Renal events

Increases in proteinuria and serum creatinine concentrations occurred more often in patients receiving everolimus than in those administered placebo in both pivotal studies, although renal failure and acute or chronic renal failure were only reported in small numbers (in both treatment groups). Most cases of elevated creatinine concentrations were of low grade; only 4 patients (1.0%) from the everolimus treatment groups in Studies C2324 and C2325 experienced a grade 3 event.

- Bleeding/thromboembolic AEs

The incidence of bleeding/thromboembolic AEs was greater for patients who received everolimus (Study C2324: 11.3%; Study C2325: 22.8%) relative to those administered placebo (Study C2324: 9.9%; Study C2325: 17.5%). When excluding haemorrhoids, the most common PT within this grouping, the incidence of all other hemorrhagic events was similar between the treatment groups in the two pivotal phase-III studies.

Minor bleeding in terms of epistaxis was reported by 21.1% and 15.3% of patients from the everolimus treatment group in Study C2324 and C2325 (*versus* 1.5% and 1.9% with placebo). Seventy-two of the

76 patients with epistaxis had a grade 1 (mild) event; the remaining 4 patients experienced a grade 2 event. No grade 3 or 4 events were reported.

A summary of key haematopoiesis and cytopenia events is shown in Table 31.

Table 31: Summary of key haematopoiesis decreased / cytopenia events

	Study C2324		Study C2325		Pooled data
	Everolimus N=204 n (%)	Placebo N=203 n (%)	Everolimus N=215 n (%)	Placebo N=211 n (%)	Everolimus N=850 n (%)
AE suspected to be drug related	**76 (37.3)**	**18 (8.9)**	**71 (33.0)**	**19 (9.0)**	**277 (32.6)**
Grade 3	31 (15.2)	5 (2.5)	17 (7.9)	4 (1.9)	85 (10.0)
Grade 4	3 (1.5)	0	2 (0.9)	0	8 (0.9)
AE leading to discontinuation					
Anaemia	1 (0.5)	0	0	0	4 (0.5)
Lymphopenia	1 (0.5)	0	0	0	2 (0.2)
Neutrophil count decreased	1 (0.5)	0	0	0	1 (0.1)
Thrombocytopenia	0	0	2 (0.9)	0	5 (0.6)
Neutropenia	0	0	1 (0.5)	0	1 (0.1)
Haemoglobin decreased	0	0	0	0	1 (0.1)
Leukopenia	0	0	0	0	1 (0.1)
AE requiring dose adjustment/interruption					
Thrombocytopenia	14 (6.9)	0	20 (9.3)	0	57 (6.7)
Anaemia	8 (3.9)	1 (0.5)	8 (3.7)	1 (0.5)	26 (3.1)
Neutropenia	6 (2.9)	1 (0.5)	4 (1.9)	0	25 (2.9)
Leukopenia	2 (1.0)	0	2 (0.9)	0	5 (0.6)
Lymphopenia	1 (0.5)	0	1 (0.5)	1 (0.5)	4 (0.5)
Neutrophil count decreased	1 (0.5)	0	1 (0.5)	0	4 (0.5)
Platelet count decreased	1 (0.5)	0	0	0	3 (0.4)
Haemoglobin decreased	1 (0.5)	0	0	0	2 (0.2)
Aplasia pure red cell	1 (0.5)	0	0	0	1 (0.1)
White blood cell count decreased	1 (0.5)	0	0	0	1 (0.1)
Febrile neutropenia	0	0	1 (0.5)	0	1 (0.1)
Lymphocyte count decreased	0	0	1 (0.5)	0	1 (0.1)
Haemorrhagic anaemia	0	0	0	1 (0.5)	0
Pancytopenia	0	0	0	0	1 (0.1)

- Pulmonary embolism

Pulmonary embolism occurred more frequently in the everolimus arms (about 2.5% vs. 0.5%) and was the cause of death for 2 everolimus-treated patients (0.2%) across the broad NET program and for 1 patient (0.5%) from the comparator arms.

- Key cardiac events

A summary of cardiac events is presented in Table 32.

Table 32: Summary of cardiac events – Studies C2324 and C2325

	Study C2324				Study C2325				Pooled data	
	Everolimus N=204 n (%)		Placebo N=203 n (%)		Everolimus N=215 n (%)		Placebo N=211 n (%)		Everolimus N=850 n (%)	
AE suspected to be drug related [a]	9	(4.4)	1	(0.5)	5	(2.3)	2	(0.9)	22	(2.6)
Grade 3	3	(1.5)	1	(0.5)	3	(1.4)	0		10	(1.2)
Grade 4	0		0		0		1	(0.5)	0	
AE leading to discontinuation [b]										
Cardiac failure	1	(0.5)	1	(0.5)	2	(0.9)	0		3	(0.4)
Cardio-respiratory arrest	1	(0.5)	0		1	(0.5)	0		2	(0.2)
Cardiac arrest	1	(0.5)	0		0		0		2	(0.2)
AE requiring dose adjustment/interruption [b]										
Cardiac failure congestive	1	(0.5)	0		2	(0.9)	0		5	(0.6)
Carcinoid heart disease	0		0		3	(1.4)	1	(0.5)	5	(0.6)
Cardiac failure	0		0		1	(0.5)	0		3	(0.4)
Tricuspid valve incompetence	0		0		2	(0.9)	1	(0.5)	2	(0.2)
Supraventricular tachycardia	0		0		1	(0.5)	0		2	(0.2)

[a] Figures are for the 'cardiac disorders' system organ class
[b] Reported in ≥ 2 patients

Studies included: C2324, C2325, and C2239

Serious adverse event / deaths / other significant events

A summary table for SAEs, deaths, and AEs leading to discontinuation is provided below in Table 33:

Table 33: Number of patients who died, had other serious or clinically significant adverse events or discontinued prematurely from them – Studies C2324 and C2325

Category	Study C2324				Study C2325				Pooled data	
	Everolimus N=204 n (%)		Placebo N=203 n (%)		Everolimus N=215 n (%)		Placebo N=211 n (%)		Everolimus N=850 n (%)	
On-treatment death	**12**	**(5.9)**	**4**	**(2.0)**	**18**	**(8.4)**	**11**	**(5.2)**	**68**	**(8.0)**
Death due to disease progression	5	(2.5)	3	(1.5)	6	(2.8)	6	(2.8)	36	(4.2)
AE as primary cause of death	7	(3.4)	1	(0.5)	12	(5.6)	5	(2.4)	32	(3.8)
Death by system organ class										
Infections and infestations	2	(1.0)	0		2	(0.9)	0		7	(0.8)
Cardiac disorders	1	(0.5)	0		3	(1.4)	2	(0.9)	5	(0.6)
General disorders and administration site conditions	1	(0.5)	0		2	(0.9)	0		5	(0.6)
Hepatobiliary disorders	1	(0.5)	0		2	(0.9)	3	(1.4)	3	(0.4)
Renal and urinary disorders	1	(0.5)	0		0		0		2	(0.2)
Respiratory, thoracic and mediastinal disorders	1	(0.5)	1	(0.5)	3	(1.4)	0		8	(0.9)
Gastrointestinal disorders	0		0		0		0		1	(0.1)
Metabolism and nutrition disorders	0		0		0		0		1	(0.1)
Serious adverse event	**82**	**(40.2)**	**50**	**(24.6)**	**122**	**(56.7)**	**73**	**(34.6)**	**415**	**(48.8)**
Suspected to be drug related	44	(21.6)	9	(4.4)	41	(19.1)	9	(4.3)	155	(18.2)
AE leading to discontinuation	**39**	**(19.1)**	**12**	**(5.9)**	**61**	**(28.4)**	**15**	**(7.1)**	**190**	**(22.4)**
Suspected to be drug related	27	(13.2)	4	(2.0)	40	(18.6)	7	(3.3)	110	(12.9)

Category	Study C2324		Study C2325		Pooled data
	Everolimus N=204	Placebo N=203	Everolimus N=215	Placebo N=211	Everolimus N=850
	n (%)	n (%)	n (%)	n (%)	n (%)

- Serious adverse events

Serious adverse events were reported more frequently for patients receiving everolimus than for the placebo groups (Table 34). The most frequently reported SAEs in patients receiving everolimus therapy (for the pooled dataset) were abdominal pain (5.2%), pyrexia (3.6%), and pneumonia (3.1%). Events within the following system organ classes were more frequent among patients receiving everolimus therapy relative to placebo: respiratory, thoracic and mediastinal disorders (Study C2324: +9.3%; Study C2325: +7.8%), infections and infestations (+6.4% and +6.9%), general disorders and administration site conditions (+4.4% and +4.6%), gastrointestinal disorders (+3.3% and +5.3%), and metabolism and nutrition disorders (+3.0% and +7.0%).

Overall, a total of 85 everolimus-treated patients (20.3%) compared with only 18 placebo-treated patients (4.3%) in the two pivotal phase-III studies reported at least 1 SAE that was suspected to be related to study drug during treatment or within the 28-day period of the end of treatment. Within the pooled dataset 155 (18.2%) of everolimus patients reported at least 1 related SAE. The most commonly reported treatment-related SAEs were pneumonitis (everolimus: 8 patients [1.9%]; placebo: 0 patients), diarrhea (6 [1.4%] ; 2 patients [0.5%]), anemia (6 [1.4%] ; 0 patients), and interstitial lung disease (5 [1.2%] ; 0 patients).

Table 34: Serious adverse events by system organ class and preferred term irrespective of relationship to treatment (at least 1% in any group)

System organ class/ MedDRA preferred term	Study C2324				Study C2325				Pooled data	
	Everolimus N=204 n (%)		Placebo N=203 n (%)		Everolimus N=215 n (%)		Placebo N=211 n (%)		Everolimus N=850 n (%)	
Any SAE	**82**	**(40.2)**	**50**	**(24.6)**	**122**	**(56.7)**	**73**	**(34.6)**	**415**	**(48.8)**
Gastrointestinal disorders	**27**	**(13.2)**	**20**	**(9.9)**	**46**	**(21.4)**	**34**	**(16.1)**	**141**	**(16.6)**
Abdominal pain	6	(2.9)	5	(2.5)	13	(6.0)	11	(5.2)	44	(5.2)
Diarrhoea	5	(2.5)	2	(1.0)	8	(3.7)	5	(2.4)	22	(2.6)
Nausea	3	(1.5)	4	(2.0)	3	(1.4)	4	(1.9)	15	(1.8)
Ascites	3	(1.5)	0		0		5	(2.4)	4	(0.5)
Vomiting	2	(1.0)	4	(2.0)	5	(2.3)	6	(2.8)	23	(2.7)
Ileus	1	(0.5)	1	(0.5)	5	(2.3)	1	(0.5)	7	(0.8)
Small intestinal obstruction	1	(0.5)	0		7	(3.3)	3	(1.4)	11	(1.3)
Rectal haemorrhage	0		2	(1.0)	3	(1.4)	0		5	(0.6)
Subileus	0		1	(0.5)	3	(1.4)	2	(0.9)	5	(0.6)
Intestinal obstruction	0		0		2	(0.9)	4	(1.9)	6	(0.7)
Respiratory, thoracic and mediastinal disorders	**23**	**(11.3)**	**4**	**(2.0)**	**22**	**(10.2)**	**5**	**(2.4)**	**77**	**(9.1)**
Pneumonitis	7	(3.4)	0		2	(0.9)	0		12	(1.4)
Dyspnoea	6	(2.9)	2	(1.0)	8	(3.7)	2	(0.9)	23	(2.7)
Pulmonary embolism	5	(2.5)	1	(0.5)	6	(2.8)	1	(0.5)	16	(1.9)
Interstitial lung disease	3	(1.5)	0		3	(1.4)	0		8	(0.9)
Pleural effusion	2	(1.0)	1	(0.5)	3	(1.4)	0		9	(1.1)
Hypoxia	1	(0.5)	1	(0.5)	3	(1.4)	1	(0.5)	4	(0.5)
Infections and infestations	**21**	**(10.3)**	**8**	**(3.9)**	**25**	**(11.6)**	**10**	**(4.7)**	**108**	**(12.7)**
Pneumonia	3	(1.5)	2	(1.0)	9	(4.2)	1	(0.5)	26	(3.1)
Infection	3	(1.5)	0		0		0		4	(0.5)
Sepsis	0		1	(0.5)	2	(0.9)	1	(0.5)	11	(1.3)
Cellulitis	0		0		3	(1.4)	0		5	(0.6)
General disorders and administration site conditions	**17**	**(8.3)**	**8**	**(3.9)**	**24**	**(11.2)**	**14**	**(6.6)**	**95**	**(11.2)**
Pyrexia	8	(3.9)	3	(1.5)	7	(3.3)	3	(1.4)	31	(3.6)
Asthenia	5	(2.5)	2	(1.0)	2	(0.9)	3	(1.4)	16	(1.9)
General physical health deterioration	1	(0.5)	1	(0.5)	6	(2.8)	2	(0.9)	15	(1.8)
Oedema peripheral	0		1	(0.5)	3	(1.4)	4	(1.9)	7	(0.8)
Non-cardiac chest pain	0		0		3	(1.4)	0		6	(0.7)
Metabolism and nutrition disorders	**15**	**(7.4)**	**9**	**(4.4)**	**21**	**(9.8)**	**6**	**(2.8)**	**70**	**(8.2)**
Dehydration	4	(2.0)	2	(1.0)	7	(3.3)	1	(0.5)	19	(2.2)
Decreased appetite	2	(1.0)	0		0		1	(0.5)	11	(1.3)
Hypercalcaemia	2	(1.0)	3	(1.5)	0		1	(0.5)	3	(0.4)
Hypokalaemia	1	(0.5)	0		4	(1.9)	0		5	(0.6)
Renal and urinary disorders	**11**	**(5.4)**	**5**	**(2.5)**	**12**	**(5.6)**	**6**	**(2.8)**	**38**	**(4.5)**
Renal failure	3	(1.5)	1	(0.5)	4	(1.9)	0		14	(1.6)
Renal failure acute	2	(1.0)	3	(1.5)	3	(1.4)	1	(0.5)	9	(1.1)
Cardiac disorders	**10**	**(4.9)**	**2**	**(1.0)**	**13**	**(6.0)**	**17**	**(8.1)**	**42**	**(4.9)**
Angina pectoris	0		0		2	(0.9)	3	(1.4)	3	(0.4)

System organ class/ MedDRA preferred term	Study C2324				Study C2325				Pooled data	
	Everolimus N=204 n (%)		Placebo N=203 n (%)		Everolimus N=215 n (%)		Placebo N=211 n (%)		Everolimus N=850 n (%)	
Blood and lymphatic system disorders	**9**	**(4.4)**	**3**	**(1.5)**	**7**	**(3.3)**	**3**	**(1.4)**	**30**	**(3.5)**
Anaemia	7	(3.4)	3	(1.5)	4	(1.9)	2	(0.9)	20	(2.4)
Thrombocytopenia	1	(0.5)	0		3	(1.4)	0		8	(0.9)
Hepatobiliary disorders	**9**	**(4.4)**	**2**	**(1.0)**	**8**	**(3.7)**	**4**	**(1.9)**	**35**	**(4.1)**
Psychiatric disorders	**5**	**(2.5)**	**3**	**(1.5)**	**1**	**(0.5)**	**1**	**(0.5)**	**13**	**(1.5)**
Confusional state	3	(1.5)	3	(1.5)	1	(0.5)	1	(0.5)	9	(1.1)
Investigations	**5**	**(2.5)**	**2**	**(1.0)**	**7**	**(3.3)**	**2**	**(0.9)**	**20**	**(2.4)**
Nervous system disorders	**4**	**(2.0)**	**5**	**(2.5)**	**12**	**(5.6)**	**7**	**(3.3)**	**33**	**(3.9)**
Injury, poisoning and procedural complications	**3**	**(1.5)**	**2**	**(1.0)**	**5**	**(2.3)**	**5**	**(2.4)**	**15**	**(1.8)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2**	**(1.0)**	**2**	**(1.0)**	**2**	**(0.9)**	**3**	**(1.4)**	**14**	**(1.6)**
Vascular disorders	**2**	**(1.0)**	**1**	**(0.5)**	**7**	**(3.3)**	**4**	**(1.9)**	**13**	**(1.5)**
Musculoskeletal and connective tissue disorders	**1**	**(0.5)**	**5**	**(2.5)**	**10**	**(4.7)**	**8**	**(3.8)**	**19**	**(2.2)**
Back pain	1	(0.5)	2	(1.0)	0		4	(1.9)	4	(0.5)
Endocrine disorders	**0**		**1**	**(0.5)**	**4**	**(1.9)**	**1**	**(0.5)**	**7**	**(0.8)**
Carcinoid syndrome	0		0		3	(1.4)	1	(0.5)	5	(0.6)

System organ classes are presented in descending order of frequency in the Study C2324 everolimus treatment group; AE preferred terms are sorted within organ class also by descending order of frequency with everolimus

Studies included: C2324, C2325, and C2239

- Deaths

Of the 839 patients participating in Studies C2324 and C2325, there were 151 (35.7%) and 135 (32.5%) deaths from the everolimus and placebo treatment groups, respectively.

'On-treatment' deaths were recorded for 45 patients (5.4%) by the 28 February 2010 and 02 April 2010 data cut-off dates for Studies C2324 and C2325, respectively. Of the 45 patients who died, 30 (7.2%) had received treatment with everolimus and 15 (3.6%) treatment with placebo.

20 of the 45 on-treatment deaths (44.4%) reported in Studies C2324 and C2325 were attributed to the underlying malignancy. The remaining 25 cases were mostly attributed to solitary events. Table 35 summarises the nature of AEs as primary cause of death and Table 36 describes the time to on-treatment death in cases where AEs were the primary cause.

One death from acute respiratory distress syndrome, in a patient receiving everolimus therapy, was suspected to be causally related to treatment. A second patient with a cause of death of 'other unknown', was diagnosed with pneumonia and interstitial pneumonitis 3 weeks earlier. The investigator had attributed death in this case to clinical disease progression. There was one death due to reactivation of hepatitis B with acute liver failure.

Nine on-treatment deaths (3.3%) were reported during the open-label phases of Studies C2324 and C2325 that were not attributed to the underlying malignancy.

Table 35: On-treatment deaths with adverse event as primary cause by system organ class and preferred term – Studies C2324 and C2325

System organ class/ MedDRA preferred term	Study C2324				Study C2325				Pooled data	
	Everolimus N=204 n (%)		Placebo N=203 n (%)		Everolimus N=215 n (%)		Placebo N=211 n (%)		Everolimus N=850 n (%)	
AE as primary cause of on-treatment death	**7**	**(3.4)**	**1**	**(0.5)**	**12**	**(5.6)**	**5**	**(2.4)**	**32**	**(3.8)**
Infections and infestations	**2**	**(1.0)**	**0**		**2**	**(0.9)**	**0**		**7**	**(0.8)**
Pneumonia	1	(0.5)	0		1	(0.5)	0		4	(0.5)
Infection	1	(0.5)	0		0		0		1	(0.1)
Pulmonary sepsis	0		0		1	(0.5)	0		1	(0.1)
Sepsis	0		0		0		0		1	(0.1)
Cardiac disorders	**1**	**(0.5)**	**0**		**3**	**(1.4)**	**2**	**(0.9)**	**5**	**(0.6)**
Cardiac arrest	1	(0.5)	0		1	(0.5)	0		2	(0.2)
Cardiac failure congestive	0		0		1	(0.5)	0		1	(0.1)
Cardiopulmonary failure	0		0		1	(0.5)	0		1	(0.1)
Cardiac failure	0		0		0		0		1	(0.1)
Arrhythmia	0		0		0		1	(0.5)	0	
Cardio-respiratory arrest	0		0		0		1	(0.5)	0	
General disorders and administration site conditions	**1**	**(0.5)**	**0**		**2**	**(0.9)**	**0**		**5**	**(0.6)**
Death	1	(0.5)	0		1	(0.5)	0		2	(0.2)
Sudden death	0		0		1	(0.5)	0		3	(0.4)
Hepatobiliary disorders	**1**	**(0.5)**	**0**		**2**	**(0.9)**	**3**	**(1.4)**	**3**	**(0.4)**
Hepatic failure	1	(0.5)	0		1	(0.5)	3	(1.4)	2	(0.2)
Hepatic function abnormal	0		0		1	(0.5)	0		1	(0.1)
Renal and urinary disorders	**1**	**(0.5)**	**0**		**0**		**0**		**2**	**(0.2)**
Renal failure acute	1	(0.5)	0		0		0		1	(0.1)
Renal failure	0		0		0		0		1	(0.1)
Respiratory, thoracic and mediastinal disorders	**1**	**(0.5)**	**1**	**(0.5)**	**3**	**(1.4)**	**0**		**8**	**(0.9)**
Acute respiratory distress syndrome	1	(0.5)	0		0		0		2	(0.2)
Pulmonary embolism	0		1	(0.5)	2	(0.9)	0		2	(0.2)
Acute respiratory failure	0		0		1	(0.5)	0		1	(0.1)
Aspiration	0		0		0		0		1	(0.1)
Hydropneumothorax	0		0		0		0		1	(0.1)
Respiratory failure	0		0		0		0		1	(0.1)
Gastrointestinal disorders	**0**		**0**		**0**		**0**		**1**	**(0.1)**
Intestinal perforation	0		0		0		0		1	(0.1)
Metabolism and nutrition disorders	**0**		**0**		**0**		**0**		**1**	**(0.1)**
Hypoglycaemia	0		0		0		0		1	(0.1)

System organ classes are presented in descending order of frequency in the Study C2324 everolimus treatment group; AE preferred terms are sorted within organ class also by descending order of frequency with everolimus

Studies included: C2324, C2325, and C2239

Table 36: Time to on-treatment death for cases where adverse events were the primary cause – Studies C2324 and C2325

Time to death (days)	Study C2324				Study C2325			
	Everolimus N=204		Placebo N=203		Everolimus N=215		Placebo N=211	
	n (%)	Cause of death	n (%)	Cause of death	n (%)	Cause of death	n (%)	Cause of death
1 to <30	1 (0.5)	Renal failure acute	1 (0.5)	Pulmonary embolism	1 (0.5)	Pulmonary embolism	1 (0.5)	Hepatic failure
30 to < 60	1 (0.5)	'Death'	0		0		0	
60 to < 90	1 (0.5)	Infection	0		2 (0.9)	Cardiac arrest, sudden death	1 (0.5)	Arrhythmia
90 to < 180	1 (0.5)	Hepatic failure	0		1 (0.5)	Pneumonia	2 (0.9)	Hepatic failure (x 2)
180 to < 270	1 (0.5)	Cardiac arrest	0		4 (1.9)	Acute respiratory failure, death, pulmonary embolism, pulmonary sepsis	0	
270 to < 360	2 (1.0)	Acute respiratory distress syndrome, pneumonia	0		2 (0.9)	Hepatic failure, hepatic functional abnormal	0	
360 to < 540	0		0		0		1 (0.5)	Cardio-respiratory arrest
540 to < 720	0		0		1 (0.5)	Cardiopulmonary failure	0	
720 to < 900	0		0		1 (0.5)	Cardiac failure congestive	0	

In study C2239 there were ten deaths (8.7%) reported on-treatment for stratum 1. Six of these ten deaths were considered by the investigator to be related to the primary disease and/or to disease progression. All 4 AE-related deaths belonged to the respiratory and infections' SOCs. In stratum 2, two on- treatment deaths (4.4%) were reported. Both were considered by the investigator to be related to the primary disease and/or disease progression.

Laboratory findings

Grade 3 and 4 hematology changes were observed in 28.0% and 29.3% of everolimus-treated patients and 7.4% and 9.9% of placebo-treated patients in Studies C2324 and C2325, respectively. Low hemoglobin occurred in 64.2% and 27.1% of patients receiving everolimus and placebo, respectively, in Study C2324 and in 74.0% and 32.7% of patients in Study C2325. Anemia was reported as an AE in 22.1% and 8.9% of patients receiving everolimus and placebo, respectively, in Study C2324 and in 27.9% and 10.4% of patients in Study C2325. Thrombocytopenia, leukopenia, lymphopenia, and neutropenia were also all reported more frequently for patients receiving everolimus (both overall and as grade 3-4 events) relative to the placebo arm.

Nearly all patients reported treatment-emergent changes in clinical chemistry laboratory results. Grade 3 and 4 changes were observed in 37.7% of patients receiving everolimus and 18.8% of the placebo treatment group in Study C2324 and in 37.2% of everolimus- and 17.0% placebo-treated patients in Study C2325. The proportion of patients experiencing grade 3 or 4 changes for hyperglycemia, hypophosphatemia, and hypokalemia were higher with everolimus than with placebo therapy. Although increases in cholesterol, AST(aspartate aminotransferase) ALT (alanine aminotransferase) and triglyceride concentrations were reported more often for everolimus, the incidence of grade 3 and 4 toxicity did not differ.

One of the more frequently documented laboratory abnormalities in the pivotal phase-III studies was hypophosphatemia, although clinical sequelae were not routinely evident. Hypophosphatemia was reported as an SAE in 2 patients and it led to the discontinuation of treatment for a single patient. No patients presented with identifiable manifestations of severe phosphate deficiency, such as rhabdomyolysis, cardiomyopathy, respiratory insufficiency, erythrocyte dysfunction, metabolic acidosis, or skeletal demineralization that were suspected to be drug related. The etiology of hypophosphatemia associated with everolimus is unknown.

Laboratory findings associated with abnormal hepatic function were evident for both treatment groups. Low grade elevations of transaminase concentrations were more common in the everolimus treatment group.

No untoward ECG changes were recorded during the two pivotal studies.

No significant changes in pulse, respiratory rate, or temperature were noted.

Safety in special populations

The median age of patients included in the pivotal phase-III trials was 58 and 60 years (Studies C2324 and C2325), respectively. The incidence of AEs was generally similar for patients < 65 years of age and those aged ≥ 65 years. Adverse events reported with ≥ 1.5-fold the incidence in >65 years old patients receiving everolimus (and were reported by ≥ 10% of patients in either treatment group) included dehydration. In contrast, upper abdominal pain, headache, hypertension, and oropharyngeal pain were reported less frequently among the older patient population.

Within the pooled dataset, the incidence of most AEs was generally similar for both Caucasians and Asians.The incidence of most AEs was generally similar for both men and women.

Specific studies in patients with severe hepatic or renal impairment were not conducted in this application. As everolimus is eliminated primarily via the hepatic route, a special warning is already included in the SmPC as exposure might be increased in patients with severe hepatic impairment. Mild elevations of serum creatinine concentration have been observed.

The safety of everolimus in paediatric patients has not been studied in these populations.

Safety related to drug-drug interactions and other interactions

Based on an *in vitro* inhibition assay, octreotide is not expected to inhibit the metabolic clearance of co-medications metabolized by CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.

In study C2325, coadministration of octreotide was found to have a 1.5-fold increase in octreotide C_{min}. In study C2239 the increase of octreotide C_{min} was only measured with 1.2-fold.

Discontinuation due to adverse events

The time to withdrawal as a consequence to adverse events was investigated. There were 16 withdrawal events and 62 censored events in the everolimus plus octreotide treatment arm. There were 11 withdrawal events and 138 censored events in the placebo arm. The impact of octreotide on the time to withdrawal was not statistically significant (HR=1.2 for a 1.5 fold increase in octreotide C_{min}; 95%CI 0.77-1.86). The hazard ratios on time to withdrawal for a 1.5-fold increase (4 ng/mL to 6 ng/mL) in octreotide C_{min} at everolimus C_{min} of 2.5, 5, and 10 ng/mL and a 2-fold increase (5 ng/mL to 10 ng/mL) in everolimus C_{min} at octreotide C_{min} of 4 and 6 ng/mL are presented in Table 37.

Table 37: Cox regression analysis of the impact of a 1.5-fold increase in octreotide C_{min} and a 2-fold increase in everolimus C_{min} on time to withdrawal (due to AE) - Study C2325 (data cut-off 02 April 2010)

Fold increase in C_{min}	Hazard ratio	95% CI	At C_{min} of octreotide or everolimus
1.5 X octreotide C_{min}	1.11	0.77, 1.61	At everolimus C_{min} of 10 ng/mL
1.5 X octreotide C_{min}	1.58	0.77, 3.28	At everolimus C_{min} of 5 ng/mL
1.5 X octreotide C_{min}	2.25	0.62, 8.19	At everolimus C_{min} of 2.5 ng/mL

Fold increase in C_{min}	Hazard ratio	95% CI	At C_{min} of octreotide or everolimus
2 X everolimus C_{min}	1.04	0.54, 2.02	At octreotide C_{min} of 6 ng/mL
2 X everolimus C_{min}	1.48	0.79, 2.78	At octreotide C_{min} of 4 ng/mL

Dose adjustments were primarily attributable to AEs (interruptions: C2324: 52.0% and C2325: 55.3%; reductions: C2324: 27.0% and C2325: 37.7%). In the pooled dataset, 63.8% of patients required dose reductions or interruptions. The most commonly reported AEs leading to everolimus dose adjustment (for the pooled dataset) were stomatitis (9.5%), diarrhea (6.7%), thrombocytopenia (6.7%), pyrexia (4.8%), pneumonitis (4.1%), abdominal pain (3.8%), and fatigue (3.5%).

The most commonly reported AEs leading to discontinuation of everolimus therapy for the pooled dataset were pneumonitis (1.4%), fatigue (1.4%), asthenia (1.1%), diarrhea (0.9%), pneumonia (0.9%), interstitial lung disease (0.8%), and pyrexia (0.8%). Discontinuations as the result of AEs from the following system organ classes were also more common with everolimus (relative to placebo): respiratory, thoracic and mediastinal disorders (Study C2324: +5.9%; Study C2325: +5.5%), general disorders and administration site conditions (+2.4% and +5.1%), and gastrointestinal disorders (+1.0% and +4.6%).

Treatment-related AEs leading to discontinuation were reported in 12.9% of patients in the pooled dataset, and differences to the placebo rate were of +11.2% in study C2324 and +15.3% in study C2325. The most commonly reported treatment-related AEs leading to discontinuation of everolimus in the two pivotal studies were pneumonitis (2.1%), interstitial lung disease (1.4%), fatigue (1.2%), and diarrhea (1.0%).

Post marketing experience

Everolimus (Afinitor) is commercially available for the treatment of patients with advanced renal cell carcinoma. A total patient exposure in excess of 1600 patient-years has been calculated based on commercial usage only from the amount of active substance sold or distributed between March 2009 and March 2010. Overall, 5,899 oncology patients have received treatment with everolimus in Novartis-sponsored studies.

Everolimus is also commercially available as Certican within the EU and other global markets for the prophylaxis of allograft rejection following renal or cardiac transplantation, in a combination immunosuppressive regimen with cyclosporine and corticosteroid therapy. A total patient exposure in excess of 51,000 patient-years has been calculated from the amount of active substance sold or distributed between June 2003 and the present time.

1.3.6. Discussion on clinical safety

The analysis and presentation of the safety of everolimus was based on comparison with placebo in the phase III studies C2324 and study 2325 in patients with advanced NET and study C2239.

Regarding all-causality AEs, there was an increase in AEs in patients treated with everolimus and from most organ systems though the adverse events recorded were in line with the previous experience. The incidence of grade 3 and 4 AEs was approximately 70% in the pooled dataset. This was 2-3-fold higher than in the previous study C2240 (RCC pivotal study) though there was 2-3-fold higher exposure time in the pooled dataset. The overall increase in grade 4 events was about 5-10% and for grade 3, about 15%. Compared with placebo, everolimus was associated with a clear increase in grade 3-4 AEs (+20-30%). The high incidences of overall AEs in the placebo arm of study C2324 (97.5%) as

well as the high rate of grade 3 (31.5%) and grade 4 (7.4%) AEs were likely to be associated to the underlying disease and co-morbidities of the study population. Both in the everolimus and in the placebo arms of study C2325, the grade 3 and 4 AE rates were >10% higher than in study C2324. Study C2239 revealed comparable differences between strata of 82.2% vs. 74.8% with or without additional octreotide treatment. The increased incidence of grade 3-4 diarrhea and hypokalaemia in study C2325 was assumed to be related to the underlying disease of carcinoid syndrome. Side effects from interactions with the additional octreotide treatment should also be taken into account, as could be observed in study C2239 in stratum 2 (+octreotide) where incidence of hypokalaemia was twice that of stratum 1.

The rate of suspected grade 3 and 4 AEs was approximately 43% with no visible differences between both phase III studies or between study C2239 treatment strata. In view that everolimus was investigated in pre-treated patients the data of grade 3 and 4 suspected adverse events were supportive that everolimus was well tolerated in these patients.

Clinically relevant AEs and event rates were as expected. They occurred 1.5 - 2 times more often in the everolimus than in the placebo arms, except for bleeding/thomboembolic and hepatic events which occurred similarly, and pulmonary events which were reported less than <1% in the placebo groups. In general, their profile was comparable to previous studies.

Pulmonary events were diagnosed in incidences similar to previous studies and were thoroughly addressed by baseline and on-study chest CT-scans/X-rays. The safety issue of pneumonitis is well addressed in the SmPC.

The number of events for the most commonly reported treatment related SAEs were 11 for pneumonia, diarrhea and anaemia (placebo: 0; 2; 0) and 7 events for interstitial lung disease.

The rate of SAEs in the pooled dataset was higher than in the previous pivotal study (C2240) but of similar nature, however abdominal pain was reported more and most frequently (5.2%). The difference in treatment duration as well as active treatment may have contributed to the higher rates of SAEs in the everolimus treatment arms. Similarly, the enhanced SAE rates in study C2325 may also be due to the add-on therapy of octreotide.

45 on-treatment deaths were reported in both phase III studies. The number of on-treatment deaths in both studies was significantly different between everolimus and placebo with 30 vs. 15 deaths, respectively. In study C2324 the number of deaths due to adverse events was 7 for everolimus and 1 for placebo. In study C2325 the total number of deaths was higher than in study C2324 with 12 and 5 events in everolimus and placebo arms, respectively. For 15 cases of death due to AE a possible relatedness could not be ruled out. A higher incidence of deaths might be expected with active treatment and in an "add-on" treatment setting, especially in an elderly population with advanced NET. However, the adverse events which were suspected to be the cause of death often belonged to the categories of identified clinically notable events/SOCs seen with everolimus (e.g. infections, pneumonia).

Everolimus is associated with a 3-4-fold increase in AEs leading to discontinuation (approx. 22 %). The incidence of grade 3 and 4 suspected AEs leading to discontinuation in the carcinoid study (10.3 %) was almost twice that in the pancreatic NET study (5.4 %).

The abnormal laboratory values were comparable to the known safety profile of everolimus and can be described as class-effects of m-TOR inhibitors. However, the frequencies reported were higher than previously recorded, which may be attributed to increased exposure in the clinical trials.

Based on blood sampling in studies C2239 and C2325, co-administration of octreotide was found to have a 1.5-fold increase in octreotide C_{min} in study C2325 and this increased exposure may have

contributed to the enhanced rate of adverse events in both the treatment arms. Though the increase of octreotide C_{min} was only measured with 1.2-fold in study C2239, an enhanced AE rate in stratum 2 was also detected. Analysis of time to withdrawal in study C2325 due to AEs showed no influence of the concentrations of octreotide and everolimus on the time to withdrawal.

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

1.3.7. Conclusions on the clinical safety

The safety of 10 mg everolimus in patients with advanced NET was adequately described.

Clinically relevant AEs occurred 1.5-2 times more often than in previous studies. Pneumonitis is a well known adverse reaction to everolimus and grade 3 events were reported in 3% of the patients (vs. <1% on placebo). Grade 3 infectious events were also more frequently reported in the everolimus arm. Both these events and stomatitis/oral mucositis represent the most important clinical issues, and each of these events can be managed effectively in the clinical setting and are adequately reflected in the SmPC. Overall, the majority of patients were either able to continue treatment with everolimus, or discontinued treatment and subsequently experienced complete resolution or improvement in their symptoms.

No additional safety concerns were raised for subpopulations of men or women, the elderly, or racial groups. The evaluation of the safety data does not indicate the need for any additional safety monitoring.

In conclusion, safety results and adverse drug reactions from the phase III studies C2324 and C2325 were largely consistent with observations in previous everolimus studies in an oncology setting, though higher frequencies were reported. In general, adverse events were low-grade, manageable, reversible and non-cumulative.

1.4. Risk Management Plan

In this application, the MAH submitted an updated RMP. The RMP has been updated to reflect the proposed indication in advanced neuroendocrine tumours (NET) of pancreatic origin as well as safety-related changes from Core Data Sheet (CDS) version 1.5. The final updated RMP for this new indication, version 5.0, dated 18th of May 2011, is considered acceptable.

Table 38: Summary of the risk management plan for Afinitor

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
Important identified risks		
Non-infectious pneumonitis	Routine pharmacovigilance activities including cumulative analysis in PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, post-marketing surveillance study reports, reports from other programs where data are being handled as solicited and all clinical trial SAE reports using a targeted product questionnaire/checklist.	This item is appropriately communicated through current labeling: SPC Section 4.4 Special warnings and precautions for use. Relevant preferred terms are included as ADRs in SPC Section 4.8 Undesirable effects.

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
Severe infections	Routine pharmacovigilance including detailed cumulative review in the PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, serious reports from other programs where data is being handled as solicited and all clinical trial SAE reports, using a targeted product questionnaire/checklist.	This item is appropriately communicated through current labeling: SPC Section 4.4 Special warnings and precautions for use. Relevant preferred terms are included as ADRs in SPC Section 4.8 Undesirable effects.
Hypersensitivity (anaphylactic reactions)	Routine pharmacovigilance including detailed cumulative review in the PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-serious marketing surveillance study reports, reports from other programs where data is being handled as solicited and all clinical trial SAE reports, using a targeted event questionnaire/checklist.	This item is appropriately communicated through current labeling: SPC Section 4.3 Contraindications, Section 4.4 Special warnings and precautions for use. Relevant preferred terms are included as ADRs in SPC Section 4.8 Undesirable effects.
Stomatitis	Routine pharmacovigilance including detailed cumulative review in the PSUR.	This item is appropriately communicated through current labeling: SPC Section 4.4 Special warnings and precautions for use. Relevant preferred term is included as ADRs in SPC Section 4.8 Undesirable effects.
Increased creatinine/Proteinuria/ Renal failure	Routine pharmacovigilance including detailed cumulative review in the PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, serious reports from other programs where data is being handled as solicited and all clinical trial SAE reports, using a targeted event questionnaire/checklist.	This item is appropriately communicated through current labeling: SPC Section 4.4 Special warnings and precautions for use. Relevant preferred term is included as ADRs in SPC Section 4.8 Undesirable effects.
Hyperglycemia/New onset diabetes mellitus	Routine pharmacovigilance including detailed cumulative review in the PSUR.	This item is appropriately communicated through current labeling: SPC Section 4.4 Special warnings and precautions for use. Relevant preferred terms are included as ADRs in SPC Section 4.8 Undesirable effects.
Wound healing complications	Routine pharmacovigilance including detailed cumulative review in the PSUR.	This item is appropriately communicated through current labeling: SPC Section 4.4 Special warnings and precautions for use. Relevant preferred term is included as ADRs in SPC Section 4.8 Undesirable effects.

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
Dyslipidemia	Routine pharmacovigilance including detailed cumulative review in the PSUR.	This item is appropriately communicated through current labeling: SPC Section 4.4, Special warnings and precautions for use. Relevant preferred term is included as ADRs in SPC Section 4.8 Undesirable effects.
Hypophosphatemia	Routine pharmacovigilance including detailed cumulative review in the PSUR.	This item is appropriately communicated through current labeling: Relevant preferred term is included as ADRs in SPC Section 4.8 Undesirable effects.
Hemorrhages	Routine pharmacovigilance including detailed cumulative review in the PSUR.	This item is appropriately communicated through current labeling: Relevant preferred term is included as ADRs in SPC Section 4.8 Undesirable effects.
Thromboembolism	Routine pharmacovigilance including detailed cumulative review in the PSUR.	This item is appropriately communicated through current labeling: Relevant preferred term is included as ADRs in SPC Section 4.8 Undesirable effects.
Important potential risks		
Cardiac failure	Routine pharmacovigilance including detailed cumulative review in the PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, serious reports from other programs where data is being handled as solicited and all clinical trial SAE reports, using a targeted event questionnaire/checklist.	This item is appropriately communicated through current labeling: SPC Section 4.8 Undesirable effects.
Lymphopenia	Routine pharmacovigilance including detailed cumulative review in the PSUR.	This item is appropriately communicated through current labeling: SPC Section 4.4 Special warnings and precautions for use. Relevant preferred term is included as ADRs in SPC Section 4.8 Undesirable effects.
Developmental toxicity	Routine pharmacovigilance including detailed cumulative review in the PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, and serious reports from other programs where data are being handled as solicited and all clinical trial SAE reports, using a targeted event questionnaire/ checklist.	This item is appropriately communicated through current labeling. SPC Section 4.2 Posology and method of administration; Section 5.3 Preclinical safety data.

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
	Study CRAD001M2301: A randomized, double-blind, placebo-controlled study of RAD001 in the treatment of patients with subependymal giant cell astrocytomas (SEGA) associated with tuberous sclerosis complex (TSC). Study M2301 includes a trial extension phase. Study CRAD001C2485: Everolimus (RAD001) therapy of giant cell astrocytomas in patients with tuberous sclerosis complex (including children). Assessments include the collection of weight and height (before and after enrollment into the study), changes in hormones (LH and FSH, all patients; estrogen, females; testosterone, males) as well as Tanner staging until sexual maturation. These potential developmental effects will continue to be assessed for an additional 4 years.	
Reproductive (teratogenicity) toxicity	Routine pharmacovigilance including detailed cumulative review in the PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, and serious reports from other programs where data are being handled as solicited and all clinical trial SAE reports, using a targeted event and pregnancy questionnaire/checklist.	This item is appropriately communicated through current labeling. SPC Section 4.6 Fertility, pregnancy, and lactation; Section 5.3 Preclinical safety data.
Important identified interactions		
Strong CYP3A4 inhibitors and PgP inhibitors Moderate CYP3A4 inhibitors and PgP inhibitors Strong CYP3A4 inducers and PgP inducers	Routine pharmacovigilance including detailed cumulative review in the PSUR. **Additional activities** Study CRAD001X2103: An open-label, two-period, fixed-sequence study to investigate the effect of everolimus on the pharmacokinetics of midazolam in healthy volunteers	This item is appropriately communicated through current labeling: SPC Section 4.4 Special warnings and precautions for use, Section 4.5 Interaction with other medicinal products and other forms of interaction.
CYP3A4 substrates and PgP substrates	Routine pharmacovigilance including detailed cumulative review in the PSUR. **Additional activities** Study CRAD001X2103: An open-label, two-period, fixed-sequence study to investigate the effect of everolimus on the pharmacokinetics of midazolam in healthy volunteers	This item is appropriately communicated through current labeling: Section 4.5 Interaction with other medicinal products and other forms of interaction.
Important missing information		
Pediatric patients less than 3 years old	Routine pharmacovigilance including cumulative analysis in PSUR.	This item is appropriately communicated through current labeling: SPC Section 4.2 Posology and method administration. Section 5.1 Pharmacodynamic properties.
Off-label use in pediatric and	Routine pharmacovigilance including	This item is appropriately

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
adolescent patients	cumulative analysis in PSUR.	communicated through current labeling: SPC Section 4.2 Posology and method administration. Section 5.1 Pharmacodynamic properties.
Pregnant or breast-feeding women	Routine pharmacovigilance including cumulative analysis in PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, and serious reports from other programs where data are being handled as solicited and all clinical trial SAE reports, using a targeted event and pregnancy questionnaire/checklist.	This item is appropriately communicated through current labeling: SPC Section 4.6 Fertility, pregnancy, and lactation.
Hormonal contraceptive use	Routine pharmacovigilance.	This item is appropriately communicated through current labeling: SPC Section 4.6 Fertility, pregnancy, and lactation.
Patients with renal impairment	Routine pharmacovigilance. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, and serious reports from other programs where data are being handled as solicited and all clinical trial SAE reports, using a targeted event questionnaire/ checklist.	This item is appropriately communicated through current labeling: SPC Section 4.2 Posology and method of administration, Section 5.2 Pharmacokinetic properties.
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 uncontrolled or significant cardiac disease Patients with impairment of GI function Patients undergoing chronic treatment with steroids or another immunosuppressive agent Patients who have undergone surgery within 2 weeks prior to treatment Race other than Caucasian	Routine pharmacovigilance.	Currently available data do not support the need for risk minimization.
Long-term safety	Routine pharmacovigilance. **Additional activities** Study CRAD001M2301: A randomized, double-blind, placebo-controlled study of RAD001 in the treatment of patients with subependymal giant cell astrocytomas (SEGA) associated with	None Currently available data do not support the need for risk minimization.

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
	tuberous sclerosis complex (TSC) Study CRAD001C2485: Everolimus (RAD001) therapy of giant cell astrocytomas in patients with tuberous sclerosis complex	
Reactivation of background diseases	Routine pharmacovigilance. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, serious reports from other programs where data is being handled as solicited and all clinical trial SAE reports, using a targeted product questionnaire/checklist.	None Currently available data do not support the need for risk minimization.

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.

1.5. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. The reason was that there were no significant changes made to the Package Leaflet. This has been found acceptable by the CHMP.

2. Benefit-Risk Balance

Benefits

Beneficial effects

The primary objective of the pivotal study C2324 was increase in PFS in everolimus-treated patients compared to placebo plus BSC-treated patients. Based on study C2324, there was a median PFS of 11.04 vs 4.60 months per INV for everolimus and placebo, respectively (HR 0.35, 95%CI 0.27-0.45; p<0.001). These results were consistent with the PFS results from the IAC and IRC.

Uncertainty in the knowledge about the beneficial effects

No advantage in OS or time to deterioration of the WHO performance were observed. Because of the cross-over design of the pivotal study, analysis of the secondary endpoints overall survival and WHO performance status was impaired. It is uncertain whether the improvement in PFS would translate into a long term beneficial effect in terms of OS. However, the effect observed in terms of PFS was considered clinically relevant and convincing even in the absence of an effect in terms of OS.

Concerning study C2325 which included patients with carcinoid tumours, the CHMP found this study problematic as PFS only reached statistical significance in a supportive analysis (INV) and not in the primary analysis (IAC) and more deaths (100 vs. 85 total) were reported from the everolimus treatment group (HR 1.22; 95%CI: 0.91-1.62; p=0.908). Therefore, the CHMP did not support the extension of the indication in advanced pancreatic NET in carcinoid tumours.

Risks

Unfavourable effects

The most common ADRs, with an incidence ≥ 10% in the pooled dataset, were stomatitis, rash, diarrhea, fatigue, nausea, decreased appetite, dysgeusia, anemia, weight decreased, peripheral edema, headache, aphthous stomatitis, hyperglycemia, asthenia, vomiting, pruritus, thrombocytopenia, and epistaxis.

The most common grade 3-4 ADRs, with an incidence of ≥ 2%, were hyperglycemia, stomatitis, diarrhea, fatigue, thrombocytopenia, anemia, neutropenia, hypophosphatemia, and asthenia.

The most frequently reported SAEs were abdominal pain, pyrexia and pneumonia.

The safety of everolimus was largely consistent with observations from previous everolimus studies in an oncology setting, though the CHMP noted that ADRs occured in higher frequencies which was likely attributed to the 2-fold increase in patient exposure to everolimus compared to that of the placebo group. Adverse events were predictable, largely low-grade, manageable, reversible and non-cumulative.

The number of on-treatment deaths for study C2324 was higher with everolimus treatment: 7 patients (3.4 %) and 1 (0.5 %) with everolimus vs. placebo, respectively. Seven deaths were reported as related to AEs, of these one death was considered as related, and for 6 cases a possible relation could not be ruled out.

During the open-label phases of studies C2324 and C2325, 9 deaths with suspected causality to AEs occurred with a similar AE profile. In study C2239 4 AE-related deaths occurred which were of the respiratory or infections' SOC.

Uncertainty in the knowledge about the unfavourable effects

The concomitant administration of somatostatin analogues (e.g. octreotide) increased the frequency of reported ADRs in patients with carcinoid tumours. It was unclear to what extent add-on to octreotide contributed to the poor tolerability. However, the analysis of the concentrations of octreotide and everolimus showed no effect on the withdrawal of carcinoid patients due to AEs suggesting a lack of influence of octreotide on the withdrawal of patients due to AEs. Data from the pNET study where octreotide co-medication was an option at the discretion of the investigator showed no increase in toxicity when both treatments were combined.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

PFS was considered an important and appropriate primary endpoint for the study C2324 in pancreatic neuroendocrine tumours. The HR and increase in median PFS were statistically significant. The cross-over design confounded the data for overall survival, thus the effect on overall survival could not be ascertained. However, the treatment effect in terms of PFS was considered clinically relevant and convincing even in the absence of an effect in terms of OS for this patient population, as few approved pharmacological treatment options are available.

Long term data on the patient population were not available. The safety of everolimus was largely consistent with observations from previous everolimus studies. The identified ADRs were mostly well tolerated and graded as mild and manageable.

Benefit-risk balance

Although the increase in PFS in study C2324 was not supported with additional endpoints, the effect still remained clinically relevant. The adverse events reported were considered acceptable for a patient population of adult patients with advanced neuroendocrine tumours of pancreatic origin. Thus, it was considered that the clinical benefit observed with the improvement of PFS outweighed the risks previously identified in the safety population.

Risk management plan

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

3. Conclusion

On 21 July 2011 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet (Attachment 1 - changes highlighted)

4. EPAR changes

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

Scope:

Extension of indication

Extension of indication to include 'Afinitor is indicated for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease'.

Consequently, sections 4.1, 4.4, 4.5, 4.8 and 5.1 of the Summary of Product Characteristics and the Package Leaflet have been updated. The Risk Management Plan statement in Annex II has been updated to the new template. The MAH also took the opportunity to update the product information in line with the QRD template (version 7.3.1) and to make minor corrections.

Summary / scientific discussion:

Please refer to Scientific discussion Affinitor-H-C-1038-II-08