Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Everolimus

Proprietary Product Name: Afinitor

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

February 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of Submission	Extension of indications
Decision:	Approved
Date of Decision:	10 July 2012
Active ingredient:	Everolimus
Product Name:	Afinitor
Sponsor's Name	Novartis Pharmaceuticals Australia Pty Ltd
Dose form:	Tablet
Strengths:	2.5 mg, 5 mg and 10 mg
Container:	Blister pack
Pack sizes:	2.5 mg: 10, 30, 90 5 and 10 mg: 30, 50, 60, 100, 120
Approved therapeutic use:	For the treatment of progressive, unresectable or metastatic, well or moderately differentiated, neuroendocrine tumours (NETs) of pancreatic origin.
Route of administration:	Oral
Dosage:	10 mg once daily
ARTG Numbers	177648, 154661, 154663

Product background

Everolimus is a signal transduction inhibitor targeting the mammalian target of rapamycin (mTOR), or more specifically, mTOR complex 1 (mTORC1). mTOR is a key serine-threonine kinase playing a central role in the regulation of cell growth, proliferation and survival. The mTOR may have additional importance in neuroendocrine cells which are able to undergo autocrine regulation through the actions of insulin-like growth factor 1 (IGF-1) on this pathway. Everolimus has been shown to block the action of IGF-1 in neuroendocrine cells (von Wichert *et al*., 2000[1])

Everolimus (under the trade name Certican) is currently approved in Australia for use as an immunosuppressant in patients with renal or cardiac transplants and (under the trade name Afinitor) for the treatment of advanced renal cell carcinoma.

This AusPAR describes the evaluation of an application by Novartis Pharmaceuticals Australia Pty Ltd (the sponsor) to register everolimus (Afinitor) for the additional indication: *the treatment of advanced neuroendocrine tumours (NETs) of gastrointestinal, lung or pancreatic origin.* The dose proposed for the new indications is 10 mg taken orally once a day and is the same as the approved dose for advanced renal cell carcinoma.

[1] von Wichert G., Jehle PM., Hoeflich A. *et al*. Insulin-like Growth Factor-I Is an Autocrine Regulator of Chromogranin A Secretion and Growth in Human Neuroendocrine Tumour Cells. *Cancer Res*. 2000; 60 (16): 4573-4581.

Changes are also proposed to the Afinitor Product Information; details of these are beyond the scope of this AusPAR.

Regulatory status

Everolimus (Certican) was first registered in Australia in March 2005 for the prophylaxis of organ rejection in adult patients at mild to moderate immunological risk receiving an allogeneic renal or cardiac transplant. A new trade name (Afinitor) and the following additional indications have since been approved:

- *For the treatment of advanced renal cell carcinoma after failure of treatment with sorafenib or sunitinib;*
- *For the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS), who require therapeutic intervention but are not candidates for curative surgical resection.*

The product is approved in the following overseas countries:

Country/ Region	Trade name	Submitted	Approved	Approved Indication
EU	Afinitor	21 Nov 10	29 Aug 11	Neuroendocrine tumours of pancreatic origin. Afinitor is indicated for the treatment of unresectable or metastatic, well- or moderately- differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease.
USA	Afinitor	5 Nov 10	May 2011	For the treatment of progressive neuroendocrine tumours of pancreatic origin (PNET) that is unresectable, locally advanced or metastatic. The safety and effectiveness of Afinitor in the treatment of patients with carcinoid tumours have not been established.
Canada	Afinitor	17 Feb 11	2 Feb 12	AFINITOR, indicated for the treatment of well- or moderately differentiated neuroendocrine tumours of pancreatic origin (PNET) in patients with unresectable, locally advanced or metastatic disease that has progressed within the last 12 months.
New Zealand	Afinitor	20 Jul 11	To Be Advised	For the treatment of patients with advanced neuroendocrine tumours of gastrointestinal, lung and

Country/ Region	Trade name	Submitted	Approved	Approved Indication
				pancreatic origin.
Switzerland	Afinitor	23 Dec 10	20 Jan 12	Advanced, progressive, well to moderately differentiated neuroendocrine tumours of pancreatic origin.

Orphan drug designation

Everolimus was designated an orphan drug for the treatment of advanced renal cell cancer on 17 July 2008 but has not been so designated for the indication requested in this application.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

No changes are proposed to the registered product formulation or strengths. Quality data provided in the submission comprised updates regarding the clinical trial formulae, encompassing studies back to 1997.

Recent Clinical Studies C2324 PNET and C2325 Carcinoid both used 5 mg tablets with slightly varying formulations. These have the same quantitative formulation but with variations in shape and markings. This is acceptable.

Quality summary and conclusions

There are no objections to registration with respect to chemistry and quality control aspects.

III. Nonclinical findings

Introduction

Nonclinical data consisted of a single study report (assessment of potential pharmacokinetic (PK) drug interactions with octreotide), and a number of literature references. Of the submitted papers, only 3 were deemed relevant and were evaluated. A number of previously submitted *in vivo* pharmacology studies are also relevant to support the proposed indication. These studies are thus also included in the assessment of the current application.

Rationale and mechanism of action

Everolimus is a signal transduction inhibitor, targeting the protein mTOR within the mTORC1 complex. The mTORC1 complex obtains signals from many upstream inputs and propagates the information *via* regulation of multiple downstream pathways, ultimately affecting cell growth, proliferation and survival. Dysregulation of the protein kinase B (Akt)-mTOR signalling pathway has been shown to occur in the majority of NETs (reported in Zitzmann *et al*., 2007[2]; reviewed in Salazar *et al*., 2011[3]), largely associated with altered protein levels of Tuberous sclerosis complex 2 (TSC2) and phosphatase and tensin homolog deleted on chromosome 10 (PTEN), inhibitors of this signalling pathway. Constitutive mTOR activation has been found to be associated with primary tumour progression. Everolimus, an mTOR inhibitor, is envisaged to inhibit cell growth and NET progression.

Pharmacology

In vitro, everolimus (≥ 1 nM for 72 h) reduced the proliferation of human pancreatic endocrine tumour (PET) cells (BON [pancreatic carcinoid] and CM [insulinoma] cells) known to have increased signalling through the Akt-mTOR pathway. Reduced proliferation (up to 40%) and attenuated phosphorylation of all downstream targets of Akt (TSC2, mTOR and p70S6K) were seen in a rat insulinoma cell line (INS1) treated with ≥ 10 nM everolimus. The combination of octreotide (1 nM) and everolimus (100 nM) significantly inhibited INS1 proliferation, but the effect was no greater than that seen with either drug alone. The concentrations of everolimus effective in inhibiting the proliferation of PET cell lines are at or below the anticipated clinical maximum concentration (C_{max})[4].

Data from previously submitted pharmacology studies demonstrated that everolimus suppressed tumour growth in rats bearing tumours of pancreatic and pituitary origin, both expressing a somatostatin receptor, a feature of NETs. Tumour growth inhibition correlated with reduced mTOR signalling, at least in the PET model. An efficacious dose (5 mg/kg orally (PO) twice per week) is approximately equivalent to the proposed clinical dose based on body surface area[5]. In rats bearing the pituitary tumours, octreotide (720 µg/kg/day subcutaneously (SC)) alone had no effect on tumour growth, and did not alter the effect of everolimus when combined with this mTOR inhibitor.

Taken together, the nonclinical pharmacology data support the proposed use of everolimus for the treatment of patients with neuroendocrine tumours.

Pharmacokinetics

Drug interactions

The sponsor submitted a study to examine the potential cytochrome P450 (CYP450) inhibitory activity of octreotide. This study was provided by the sponsor *"for ease of review as octreotide was part of the comparator arm in pivotal study C2325 Carcinoid and this study is referenced in the Summary of Clinical Pharmacology"*. No clinically-relevant

[2] Zitzman, K., De Toni, EN., Brand, S. *et al*. The novel mTOR inhibitor RAD001 (everolimus) induces antiproliferative effects in human pancreatic neuroendocrine tumour cells. *Neuroendocrin.* 2007; **85:** 54-60.

[3] Salazar, R, Reidy-Lagunes D and Yao, J. Potential synergies for combined targeted therapy in the treatment of neuroendocrine cancer. *Drugs* 2007; **71:** 841-842.

[4] Based on a clinical blood C_{max} of 62 ng/mL (63.7 nM) and 80% uptake into blood cells (data from a previous submission).

[5] In rats, a dose of 10 mg/kg/7 days is equivalent to 8.6 mg/m^2/day using a mg/kg to mg/m^2 conversion factor of 6. The proposed clinical dose is 10 mg/day or 6.6 mg/m^2/day using a mg/kg to mg/m^2 conversion factor of 33 for a 50 kg individual.

inhibitory activity was seen on human CYP450 isozymes (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4) with octreotide.

Nonclinical summary and conclusions

- Nonclinical studies consisted of a single study report and a number of published papers. No major deficiencies were identified.
- *In vitro*, everolimus reduced the proliferation of human and rat pancreatic tumour cells. Previously submitted studies demonstrated that everolimus suppressed tumour growth in rats bearing neuroendocrine tumours of pancreatic and pituitary origin. The efficacious doses/concentrations were approximately equivalent to the clinical doses/plasma levels, thus supporting the proposed indication.
- No additional safety concerns are indicated by the submitted data.
- There are no nonclinical objections to the proposed extension of indications.

IV. Clinical findings

Introduction

Clinical rationale

Neuroendocrine tumours are classified according to their embryological origin, as arising from the foregut (for example, bronchial or gastric carcinoid), midgut (for example, small intestine or appendiceal carcinoid) or hindgut (for example, colon or rectal carcinoid). The main primary sites of origin are the gastrointestinal tract (62% to 67%) and the lung (22% to 27%)[6]. NETs are usually subclassified as carcinoid tumours or pancreatic NETs (PNETs).

The term 'carcinoid' is typically used to describe a well-to moderately-differentiated NET arising outside the pancreas, and is the usage recommended by the *National Cancer Institute* (USA) in its *Physician Directed Query* (PDQ) for gastrointestinal carcinoids. Overall, 40% to 60% of patients are asymptomatic at presentation. Midgut tumours are more commonly symptomatic; characteristic symptoms of carcinoid syndrome include flushing (affecting 90% of patients), diarrhoea (70%), abdominal pain (40%), valvular heart disease (40% to 45%), teleangiectasia (25%) and wheezing (15%). Metastatic disease occurs in approximately 30% to 50% of patients with NETs with carcinoid syndrome; of note, 12% to 22% of patients have disseminated disease at diagnosis. The most common sites of metastasis from midgut carcinoid tumours are the mesenteric lymph nodes and liver.

Pancreatic neuroendocrine tumours include both functional (gastrinomas, insulinoma and so on) and non-functional tumours arising in the pancreas. Both PNET and carcinoid tumours may be of low, intermediate, or high grade. An examination of the prognosis of patients with low and intermediate grade PNETs using data from the *Surveillance, Epidemiology, and End Results* (SEER) register, from 1973 to 2000 found a median survival of 17 months for patients with distant metastases and 69 months for patients with regionally advanced disease. Prognostic factors in patients with PNET included functional

[6] Halfdanarson TR, Rabe KG, Rubin J, Petersen GM. Pancreatic neuroendocrine tumours (PNETs): incidence, prognosis and recent trend toward improved survival. *Ann Oncol* 2008; 19: 1727-1733.

tumour status (when corrected for stage), age, stage, sex (females did better), and grade.[7] In this study, the median overall survival (OS) of patients with histological Grades 1 and 2 were similar as were those with Grades 3 and 4, while the former (Grades 1-2) had a significantly longer median OS of 51 months compared to 7.5 months for the latter group (Grades 3-4).

> **Evaluator comment:** One caveat in these data is that of the 1483 patients studied, only 311 (21%) of tumours were graded. The histological grade of NETs is important in this evaluation because only patients with tumours of low or intermediate grade were included in each pivotal study. The indication requested does not specify the histological grade of the tumour to be treated.

The prognosis of patients with carcinoid tumours was examined in another study using SEER data from 1973 to 2004. This analysis included a small number of patients with pancreatic carcinoids, but the majority of patients had tumours of gastrointestinal or tracheobronchial origin. Median survival in patients with Grade 1-2 disease who presented with distant metastases was 33 months while patients with regional spread had a median survival of 111 months. Prognostic factors included stage, grade, sex (females did better), age and primary tumour site[7]. As well, this study showed that median OS from the date of initial diagnosis in patients with metastatic well to moderately differentiated NETs of the small bowel, caecum, appendix, rectum, lung, and colon were 65, 55, 31, 26, 17 and 7 months, respectively.

> **Evaluator comment:** The NETs of the gastrointestinal tract show a wide range of values of OS. In the pivotal Study C2325 Carcinoid in the present application, the NETs are classed as "gastrointestinal" without reference to their site of origin. The origin of the gastrointestinal NETs, if given, would have allowed a comparison of the distribution of those NETs of different origin with different prognoses.

Treatment of NETs with chemotherapy is limited to Sunitinib (Sutent), which is approved in Australia for the treatment of unresectable, well differentiated pancreatic neuroendocrine tumours. The PI for this product states that it increases the median progression-free survival (PFS) from 5.5 to 11.4 months. An effect on OS has not been demonstrated. Octreotide modified release injection (Sandostatin LAR 10 mg, 20 mg and 30 mg vials) is approved in Australia for the relief of symptoms associated with functional tumours of the gastroenteropancreatic endocrine system, including carcinoid tumours with features of the carcinoid syndrome, and Vasoactive Intestinal Peptide secreting tumours (VIPomas), in patients who are adequately controlled on SC treatment with Sandostatin. In addition, interferon-alpha has been reported, like somatostatin analogues, to provide symptom relief in about 75% of patients.

Scope of the clinical submission

The clinical submission documented the clinical development program to extend the indications of everolimus to include the treatment of patients with advanced NETs of gastrointestinal, lung or pancreatic origin. The submission contained the following clinical information:

- Clinical pharmacology studies that formed part of each of the three studies submitted and provided PK and pharmacodynamic data.
- Two pivotal efficacy/safety studies, Study 2324 PNET ("RADIANT-3") and Study 2325 Carcinoid ("RADIANT-2") were provided.

[7] Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE *et al*. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumours in 35, 825 cases in the United States. *J Clin Oncol* 2008; 26: 3063-72.

- One Phase II study (Study 2239) of patients with *pancreatic* NETs was included.
- One periodic safety update report (PSUR); and a '90-day Safety Update' (an update of the sponsor's *Summary of Clinical Efficacy* and *Summary of Clinical Safety*) were included.

No population PK analyses were provided

Paediatric data

The submission did not include any paediatric data. Epithelial neuroendocrine neoplasms arising outside the appendix are extremely rare in the paediatric population. Broaddus *et al*., 2003[8] have reported 13 cases, noting that *"These neuroendocrine neoplasms have the ability to metastasise, regardless of histology at initial diagnosis"*. However the rarity of this disease in children justifies the lack of paediatric data in the present application.

Good clinical practice

All trials in the everolimus NETs clinical development program were conducted in full compliance with Good Clinical Practice (GCP).

Pharmacokinetics

Studies providing pharmacokinetic data

The PK data in this application are complex because they supplement and extend those from previous submissions. The present PK data were obtained from studies included in each of the three studies submitted. There were no excluded PK studies.

Summary of pharmacokinetics

The information in the following summary is derived from conventional PK studies unless otherwise stated.

Physicochemical characteristics of the active substance

The following information is derived from the Australian PI for Afinitor: The active ingredient of Afinitor is everolimus. The chemical name is 40-O-(2-hydroxyethyl)-rapamycin or 40-O-(2-hydroxyethyl)-sirolimus. Its molecular formula is $C_{53}H_{83}NO_{14}$ and its molecular weight is 958.2.

Pharmacokinetics in the target population

Values for the PK parameters of everolimus from previous studies and from the present studies are given in Table 1 below.

[8] Broaddus RR, Herzog CE, Hicks MJ. Neuroendocrine tumours (carcinoid and neuroendocrine endocarcinoma) presenting at extra-appendiceal sites in childhood and adolescents. 2003; *Arch Pathol Lab Med*. 127: 1200-1203.

Table 1. Summary PK data for everolimus

Study		Dose	food	N	C_{max}, ng/mL	AUC[a] ng.h/mL	CL/F (L/h)	$T_{1/2}$ h
C2119	Healthy male and female subjects	2 X 5-mg MF tablets sd	fasting	40	64.4 ± 17.8	536.7 ± 174.2	20.6 ± 6.8	36.9 ± 9.5
		2 X 5-mg FMI tablets sd	fasting	40	68.6± 20.0	538.7 ± 185.5	20.7 ± 7.2	37.3 ± 7.5
		1 X 10-mg FMI tablet sd	fasting	39	61.2 ± 19.1	537.8 ± 206.6	20.8 ± 6.8	36.5 ± 10.6
C2120	Healthy male and female subjects	10-mg MFI tablet sd	fasting	20	71.8 ± 27.4	680 ± 189	15.8 ± 4.37	35.6 ± 6.42
			low fat meal	22	43.8 ± 20.2	464 ± 94.7	22.5 ± 4.82	39.6 ± 5.92
			High fat meal	19	33.2 ± 11.4	529 ± 136	20.1 ± 5.18	40.5 ± 8.21
C2121	Healthy male and female subjects	5X1-mg intact tablets sd	Low fat meal	39	28.79 ± 11.62	205.82 ± 77.97	nd	36.04 ± 8.67
		5X1-mg tablets in suspension sd		36	20.77 ± 8.73	184.33 ± 75.72	nd	35.92 ± 7.99
C2102	Oncology male and female patients	5 mg qd	Fasting or after a light fat-free snack	4	31.5 ± 9.4	223 ± 74	24.8 ± 10.0[b]	Nd
		10 mg qd		7	59.7 ± 16.9	560 ± 283	24.5 ± 19.2[c]	Nd
C2102	Oncology male and female patients	5 mg qw	Fasting or after a light fat-free snack	4	32.4 ± 15.3	280 ± 51	18.4 ± 4.0	25.6 ± 3.8
		10 mg qw		4	69.1 ± 8.1	571 ± 261	22.1 ± 14.1	39.3 ± 17.0
		20 mg qw		2	93.5 ± 0.4	1001 ± 302	20.9 ± 6.3	32.1 ± 9.4
		30 mg qw		5	72.2 ± 15.3	1761 ± 763	19.4 ± 7.6	36.2 ± 4.6
		50 mg qw		5	160 ± 78	2613 ± 665	20.3 ± 5.8	26.6 ± 5.1
		70 mg qw		6	167 ± 67	3613 ± 1494	21.6 ± 6.8	26.0 ± 2.8
C2101	Oncology patients	20 mg qw	Fasting or after a light fat-free snack	4	67 ± 16	721 ± 73	nd	25 ± 3
C2324	patients with advanced pancreatic neuroendocrine tumor	10 mg qd[d]	Fasting or after a light fat-free snack	5	56.3 ± 11.8	430 ± 79[e]	24.0 ± 4.9	Nd
C2325	Patients with advanced carcinoid tumor	10 mg qd	Fasting or after a light fat-free snack	5[f]	74.8 ± 33.6	578 ± 243	19.5 ± 6.8	Nd
C2240	Patients with renal cell carcinoma	10 mg qd	Fasting or after a light fat-free snack	12	76.7 ± 39.3	729.1 ± 262.7	15.4 ± 5.3	Nd

[a] $AUC_{0-\infty}$ for single dose (sd), $AUC_{0-\tau}$ for daily dosing (qd) and weekly dosing (qw) at steady-state
[b] excluding one patient with a high CL/F value of 39.2 L/h, mean ± sd CL/F was 20.0 ± 3.5 L/h
[c] excluding one patient with a high CL/F value of 66.8 L/h and one patient with an unusually high concentration value at 24 hour post-dose, mean ± sd CL/F was 19.05 ± 3.25 L/h
[d] Excluded two patients with unusually high concentration values at 24 hour post-dose.
[e] $AUC_{0-tlast}$, where tlast was approximately 24 hours post-dose
[f] n=9 for C_{max}
nd = not determined
Source: Study C2119, Study C1101, Study C2101 CP report, amended Study C2102 CP report, updated CSR for Study C2240, Study 2120, Study C2121, Study C2324, and Study C2325.

Study 2324 PNET

Objectives

Pharmacokinetics

1. To confirm previous values for PK parameters and the dose proportionality of minimum concentration (C_{min}) values
2. To determine C_{min}values in two subsets of patients and intersubject variability
3. To determine apparent oral clearance of everolimus
4. To compare C_{min}values in Japanese and non-Japanese patients
5. To determine the effect on C_{min}values of substrates, weak inhibitors and inducers of CYP3A4
6. To determine the effect of octreotide on everolimus exposure after the 10 mg daily dose.

Pharmacodynamics

1. To relate the values of $C_{min}$to patient response as PFS, tumour size and increased risk of the clinically notable adverse events (AEs).

Methodology

Design

Study C2324 PNET was a randomised double blind Phase III study of everolimus 10 mg/day plus best supportive care versus placebo plus best supportive care in the treatment of patients with PNET.

Entry criteria

1. Unresectable or metastatic PNET;
2. Low or intermediate grade neuroendocrine carcinoma;
3. Disease progression < 12 months prior to entry;
4. Measurable disease according to the Response Evaluation Criteria In Solid Tumours (RECIST[9]);
5. No hepatic embolisation < 6 months prior to entry (1 month if other sites of measurable disease);
6. No cryoablation or radiofrequency ablation < 2 months prior to entry;
7. Performance status (PS) 0-2.

Treatments

Patients were instructed to take two 5 mg tablets of everolimus or matching placebo PO with a glass of water, once daily at the same time each day either under fasting conditions or after eating no more than a light, fat-free meal. Of note, some patients in the study had dose reduction to 5 mg/day or 5 mg every other day.

PK sampling and analysis

Pre-dose trough assessments: Pre dose blood samples for everolimus concentration determination were collected immediately before everolimus administration from all patients at all investigational sites. Pre dose blood samples (C_{min}) were collected at Cycle 1

[9] The RECIST is a voluntary, international standard using unified, easily applicable criteria for measuring tumour response using X-ray, computer tomography and magnetic resonance imaging.

Day 15, Cycle 2 Day 1 and every cycle Day 1 thereafter until the end of the core phase. Pre dose blood samples collected from placebo patients were not analysed.

Full PK profile assessments at steady-state: Serial blood samples for everolimus concentration determination (for a full PK profile) were collected during a 24 h dosing interval at steady-state in patients who did not take depot octreotide, chronic Sandostatin injection or other long-acting somatostatin analog during the study as a concomitant medication. At steady-state, full PK profile assessments were done on Day 1 of Cycle 2 as follows: pre dose, 0.5, 1, 2, 5 and 24 h post dose. Blood samples collected from placebo patients were not analysed.

Study participants

Enrolled: All patients were planned to have pre dose trough assessment and 40 patients to have full PK profile determined. The full PK profile assessments were planned for a total of 40 patients at three pre selected investigational sites in order to obtain approximately 20 full steady-state profiles in the everolimus group. The 40 patients were selected as above.

Completed and analysed: Although 207 patients were randomised to receive everolimus and to have C_{min}assessments, only 120 had this assessment in Cycle 1, only 55 in Cycle 10 and 12 in Cycle 20. Eight patients had full kinetic profiles not the 20 of 40 as planned. No reason was given for the reduced numbers. Two of the 8 patients had unusually high concentration values (57.1 and 85.8 ng/mL, respectively) at 24 h post dose. The data were analysed with and without the results of the two patients included.

> **Evaluator comment:** No reasons were given for the failure to meet the planned numbers. Elsewhere, the report states that patients not at steady-state were not included nor those who had vomited within 4 h after taking the last everolimus dose. Whether this was also the reason for the small numbers of subjects (8 instead 40) with complete PK analyses is not stated.

Pharmacokinetics results

1. *Confirmation of PK parameters, and dose proportionality; determination of intersubject variability and oral clearance (CL) in relation to PO bioavailability (F): CL/F*

Summary statistics of the PK parameters of the patients with full PK profiles after the 10 mg daily dose and the 5 mg daily dose (1 patient) are summarised in Table 2:

Table 2. PK Parameters from C2324 PNET

Regimen	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}tlast}$ (ng.h/mL)	CL/F (L/h)	C_{min} (ng/mL)
10 mg daily (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 daily [1] (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%)
5 mg daily (n=1)	27.4	3.0	481	10.7	12.2

[1] Excludes data from the 2 patients (Patient C2324-0501-00007 and Patient C2324-0501-00015) with atypically high concentrations at 24-hours postdose.
Values are mean ± standard deviation (coefficient of variation %) excluding t_{max} where median (range) is summarized.

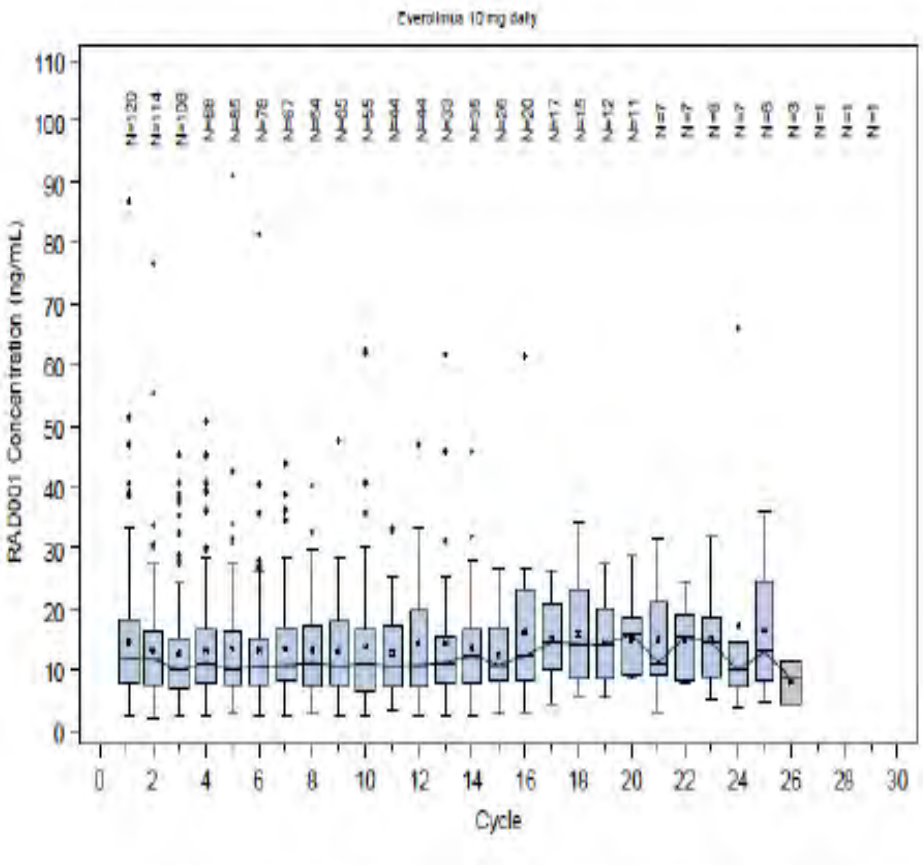
> **Evaluator comment:** The C_{min} values of the two patients excluded were 57.1 ng/mL and 85.8 ng/mL, which is 15 times and 23 times the standard deviation (SD), respectively, so their exclusion is reasonable on the grounds that the samples were probably taken post dosage rather than pre dosage with everolimus. Exclusion of these subjects reduces as expected the coefficient of variation (CV) from high values (for example, 53% for area under the plasma concentration curve (AUC)) to a moderate value (18%). The study report states *"mean Cmax, Cmin, and*

CL/F (values) with the 10 mg daily dose were similar to those reported in previous studies". However, the CL/F value is approximately half that stated in the European Summary of Product Characteristics (SPC). Although dose proportionality was shown between the two values for C_{max} for the 5 and 10 mg doses, this was not the case for AUC values. However, the comparison was not robust because there were data from only a single patient at the 5 mg dose.

2. *Cmin values during treatment cycles*

Median C_{min} values appeared to be stable over time (Figure 1). Several pre dose samples had concentrations > 35 ng/mL; these samples were believed to have been collected post dose. In general, C_{min} values observed with the 10 mg daily dose were similar to those reported in an earlier study (2239; see below) of patients with advanced pancreatic NETs who had mean values of 15.7 ± 15.82 ng/mL. Intersubject variability in C_{min} values ranged from 39.6% to 127%.

Figure 1. C_{min} everolimus versus time from Study C2324 PNET



Note: No legend was provided for the above figure

Evaluator comment: From the table of values on which Figure 1 was based, the mean C_{min} value ranged from approximately 12 to 14 ng/mL. The samples with concentrations > 35 ng/mL were about 3 times the mean and so can be accepted as post dose rather than pre dose samples. The CV in this population was high - 40% to 127% compared to 18% in the small sample above.

3. *Comparison of C_{min} values in Japanese and non-Japanese patients*

This comparison had been made in previous submissions (for renal cell cancer) and Studies C1101 and 2102 not in the present submission. The results of these studies *"suggested that CL/F is similar in Japanese and Caucasian cancer patients with similar liver functions."*

Results tabulated in the sponsor's *Summary of Clinical Pharmacology* at a dose of 10 mg daily of everolimus showed a oral clearance (CL/F) value of 8.6 (SD 2.3) L/hr/m^2 for Japanese patients and were 12.2 (10.6) L/hr/m^2 for non-Japanese patients and AUC values of 711 ng.h/mL and 560 ng.h/mL, respectively. C_{min} values from the Appendix to the sponsor's *Summary of Clinical Pharmacology* shows the values given in Table 3, below, in which the C_{min} for Japanese patients was about 50% higher than in non-Japanese patients.

In the present study, the sponsor's *Summary of Clinical Pharmacology states "…that mean C_{min} values after the 5 mg daily dose (n = 6) and 10 mg daily dose (n = 21) were slightly higher in Japanese patients than after the respective dose groups in non-Japanese patients (n = 35 and 154, respectively) and the differences are not considered clinically significant"*.

Table 3. Cmin of Japanese and others

Table PT-3-1 (Page 1 of 1)
Geometric mean Cmins and 90% CIs in Japanese and non-Japanese patients by dose group (daily dose only)
Full Analysis Set

Population	Dose	N. Patients	N. Samples	Geometric Cmin Geomean	90 % CI Lower	90 % CI Upper
Japanese	10mg daily	21	157	16.998	14.106	20.484
	5mg daily	6	48	8.865	6.928	11.343
Others	10mg daily	154	985	10.762	10.042	11.533
	5mg daily	35	192	5.445	4.956	5.982

The number of patients in all groups except the 5 mg Japanese group (n = 6) are substantial and the 90% confidence interval (CI) clearly shows the C_{min} values of the Japanese groups at both doses to be higher than those of the non-Japanese group with no overlap of the CIs.

> **Evaluator comment:** Taken together, these data are consistent and indicate a 40% to 50% increase in AUC, a 50% decrease in clearance (CL/F/m^2) and a statistically significant increase in C_{min} values of 40 to 50%, in Japanese patients compared to non-Japanese patients. The statement in the present Australian PI that *"Oral clearance (CL/F) is similar in Japanese and Caucasian cancer patients with similar liver functions"* requires rewording and further information to be added. This is not to say the difference is clinically significant. Such significance will depend on comparisons of efficacy and toxicity in the two populations.

4. Determination of substrates, weak inhibitors and inducers of CYP3A4 on Cmin values

No primary data were given in either the report of Study 2324 PNET or in the sponsor's *Summary of Clinical Pharmacology*, which states none of these impacted on the C_{min} values of everolimus.

> **Evaluator comment:** The method of this study was not described in the body of the study report. The statistical methods describes the grouping of patients taking concomitant medications into different categories based on the effect of those medications on CYP3A4 metabolism; for example, these data show the CV ranged from about 50% to over 100%. No firm conclusion can therefore be made and the changes proposed to the PI cannot be accepted at this time[10].

[10] Note that details of discussions regarding PI amendments are beyond the scope of this AusPAR.

5. Everolimus-octreotide interaction

In Study 2324 PNET, some patients in the study also received concomitant treatment of a somatostatin analog. There was no apparent difference in C_{min} after the 10 mg daily dose between the two groups of patients. However, it appeared that the mean C_{min} for patients with dose reduction to 5 mg/day were slightly higher in patients not taking the somatostatin analog (n = 29) than in patients who did (n = 12). The difference, however, is not considered clinically significant and was most likely to be attributable to elevated values in some outliers.

> **Evaluator comment:** The methods used and the results of this study were not provided in the study report, only the above statement in the sponsor's *Summary of Clinical Pharmacology*. This interaction is more seriously investigated in the next Study, C2325 Carcinoid, and will be discussed further below.

Pharmacodynamics

Methods

Relationship between efficacy endpoints and C_{min}: The relationship between C_{min} and PFS was investigated by a Cox regression model including the C_{min} (log-transformed and time-normalised), prior use of somatostatin analog therapy and concomitant use of somatostatin analog therapy as separate covariates. A figure showing the relative risk by time-normalised C_{min} was derived from the model.

The time dependency of tumour size at time *t*, was investigated by a linear mixed model including the covariates log C_{min}, represented by the log-transformed individual's geometric mean of pre dose concentrations of the preceding 84 days, time (in study days), baseline tumour size and history of depot octreotide treatment and concomitant medication with Sandostatin as separate covariates. A figure showing the mean tumour size at time *t* by C_{min} was generated. These analyses were also performed on the Japanese subgroup.

Relationship between safety endpoints and C_{min}: The relationship between C_{min} and time to first clinically notable AE was investigated. For this safety endpoint, a Cox regression model was fitted and included the C_{min} (log-transformed and time-normalised) as a covariate. These analyses were also performed on the Japanese subgroup.

A figure showing the relative risk by time-normalised C_{min} was derived from the model. Probability plots of first occurrence of clinically notable AEs were generated showing Kaplan-Meier analyses for three subgroups of time-normalised C_{min}. Total bilirubin and albumin concentrations at time t were separately correlated to the geometric mean of C_{min}. A scatter plot was produced for visualization.

> **Evaluator comment:** In the above analysis, 'time normalised' was defined as area under the pre dose concentration-time curve to the start of the AE divided by the time to start of AE. An amendment to the protocol plan changed the analysis population from Intention-to-Treat (ITT) population to the safety population. The latter was defined as those patients receiving at least one dose of drug. The change therefore appears reasonable with no obvious bias.

Results

Efficacy end points: No statistically significant difference in PFS was found with higher values of C_{min}(risk ratio: 0.73; 95% CI: 0.50, 1.08). Similarly a linear mixed model statistical analysis showed no significant impact of log-transformed geometric mean C_{min} values on the change in tumour size over time. Complicated statistical manipulation however claimed a more significant impact with a change in exposure from 5 ng/mL to 10 ng/mL.

Evaluator comment: Although the latter statistic claimed an odds ratio of 1.62, favouring the higher $C_{min}$of 10 ng/mL and a probability (p) value of 0.001, the 95% CI was wide (1.29, 2.040). The result was based on measurements of tumours on imaging by investigators. As discussed below, even estimates of disease progression by such measurements are difficult with this particular tumour and differ between investigators and independent reviewers. For these reasons, confirmation of the conclusions in further independently monitored studies is required before accepting them. The proposed incorporation of this conclusion in the PI therefore cannot be accepted at this time[11].

Safety end points

No consistent trends were evident from the Kaplan-Meier and Cox regression analyses, with the exception of stomatitis/oral mucositis/ulcers and renal events. For stomatitis/oral mucositis/ulcers, both analyses suggested higher C_{min} was not indicative of a higher probability/risk while for renal events both analyses demonstrated no impact of C_{min} on the probability/risk of the event. Overall, time-normalised predose concentrations were not indicative of an increased risk with higher C_{min} within the C_{min} range in the study.

Study 2325 Carcinoid

Objectives

Pharmacokinetics

6. Determination of PK parameters of everolimus
7. Determination of C_{min} values during treatment cycles of everolimus and octreotide administered singly and when co-administered.

Pharmacodynamics

The objective seems to be the same as in the previous study (C2324 PNET); that is, to relate the values of C_{min} to patient response as PFS, tumour size and increased risk of the clinically notable AEs.

Methodology

Design

Study C2325 Carcinoid was a randomised double blind, placebo controlled, multicenter Phase III study of patients with advanced carcinoid tumour receiving Sandostatin LAR Depot and everolimus 10 mg/day or Sandostatin LAR Depot and placebo.

Entry criteria

1. Unresectable or metastatic carcinoid tumour;
2. Low or intermediate grade neuroendocrine carcinoma;
3. Disease progression < 12 months prior to entry;
4. Measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST);
5. No hepatic embolisation < 6 months prior to entry (1 month if other sites of measurable disease);
6. No cryoablation/radiofrequency ablation < 2 months prior to entry;
7. PS 0-2;

[11] Note that details of discussions regarding PI amendments are beyond the scope of this AusPAR.

8. History of diarrhoea/flushing or both; symptoms not required at entry.

Treatments

In both treatment arms everolimus or placebo was given by continuous oral (PO) daily dosing of 10 mg/day (two 5 mg tablets) along with the dose of Sandostatin LAR Depot 30 mg intramuscularly (IM) every 28 days. Patients were instructed to take two tablets of everolimus or matching placebo PO with a glass of water, once daily at the same time each day either under fasting conditions or after having eaten no more than a light, fat-free meal. Of note, some patients in the study had dose reduction to 5 mg/day or 5 mg every other day.

PK sampling and analysis

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 h post dose. Of these 11 full PK profiles, 1 was not collected at steady-state and another one was associated with the daily dose of 5 mg. Pre dose blood samples for everolimus concentration determination were collected from all the patients at pre dose on Day 15 of Cycle 1 and then on Day 1 of every Cycle thereafter. Pre dose blood sample for concentration determination of octreotide in plasma were collected for all patients on Day 1 of every cycle at pre dose and on Day 15 of Cycle 1. The effect of co-administration of everolimus on octreotide pre dose concentrations was assessed by a linear mixed effect model including dose and treatment as fixed effects and subject as a random effect.

Study participants

Enrolled: As in the previous study, C2324 PNET, all patients were planned to have pre dose trough assessment and 40 patients to have full PK profile determined.

Completed and analysed: Although 429 patients were randomised and were to have C_{min} assessments, only 114 had this assessment in Cycle 1, only 40 in Cycle 10 and only 23 in Cycle 20. Five patients had full kinetic profiles, not the 20 of 40 as planned. Nine had determinations of C_{max}, C_{min} and time to reach maximum concentration (t_{max}).

> **Evaluator comment:** As in the previous study, no reasons were given for the failure to meet the planned patient numbers.

Pharmacokinetics results

1. Determination of PK parameters:

Full everolimus PK profiles were available for 11 patients. Two patients were excluded and the data for the remainder presented as Table 4:

Table 4. PK parameters for everolimus from Study 2325 Carcinoid

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=9) [a]	74.8 ± 33.6 (49.9%)	0.50 (0.50-5.0)	578 ± 243 (42.1%)	19.5 ± 6.8 (35.0%)	9.47 ± 2.59 (27.3%)

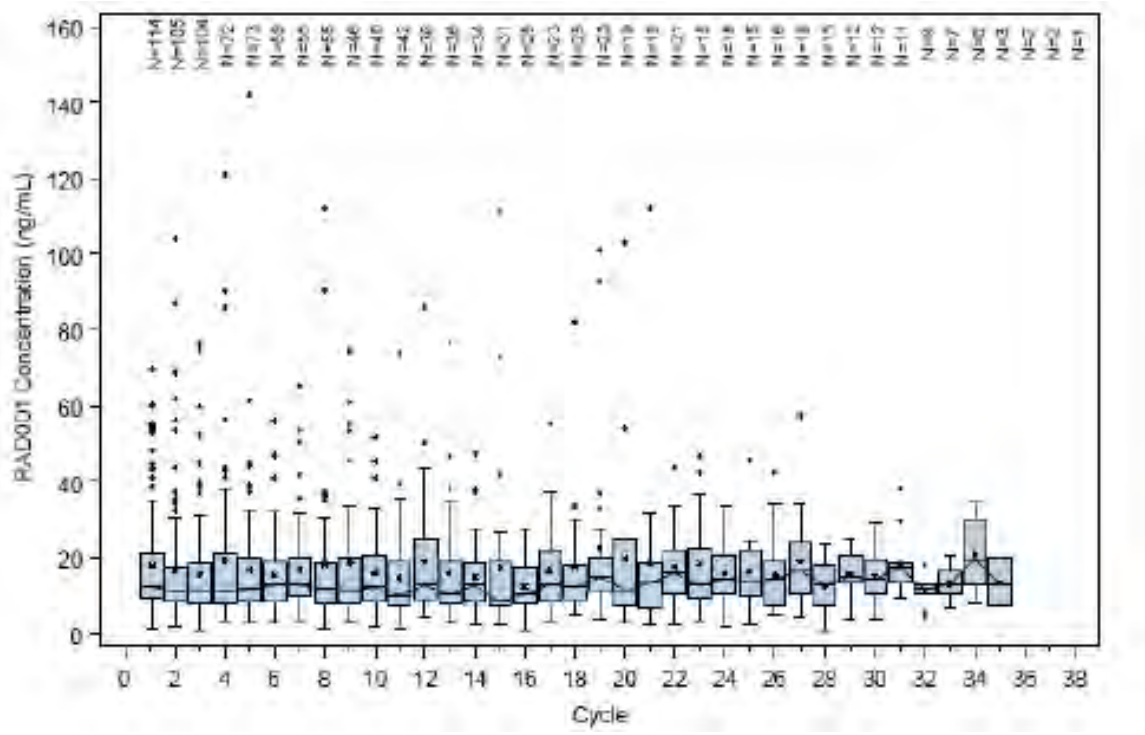
Values are mean ± standard deviation (coefficient of variation %) with the exception of t_{max} where median (range) is summarized
[a] n=5 for $AUC_{0\text{-}\tau}$ and CL/F

> **Evaluator comment**: One patient was excluded because the dosage was not at steady-state and another patient was excluded because the dosage of everolimus was 5 mg not 10 mg daily. The values show a high inter-patient variability for C_{max}, AUC and CL/F (CV 50%, 42%, 35%, respectively).

2. C_{min} values during treatment cycles

Median C_{min} values appeared to be stable over time (Figure 2). Several pre dose samples had concentrations > 35 ng/mL; these samples were believed to have been collected post dose. In general, C_{min} values observed with the 10 mg daily dose were similar to those reported in an earlier study (2239; see below) of patients with advanced pancreatic NET who had mean values of 15.7 ± 15.82 ng/mL. Inter-subject variability in C_{min} ranged from 33% to 130%. These values were from the table of values on which Figure 2 was based.

Figure 2. C_{min} everolimus versus time (from C2325 Carcinoid)



Note: No legend was provided for the above table

Evaluator comment: Results of Cox regression suggested a trend of longer PFS with higher time-normalised everolimus C_{min} (risk ratio = 0.66 [95% CI: 0.40, 1.08]) and prior treatment of somatostatin analog had no significant effects on this relationship. There was a very minor impact of log-transformed everolimus C_{min} values on the change of the tumour size over time.

No consistent trends of everolimus C_{min} with probability/risk of the clinically notable AEs were evident in the Kaplan-Meier and Cox regression analyses, with the exception of:

- Pulmonary and metabolic events: both analyses demonstrated higher probability/risk with higher everolimus C_{min} (risk ratio of 2.35 with 95% CI of 1.3-4.3 for pulmonary events and 2.12, and 1.5-3.1 for metabolic events).
- Renal events, both analyses demonstrated no impact of everolimus C_{min} on the probability/risk of the event.

3. Octreotide PK

Pre dose octreotide concentrations appeared to be stable over the study period (figures not shown in this evaluation). Co-administration of everolimus and depot octreotide increased octreotide C_{min} with a geometric mean ratio (everolimus/placebo) of 1.47 (90% CI: 1.32, 1.64). Geometric mean octreotide C_{min} was 5.19 ng/mL (n = 141) and 3.53 ng/mL (n = 148) for the everolimus and placebo treatment groups, respectively. The study report authors comments that it is unlikely that this increased octreotide level resulted from a metabolism-mediated drug interaction or protein binding interaction with everolimus,

because previous data had shown no CYP450-mediated metabolism of octreotide and low plasma protein binding. The actual mechanism of interaction is not known. In the sponsor's *Summary of Clinical Pharmacology*, the sponsor reports that octreotide is eliminated as unchanged drug in urine (32% of the administered dose) and literature data indicate that radioactively labeled (^{123}I-Tyr^{3})-octreotide is excreted *via* the bile into the intestines in human. In addition, *in vitro* data indicate that hepatic uptake of octreotide is mediated by a carrier-mediated transport system and octreotide is a substrate for both P-glycoprotein (PgP) and multidrug resistance associated protein2 (mrp2) transporters in the renal proximal tubules. The sponsor states: *"As everolimus is a moderate inhibitor of PgP, the observed rise in octreotide exposure when co-administered with everolimus in this study may be due to inhibition of octreotide transporters in the liver and kidney by everolimus"*.

> **Evaluator comment:** The explanation given is reasonable. The clinical significance of the increase in octreotide PK parameters is unknown. A possible effect on the efficacy endpoint, PFS, was explored (see below under *Pharmacodynamics*).

4. Effects of substrates, inhibitors and inducers of CYP3A4 and/or PgP on everolimus C_{min}

No differences were observed in the values of C_{min} for everolimus with substrates, inhibitors or inducers of CYP3A and/or PgP although the numbers of patients in each group were small and in some cases too few for analysis.

Pharmacodynamics

Methods

Relationship between PFS and C_{min} for everolimus: The result for the risk ratio (0.66) failed to show that a longer PFS was associated with a higher value of C_{min} for everolimus. The 95% CI was wide (0.4, 1.08) and included unity.

Relationship between PFS and C_{min} for octreotide: In the placebo arm, where octreotide was administered alone, the hazard ratio (HR) for a longer PFS with a higher C_{min} for octreotide was not significant (p = 0.13) with a value of 0.89 (95% CI: 0.76, 1.03). In the everolimus treatment arm, when octrotide was co-administered, the overall impact of octreotide log-C_{min} on PFS was not statistically significant (p = 0.17).

Study 2239

Objectives

Pharmacokinetics

1. To assess the steady state exposure to everolimus and to estimate the effect of co-administering Sandostatin LAR Depot on such exposure.

Methodology

Design

Study 2239 was a global multi center, open label, stratified, expanded two-stage study of everolimus in patients with advanced pancreatic NET after failure of cytotoxic chemotherapy. Patients were stratified according to whether or not they had received prior treatment with Sandostatin LAR Depot.

- Stratum 1 patients (100 patients planned) who were not receiving regular Sandostatin LAR Depot therapy. These patients were to receive everolimus monotherapy at 10 mg/day.
- Stratum 2 patients (44 patients planned) who had received at least three consecutive months of Sandostatin LAR Depot therapy prior to enrollment.

The exposure-response relationships were explored by comparing the efficacy in subgroups of patients with different C_{min} values. The average C_{min} value was calculated for each patient using his/her available C_{min} values in the study. Patients were assigned to three C_{min} subgroups in each stratum based on their average C_{min} values: 0-10 ng/mL (low C_{min} group), 10-35 ng/mL (median C_{min} group), and > 35 ng/mL (high C_{min} group).

Treatments

These patients were to receive everolimus 10 mg/day in addition to continuing their entry dose of Sandostatin LAR Depot.

PK sampling and analysis

For all patients in both strata, everolimus trough level determinations were assessed at Day 15, Day 30 and every month thereafter. Octreotide PK blood samples were assessed for patients in Stratum 2 only and were measured at baseline, Day 15, Day 30 and every month thereafter.

Study participants

The total number of patients planned was a maximum of 144 patients, depending on interim analyses for futility. The final study population resulted from 186 patients having been screened for a total of 115 patients in the full analysis set (FAS) for Stratum 1 and 45 patients in the Stratum 2 FAS.

Pharmacokinetics results

Stratum 1. Excluding the mean C_{min} after Cycle 16 where n = 1, mean ± SD C_{min} values ranged from 10.4 ± 7.01 ng/mL (n = 64) in Cycle 6 to 15.7 ± 15.34 ng/mL (n = 87) in Cycle 3. Inter-subject variability (coefficient of variation - CV) calculated as a sensitivity analysis ranged from 33.9% to 135.6%.

Stratum 2. Excluding the mean C_{min} values in Cycles 18 onward where n < 3, mean ± SD C_{min} values ranged from 8.2 ± 5.03 ng/mL (n = 22) in Cycle 7 to 27.7 ± 37.7 ng/mL (n = 4) in Cycle 17. Inter-subject variability (CV) calculated as a sensitivity analysis ranged from 34.1% to 100.2%.

The effect of co-administration of Sandostatin LAR Depot and everolimus on everolimus C_{min} was assessed by comparing the log-transformed everolimus C_{min} in Stratum 1 and Stratum 2 at Cycle 1 Day 15. The ratio of geometric means of C_{min} was close to 1 (90% CI: 0.88; 1.54), suggesting that co-administration of Sandostatin LAR and everolimus did not have a clinically significant effect on the exposure of everolimus.

The effect of co-administrating of everolimus and Sandostatin LAR on the pre dose plasma concentrations of octreotide was assessed in Stratum 2 by comparing the octreotide plasma C_{min} at Cycle 2 Day 1 with that at Cycle 1 Day 1. The geometric mean ratio of octreotide plasma C_{min} was 1.21 (90% CI: 1.02, 1.44) with upper bound of the 90% CI lower than 1.5, suggesting that co-administration of everolimus and Sandostatin LAR did not have clinically significant effects on the exposure of octreotide.

Evaluator's overall conclusions on pharmacokinetics and pharmacodynamics

Pharmacokinetics

The application provided no new information on the absorption, distribution, metabolism and excretion of everolimus in cancer patients.

- The PK and pharmacodynamic studies were weakened by the failure in the major studies, C2324 PNET and C2325 Carcinoid, to achieve the planned numbers of patients, resulting in high variability of results and small numbers of subjects for analysis. However, the results from all three studies were generally consistent.

- Contrary to the conclusions in Study 2324 PNET, Japanese patients showed a consistent pattern of reduced clearance, higher AUC values and with statistically higher C_{min} values compared to non-Japanese patients. Whether this is clinically significant, as claimed in the sponsor's *Summary of Pharmacokinetics*, depends on the comparison of safety in the two populations.
- The studies were consistent in showing that octreotide administered concurrently with everolimus did not affect the C_{min} value of everolimus in a clinically significant way. Everolimus however co-administered with octreotide resulted in a statistically significant increase of about 50% in the C_{min} of octreotide. The clinical significance of this is unknown.
- No differences were observed in the values of C_{min} for everolimus with substrates, inhibitors or inducers of CYP3A and/or PgP although numbers were small in several cases and the variability high.

Pharmacodynamics

- A "trend" was claimed showing that a higher value of the C_{min} for everolimus was associated with a longer duration of PFS. This association was not consistently significant within Study C2324 PNET and not found in C2325 Carcinoid. A convincing result of such an association is difficult to demonstrate because of high inter-subject variability in C_{min} values with wide CI values. As well, an association does not mean a cause and effect, especially since the action of a drug such as everolimus in reducing the size of a tumour mass and maintaining it would be a complex function of drug concentration. This claim therefore is not acceptable in the PI at this time.
- The relationship between most safety events and the value of C_{min} for everolimus was mostly inconsistent in Study C2324 PNET and not examined in Study C2325 Carcinoid.

Pharmacodynamics

Studies providing pharmacodynamic data

The description and results of the pharmacodynamic data from the submitted studies have been incorporated into the pharmacokinetic sections, above.

Summary of pharmacodynamics

See Summary of pharmacokinetics, above.

Evaluator's overall conclusions on pharmacodynamics

See Evaluator's overall conclusion on pharmacokinetics and pharmacodynamics, above.

Efficacy

Dosage selection for the pivotal studies

The clinical dose and schedule for confirmatory testing in the Phase III trials was selected on the basis of the relationship between systemic drug exposure and pharmacodynamic markers within the phosphatidylinositol 3 kinase (PI3K)/Akt/mTOR pathway and clinical experience in the Phase I/II programs.

The observed systemic drug exposure (C_{min}) following 5 and 10 mg daily dosing and the associated inter-patient variability were 7.2 ng/mL (90% CI: 5.2, 9.4) and 16.0 ng/mL

(90% CI: 8.6, 23), respectively. *In vivo* data based on the inhibition of the phosphorylation of various proteins involved in relevant signal transduction pathways (S6K1, 4E-BP1 and eIF-4G) suggested that a daily dose of ≥ 10 mg everolimus is required to achieve this inhibition in the majority of patients.

Clinical data supported the selection of the 10 mg daily dose for further development of everolimus because the 5 mg daily dose provided no appreciable safety advantage over 10 mg in the previous Phase I study and the 10 mg daily dose showed encouraging clinical benefit in previous Phase II trials. The approved dose for the treatment of renal cell cancer is also 10 mg daily.

In the pivotal trial C2325 Carcinoid, patients in the control arm received treatment with octreotide (Sandostatin LAR) and in the trial arm octreotide combined with everolimus. Somatostatin analogs have been reported to provide reliable control of hormone-mediated symptoms and recent evidence indicated that they may also exert an antiproliferative effect[12] and that they reduce the expression of tumour growth factors, including IGFs and epidermal growth factor (EGF). These observations suggested that everolimus may work synergistically with depot octreotide (Sandostatin LAR Depot) to arrest growth and control hypersecretory activity in carcinoids and pancreatic NETs through the dual inhibition of mTOR and growth factors. Dosage of everolimus was 10 mg daily and that of Sandostatin LAR 30 mg administered intramuscularly (IM) every 28 days.

> **Evaluator comment:** The dose of Sandostatin LAR used in the study exceeded the dose of 20 mg IM monthly recommended in the Australian PI, to be used after effectiveness was shown with the subcutaneous (SC) preparation. However the 30 mg dose in the study was probably safe since the PI reports hot flushes as the only AE after overdoses of Sandostatin LAR ranging from 100 mg to 163 mg/month. Also cancer patients receiving doses of Sandostatin LAR up to 60 mg/month and up to 90 mg/2 weeks have been reported. These doses were in general well tolerated; however, the following AEs have been reported: frequent urination, fatigue, depression, anxiety and lack of concentration. In Study C2325 Carcinoid, exposure of patients to octreotide was increased about 50% with concomitant use of everolimus, so this would equate to a monthly dose of about 45 mg IM. The safety results of the study comparing the two arms of the study are described in the sections on safety, below.

Treatment of advanced NETs of gastrointestinal, lung or pancreatic origin.

Pivotal efficacy studies

Two pivotal studies were provided, one for advanced NETs of pancreatic origin (Study C2324 PNET) and the other for advanced NETs mainly of gastrointestinal or lung origin (Study C2325 Carcinoid). Since both studies were of similar design and treated similar cancers, their evaluation has been combined.

Studies C2324 PNET and 2325 Carcinoid

Study design, objectives, locations and dates

Study C2324 PNET was a randomised, double blind, Phase III study of everolimus 10 mg per day plus best supportive care versus placebo plus best supportive care in the treatment of patients with advanced pancreatic NETs. The primary objective was to assess the efficacy and safety of everolimus in the treatment of pancreatic NETs. The study was

[12] Rinke A, Müller H-H, Schade-Brittinger C, *et al*. Placebo-controlled, double blind, prospective, randomised study on the effect of octreotide LAR in the control of tumour growth in patients with metastatic neuroendocrine midgut tumours: a report from the PROMID Study Group. *J Clin Oncol.* 2009; 27: 4656-4663.

carried out in 82 centers in Belgium, Brazil, Canada, France, Germany, Greece, Italy, Japan, Republic of Korea, Netherlands, the Slovak Republic, Spain, Sweden, Switzerland, Taiwan, Thailand, the United Kingdom and the USA (the USA contributed 40.2% of patients) from 17 August 2007 until the data cut-off date of 28 February 2010.

Study C2325 Carcinoid was a randomised, double blind Phase III study of everolimus 10 mg per day or placebo plus Sandostatin LAR Depot in patients with advance carcinoid tumours. The primary objective was to assess the efficacy and safety of everolimus in treating NETs, mainly of gastrointestinal and pulmonary origin. The study was carried out in 93 centers in Australia, Belgium, Canada, the Czech Republic, Finland, France, Germany, Great Britain, Greece, Israel, Italy, Netherlands, the Slovak Republic, Spain, Sweden, Turkey, and the United States (the US contributed 43.6% of patients) from 10 January 2007 until the data cut-off date of 2 April 2010.

Changes to the protocol and study analysis:

C2324 PNET Protocol amendments: The study protocol was amended once. The above section describes the study conduct as amended. The main amendments (on 22 January 2010) are summarised in Table 5, below. The changes in this amendment were made prior to study unblinding and were considered by the sponsor as having no effect on the interpretation of study results.

Table 5. Main amendments - Study C2324 PNET

Amendment change	Rationale for change
Data source for the primary endpoint was changed from progression-free survival by central radiology review to progression-free survival (PFS) by investigator (local radiology) review. The analysis of primary endpoint by central radiology was still to be performed and reported as supportive analysis	Centrally assessed PFS is likely to be affected by informative censoring (Fleming et al 2009 and Dodd et al 2008)
Progression-free survival discrepancies between local and central radiology were adjudicated by a radiologist and an oncologist, both experts in NETs, while maintaining the independent and blinding of the central review process	Discrepancies between local and central readers are common (as high as 49%) (Borradaile et al 2009). Thus, PFS discrepancies between local and central reviewers were adjudicated by experts to establish whether the local or central read better reflects the true results
Cancellation of interim analysis	Overestimation of time requirement between interim and final analyses
Key secondary endpoint (overall survival [OS]) analysis	Redefinition of hierarchical testing procedure and timing of the final OS analysis

NET = Neuroendocrine tumor

C2324 PNET Changes in the study analyses: see Statistical methods, below.

C2325 Carcinoid Protocol amendments: The study protocol was amended on 3 occasions; the study methods above are as amended. The key features of each amendment are summarised in Table 6, below:

Table 6. Main amendments – Study C2325 Carcinoid

Amendment no. (date) / number of patients recruited	Summary of amendment	Rationale and justification
Amendment 1 (26-Mar-2007) 7 patients	Increase in number of sampling times for prothrombin time	Patient safety – to monitor possible coagulation disorders
Amendment 2 (15-Jun-2007) 49 patients	Patient population restricted to include only patients with functional tumors, defined as patients with a history of symptoms of diarrhea or flushing or both (and were attributed to their carcinoid tumor) Randomization changed from stratified to non-stratified	To reflect patient population for whom depot octreotide (Sandostatin LAR® Depot) is approved Stratification no longer considered necessary as only patients with functional tumors were eligible
	Expand and make minor corrections throughout protocol	To provide clarification
Amendment 3 (22-Jan-2010) 429 patients	Change in data source for primary PFS analysis from central radiology review to adjudicated central assessment (PFS analysis as per central radiology retained and conducted as supportive analysis)	Unexpected discrepancy in PFS between central radiology review and local investigator assessments impacting results of second interim analysis (Bushnell et al 2009). Informative censoring (affecting central radiology data) was considered to play a key role. Independent adjudicated central assessment subsequently proposed for primary analysis.
	Change in timing of final statistical analysis from event driven date (once 287 PFS events were recorded) to fixed calendar timepoint (02-Apr-2010)	Trial unlikely to ever reach original planned number of PFS events due to marked slowing in event rate and informative censoring Fixed calendar timepoint corresponded to approximately 2-years follow-up for last patient enrolled
	Redefinition of hierarchical testing procedure and timing of final OS analysis	To elevate OS ahead of ORR as a secondary endpoint and to provide further clarification
	Addition of screening and management guidelines for patients with hepatitis B or C	Patient safety – use of antiviral agents shown to reduce risk of reactivation
	Updates on: management of hyperglycemia and pneumonitis; use of CYP3A4 and/or PgP inducers or inhibitors; timing of administration with respect to food intake	To provide additional information and further clarification

The study report claims that the initial two amendments (both prior to the first Independent Data Monitoring Committee (IDMC) meeting and database lock) did not affect the interpretation of the study results, as the changes occurred during the early stages of the trial at a time where all centers were still recruiting patients into both treatment groups.

> **Evaluator comment:** The changes in Amendment 3 (see Table 6) were made because of the result of the second interim analysis (see below) that showed no statistically significant difference[13] in the PFS (HR: 0.9, 95% CI: 0.66, 1.21 with a p value of 0.233 [0.004 was needed for significance]) between the two arms, based on the assessments of the central radiology review (by an Independent Radiology Committee; IRC). At this time, the assessments by local investigators (INV) resulted in a HR of 0.69 (CI: 0.53, 0.91) and a p value of 0.003 in favour of the test arm [p value of 0.010 was needed for significance]. If the original protocol had been followed, the trial would have been stopped since the "futility boundary" originally agreed on with the FDA had been crossed. Instead the sponsor changed the primary efficacy assessment as in the table above so that when the two assessments differed, the final assessment would be decided by an adjudicated central radiology review (by an independent adjudication committee; IAC). Details of the methodology of this new arrangement were provided. The study report (above) claims no effect on the study results for the first two amendments but does not claim this for the third amendment, which changed the analysis of the primary endpoint after 429 patients had already been enrolled up to 22 January 2010. The sponsor justified the third amendment on the grounds that informative censoring introduced bias into the assessments of the IRC.

[13] The sponsor commented that the changes were done due to differences in results observed between sources, which could be explained by informative censoring.

C2325 Carcinoid Changes in study analysis: see Statistical methods, below.

Inclusion and exclusion criteria

In Study C2324 PNET, the main inclusion and exclusion criteria were:

1. Unresectable or metastatic PNET;
2. Low or intermediate grade neuroendocrine carcinoma;
3. Disease progression < 12 months prior to entry;
4. Measurable disease according to RECIST;
5. No hepatic embolisation < 6 months prior to entry (1 month if other sites of measurable disease);
6. No cryoablation/radiofrequency ablation < 2 months prior to entry;
7. PS 0-2.

In Study C2325 Carcinoid, the main criteria were:

1. Unresectable or metastatic carcinoid tumour;
2. Low- or intermediate grade neuroendocrine carcinoma;
3. Disease progression < 12 months prior to entry;
4. Measurable disease according to RECIST;
5. No hepatic embolisation < 6 months prior to entry (1 month if other sites of measurable disease);
6. No cryoablation/radiofrequency ablation < 2 months prior to entry;
7. PS 0-2.
8. History of diarrhoea/flushing or both; symptoms not required at entry.

Evaluator comment: The chief differences in the criteria for the two studies were that the second study included NETs of any organ of origin and required a history of symptoms indicating carcinoid syndrome. As a result of Amendment 2 (June 2007), the patient population in C2325 Carcinoid was restricted to patients with functional tumours, defined as patients having a history of symptoms of diarrhoea and/or flushing which were attributed to their carcinoid tumour, that is, the patient population for whom Sandostatin LAR Depot is approved.

Study treatments

C2324 PNET: Patients were given everolimus 10 mg/day as 5 mg tablets or matching placebo tablets daily. Patients in the placebo arm could cross-over to open label everolimus after an investigator determined that disease progression had occurred.

C2325 Carcinoid: Patients were given everolimus 10 mg/day plus octreotide (Sandostatin LAR Depot) 30 mg IM every 28 days (q28d), or placebo daily plus octreotide 30 mg IM q28d. Patients in the placebo arm could cross-over to open label everolimus after an investigator determined that disease progression had occurred.

Duration of treatment: Therapy was to be continued until progression of tumour, occurrence of unacceptable toxicity or until the investigator or patient decided that continuation was not in the best interest of the patient. Patients were to continue in the same treatment arm and to enter an extension phase following primary analysis, based on a pre specified number of events (PFS) or to continue with everolimus if study results were favourable.

Efficacy variables and outcomes

The main efficacy variable and the primary efficacy outcomes were as follows:

C2324 PNET: PFS as assessed by the local investigator.

C2325 Carcinoid: PFS as assessed by an independent adjudicated central assessment committee and referred to as an adjudicated review.

Other efficacy outcomes included:

C2324 PNET: OS; response rate, assessed by investigators; and duration of response.

C2325 Carcinoid: OS; response rate by adjudicated review; and duration of response

Method of assessment: In both studies, imaging was performed at baseline with computer tomography (CT) and magnetic resonance imaging (MRI) scans, repeated every 12 weeks until progressive disease was determined by the investigator or until new cancer therapy (usually cross-over to everolimus treatment for placebo patients) was started. Both studies included a central radiology review of all scans by two radiologists. A third radiologist adjudicated any discrepancies between the two radiologists. The radiologists determined only radiologic progression and had no clinical information.

> **Evaluator comment:** The determination of PFS depends on a number of factors and has problems such as the inherent difficult in assessing the results of CT and MRI imaging in these tumours and which lesion is chosen as the target for assessment. One published study has found that imaging during the correct contrast phase is essential since these tumours can appear isodense with the liver (the most frequent site of metastatic lesions) in uniphasic scans.[14] In the present studies, RECIST guidelines were to be followed for imaging and assessment and these required the same method of assessment (CT with or without contrast, MRI with or without contrast) to be used on each occasion. However in the present studies, the sponsor gave reasons such as site error and patients' renal dysfunction to explain why this was not done. Instead assessments were accepted *"regardless of the imaging modality"*. The failure to follow RECIST criteria may explain in part the differences occurring between assessments by IRCs and by local investigators.[15] As well the IRC and local investigators could choose a different lesion for assessment in the same patient. When the IRC found no progression of disease in cases where investigators had found progression, the event was censored.[16] This "informative censoring" has been claimed to introduce bias into the IRC analysis. An FDA briefing document for NDA 22334 (dated April 12, 2001)[17] submitted to the Oncological Drug Advisory Committee (ODAC) of FDA reviewed this question. As a result, the sponsor changed the method of data analysis, as described above, *Changes in the Study Analysis*, changing the primary endpoint of C2324 PNET from that assessed by the IRC (as agreed on with the FDA on August-September 2007) to PFS as assessed by local investigators and in the case of C2325 Carcinoid to PFS as assessed by an adjudicated central review committee (IAC).

[14] Tamm EP, Kim EE, Ng CS. Imaging of Neuroendocrine Tumours. ***Hematology Oncology Clinics of North America* 2007; 21:** 409-432.

[15] The sponsor noted that RECIST criteria were followed according to protocol, however, some flexibility in interpretation was allowed in certain situations.

[16] The sponsor noted that the patient was censored (for the IRC analysis) due to the start of further antineoplastic therapy based on investigators assessment or lack of further assessments. This censoring process was suspected to be "informative" (that is, not at random). Censoring did not occur for the investigator analysis.

[17] http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM250378.pdf

Randomisation and blinding methods

Randomisation

Both studies: The randomisation list was generated using a validated system that automated the random assignment of patient numbers to randomisation numbers, and linked the patient to one of the two treatment groups and also specified a unique medication number for the first package of study drug to be dispensed to the patient. The randomisation scheme for patients was reviewed and approved by a member of the Novartis Biostatistics Quality Assurance Group and was locked and stored by them until authorised release.

C2324 PNET: Randomisation was stratified by whether or not patients received prior cytotoxic chemotherapy and by World Health Organization (WHO) PS (0 versus 1 or 2) at baseline.

C2325 Carcinoid: There were two treatment groups, A = everolimus, and B = placebo, allocated in a 1:1 ratio. Originally, before Protocol Amendment 2, released on 15 June 2007, a stratified randomisation approach was used based on the primary site of the tumour. As a result of the Protocol Amendment, the patient population was restricted to include only patients with functional tumours, defined as patients having a history of symptoms of diarrhoea and/or flushing which were attributed to their carcinoid tumour, that is, the patient population for whom Sandostatin LAR Depot is approved. The patient population was therefore redefined according to the amendment by modifying study eligibility criteria and the need for stratification by tumour origin was deemed not necessary.

Blinding

C2324 PNET: In both treatment arms, a 10 mg dose of everolimus or matching placebo was given by continuous PO daily dosing of two 5 mg tablets. The identity of the treatments was concealed by the use of study medications (everolimus and matching placebo) that were all identical in packaging, appearance (tablet size, color, unit dose), and schedule of administration.

C2325 Carcinoid: In this study, the identity of the treatments was concealed by the use of everolimus and placebo that were identical in packaging, labeling, schedule of administration, and in appearance.

Analysis populations

Both Studies: The *FAS* consisted of all patients who were randomised. Following the ITT principle, patients were analysed according to the treatment group he/she was assigned to at randomisation. The FAS was the primary population for efficacy analyses. The *Safety Set* consisted of all patients who received any study drug and had at least one post-baseline safety assessment. Patients were analysed according to the actual treatment received. If a patient took at least one dose of study drug to which he/she was randomised, then the treatment actually received was the randomised treatment. Although there was no formal *Pharmacokinetic Set*, the PK analyses included all patients in the Safety Set and used all valid blood samples (trough levels, PK profiles). The *Open-Label Set* consisted of all patients who received at least one dose of open label everolimus treatment and had at least one post-baseline safety assessment during the open label phase.

C2324 PNET: The **Per-protocol Set** (PP) consisted of all patients from the FAS without a major protocol deviation who were evaluable for efficacy and who either completed a minimum exposure requirement (that is, no cumulative interruptions of more than 6 weeks in the first 12 weeks since start of study drug) or had progression before this minimum exposure requirement. Those patients, who progressed as per the local investigator assessment and discontinued due to an AE or died before the minimum

exposure requirement was met, or before he/she became evaluable for efficacy, were included.

C2325 Carcinoid: The PP consisted of all patients from the FAS who were evaluable for efficacy (that is, with a best overall response different from unknown) without any major protocol deviation and who either completed a minimum exposure requirement or discontinued for early disease progression, AE, or death. The minimum exposure requirement was defined as a minimum dose intensity corresponding to 50% of the planned doses over the initial 12 weeks of treatment. Patients were analysed according to the treatment they were assigned to at randomisation.

Sample size

C2324 PNET: Using an unstratified log-rank test at the one-sided 2.5% significance level (see below), 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.

The numbers enrolled were 474 patients, of whom 410 were randomised.

> **Evaluator comment:** The planned enrolment was achieved and a risk reduction of 65% (HR 0.35) found with a median increase in PFS 6.4 months so the predicted values above were accurate.

C2325 Carcinoid: Using a log-rank test at the one-sided 2.5% significance level, a total of 287 PFS events were originally targeted to allow for 92.2% power to demonstrate a 33% risk reduction (assuming that PFS followed an exponential distribution with a median PFS of 9.0 months for the placebo group and 13.5 months for everolimus in a traditional parallel-group design and without an interim analysis). With two planned interim analyses (both allowing early stopping for outstanding efficacy as well as for futility), the resulting overall power was to exceed 90%.

With a uniform accrual of 29 patients per month over 60 weeks and a minimum follow-up period of 90 weeks, it was estimated that a minimum of 350 patients were required to obtain 287 PFS events. With an estimated 10% of patients lost to follow-up, a total sample size of 390 randomised patients was originally targeted.

As the result of a marked slowing in PFS events and issues with informative censoring affecting the central radiology PFS data that would likely prevent the trial from reaching the originally planned number of events, the final analysis was performed at a predefined fixed calendar time-point (2 April 2010 data cut-off) irrespective of the number of PFS events observed. As a result, the final number of adjudicated central radiology PFS events was expected to be lower than originally foreseen. Under the initial alternative hypothesis (33% risk reduction in PFS), the expected power was 80% if at least 200 adjudicated central PFS events were observed by the data cut-off of 02 April 2010.

> **Evaluator comment:** The issue of informative censoring and the differences in the results of assessments by investigator and the central radiological review forms a major problem with the studies and is discussed in more detail below. The risk reduction for the primary endpoint was claimed to be 23% (HR 0.77) instead of the 33% predicted above, with an extension of the PFS of 5.1 months, close to the figure used above (4.5 months) for the positive effect of everolimus alone compared to placebo. These results were not confirmed in the analysis and assessment by the central radiology review that found no statistically significant

difference in the primary endpoints (see below). Originally, 350 patients were planned for enrolment with 287 PFS events predicted. The amended protocol required 200 PFS events or more at the cut-off date. The numbers obtained were 429 patients enrolled with 223 PFS events. The problem with sample size appeared to be not with slow recruitment as claimed but too high a predication of disease progression during the study.

Statistical methods

Hypothesis and test statistic

The null hypothesis stating that survival distributions of the two treatment groups are equivalent were tested against a one-sided alternative. The significance level of 2.5% was used. If $S_E(t)$ and $S_P(t)$ are the survival functions in everolimus 10 mg and placebo groups, respectively, the null hypothesis H_0: $S_E(t) = S_P(t)$ was tested against the one-sided alternative hypothesis H_{a1}: $S_E(t) > S_P(t)$.

Methodology

Because the study was placebo controlled, the primary objective was for a better outcome, so a one-sided test at 2.5% significance level was used to test the primary endpoint (PFS) and also in the test of OS and time to definitive worsening of WHO PS. The 95% CI was not used for decision making and only used for estimation and will therefore always be two-sided.

Stratified log-rank test adjusting for the strata used in the randomisation was used to test the difference between PFS in the treatment arms. An estimate of the survival function in each treatment group was constructed using the Kaplan-Meier (product-limit) method. Hazard ratio as a treatment effect measure was derived from the Cox proportional hazards model.

Patients who progressed on placebo were allowed to cross-over to open label everolimus. The primary analysis of OS used the strict ITT approach; that is, “analyse as randomised” and ignored the treatment switch following progression (and ignored additional anticancer therapies administered after study treatment discontinuation). In addition, the “Rank-preserving structural failure time method” and the “Cox model with Inverse Probability of Censoring Weighting” analyses were used to correct for the cross-over effects of survival.

Between group comparisons: categorical variables

C2324 PNET: Comparison of response rates: The exact Cochran-Mantel-Haenszel test was used to test the difference in response rates between the two arms. The Cochran-Mantel-Haenszel strategy potentially removed the confounding influence of the explanatory variables that comprise the stratification and so can provide increased power for detecting association by comparing like subjects with like subjects. The test was performed by running a stratified version of the Cochran-Armitage permutation test.

C2325 Carcinoid: The exact Fisher test was used to test the difference in response rates between the two arms

Censoring: Both studies used identical criteria for censoring in the estimation of PFS. Patients were censored if they: were ongoing without a PFS event; were lost to follow up or withdrew consent; did not have a tumour assessment available (this included patients who discontinued without a PFS event); began a new cancer therapy (including cross-over to everolimus) in the absence of a PFS event; and had a PFS event which occurred after > 2 missing tumour assessments (26 weeks).

These patients were censored at their last adequate tumour assessment. Patients with no measurable disease at baseline were not censored.

Evaluator comment: In the C2325 Carcinoid study, "informative censoring" was claimed to be the cause of the failure of the IRC and the local investigators assessments to agree in a number of cases and were the justification for changing the protocol that had been agreed on originally with the FDA (see below, *Protocol Amendments* and *Study design, objectives, locations and dates,* above)

Interim analyses

No interim analyses were conducted in the C2324 PNET study as amended. The C2325 Carcinoid study was to conduct two interim analyses (at approximately 20% and approximately 60% of events) and a final analysis at 287 events. Both studies planned to perform an interim analysis of overall survival at the time of the final PFS analysis. In both studies, the final analysis of OS would occur when approximately 60% of events had occurred. Both studies were to have 80% power to demonstrate a 30% improvement in overall survival compared to control using a one sided p = 0.025. In C2325 Carcinoid, the results of the second interim analysis have been described above (see *Study design, objectives, locations and dates*) in the context of the change in study design and data analysis. The final analysis found that there was no significant difference in PFS between patients in the two arms of the C2325 Carcinoid trial using assessments by the IRC, whereas a significant difference was claimed when assessments by local investigators were used instead.

Changes in the study analysis

C2324 PNET: The list of unplanned analyses added after un-blinding were as follows:

- To address FDA requests:
  - Results from an unstratified one-sided log-rank test and unstratified Cox proportional hazard model for PFS using investigator assessment were provided;
  - By-patient listings showing tumour assessments by central radiology and by investigator, together with PFS results and the IAC comments, were provided.
- To address the difference in censoring patterns between the treatment groups and to assess the potential for a bias that might be introduced, *sensitivity analyses* for PFS by adjudicated central radiology review and PFS by central radiology review were performed.

  Evaluator comment: Note that the primary efficacy endpoint assessed by an IRC and agreed with the FDA on August-September 2007 was changed so that the primary endpoint would be as assessed by local investigators.

Other changes of a supportive nature were also made.

C2325 Carcinoid: The changes to the study analysis were presented above (see Table 6). Further changes to the planned analyses included the following:

- To address Health Authority requests by-patient listings showing tumour assessments by local investigator and central radiology review, together with PFS results and comments from the adjudicated central radiology review, were provided.
- To account for known prognostic factors, additional adjusted Cox models were constructed including the preplanned covariates (age, gender, WHO PS, prior use of somatostatin analog) and two additional covariates (histology and primary tumour site). These were applied to the preplanned PFS analyses.
- Adding a listing (with comments) of patients discontinuing the study due to 'clinical' disease progression without documented RECIST tumour assessments.
- Two planned exploratory analyses were to be performed to correct the overall survival treatment effect estimate for bias introduced by treatment cross-over using a

marginal structural Cox model using inverse probability of censoring weights (IPCW) and a rank-preserving structural failure time (RPSFT) model. Results for these analyses were to be presented at the time of the survival update when more mature data was available.

Evaluator comment: The results of the second interim analysis led to a change in the primary endpoint of the study from that assessed by the IRC (as agreed on with the FDA on August-September 2007) to that assessed by an IAC. As well the cut-off date for the final analysis of PFS was changed from 287 events to a specified date.

Regulatory concerns about the changes to the study design

In August-September 2007, agreement was reached in a Special Protocol Assessment (SPA) meeting between the sponsor and the FDA for both Phase III trials that assessment of PFS would be based on the assessments of the IRC. The application describes further consultations with the FDA in the sponsor's *Clinical Overview*. A key passage states *"Modifications to the NET development plan were further discussed with FDA after Novartis Management was alerted to a discrepancy in PFS assessment between the independent central radiology review (IRC) and local investigator assessment affecting the results of the second interim analysis for Study C2325 Carcinoid.* ***No formal agreement was reached on a strategy to address these study design issues*** [evaluator's emphasis]*; FDA recommended that both studies continue as planned and that PFS as per independent central radiology review be retained as the primary analysis."*

> **Evaluator's comment:** This is in agreement with the statement in the FDA's briefing document of April 2011 to the ODAC that *"During a pre-NDA* (New Drug Application) *meeting in August of 2010, FDA noted that both SPA (Special Protocol Assessment) agreements had been invalidated by this change in primary endpoint and that the acceptability of the revised statistical plans would be a review issue"*[18].

Supplementary statistics evaluation

Because of the multiple statistical issues associated with this trial, the TGA sought independent expert advice on the statistical methods used in Study C2325 Carcinoid. The evaluator's conclusions are given under the section on *Supplementary statistics evaluation - conclusion*, below.

Study drug

Duration of study drug exposure, cumulative dose, dose intensity and relative dose intensity were calculated for the drug administered. In addition, the duration of exposure to study drug was categorised into time intervals, and frequency counts and percentages were presented for the number of patients in each interval. The number of patients who had dose reductions or interruptions and the reasons why were summarised by drug administered.

Participant flow

C2324 PNET: Informed consent was signed by 474 patients and of these 64 were screening failures. The primary reason for screening failure was inadequate baseline laboratory data (28 patients). Thus, 410 patients were randomised; 207 (50.5%) patients to the everolimus group and 203 (49.5%) patients to the placebo group. Study treatment was discontinued by 318 (77.6%) patients during the double blind treatment phase. The main reason for discontinuation was disease progression, with the incidence on placebo approximately twice that in the everolimus group. Treatment discontinuation due to an AE suspected to be related to treatment was more frequent with everolimus, with 27 (13.2%)

[18] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm254392.htm Accessed 27 August 2011

everolimus patients and 4 (2.0%) placebo patients. Exposure to everolimus was significantly longer with median durations of treatment of 37.8 weeks for everolimus compared with 16.1 weeks for placebo.

Patients initially randomised to placebo were able to cross-over to open label everolimus once disease progression was documented. Of the 163 patients who had disease progression on placebo, a high proportion (148 [90.8%] patients) crossed over to everolimus. Thus, 148 (72.9%) out of 203 placebo patients were crossed over to open label everolimus. One additional patient who received everolimus treatment during the double blind phase entered the open label phase. Of these 149 patients treated with open label everolimus, 92 (61.7%) patients discontinued treatment during the open label phase. Disease progression was the primary reason for study medication discontinuation in 53 (35.6%) patients.

C2325 Carcinoid: In total, 429 patients were evaluated as part of this study; 216 were randomised to treatment with everolimus plus depot octreotide and 213 to treatment with placebo plus depot octreotide. Treatment discontinuation was comparable for both treatment arms. Disease progression was the primary cause of discontinuation for both treatment groups although the rate with placebo was > 1.5-fold that for everolimus. Treatment discontinuation attributable to AEs was more frequent with the combination of everolimus plus depot octreotide, 26.4% versus 6.6% for placebo, and for the AEs considered to be drug related, 18.6% and 3.3%, respectively. Cross-over occurred for 124 of the 213 patients (58.2%) initially randomised to placebo. Of these 146 developed progressive disease and 124 (84.9%) crossed over to open label treatment with everolimus.

Major protocol violations/deviations

Each pivotal trial defined a major protocol violation as follows:

Incomplete documentation of an advanced (unresectable or metastatic) biopsy-proven pancreatic NET; no radiological documentation of progression of disease within 12 months of randomisation; no measurable lesion at baseline (according to RECIST); WHO PS > 2; low-grade or intermediate-grade neuroendocrine carcinoma not confirmed; prior therapy with mTOR inhibitors (sirolimus, temsirolimus, everolimus); patient with chronic treatment of corticosteroids or another immunosuppressive agent. The major violations listed excluded patients from the PP population.

All protocol violations were grouped and presented in a post text table for the FAS. The groupings were by severity (1, 2, 4 and 9) with the code as follows: 1 = Exclude from PP analysis, 2 = Exclude from data analysis from this date, 4 = Exclude from data analysis on this date, 9 = Include in all efficacy analysis. Although not stated, Code 1 would be major deviation, which would exclude patients from the PP population. The frequency of Code 1 violations was as follows: C2324 PNET: everolimus arm, n = 6 (2.9%); placebo arm, n = 7 (3.4%). C2325 Carcinoid: everolimus arm n = 11 (5.1%); placebo arm n = 6 (2.8%).

In the C2324 PNET trial, protocol deviation of any kind occurred in 72.9% of patients in the everolimus and 62.6% of patients in the placebo arm. In the C2325 Carcinoid trial, protocol deviation of any kind occurred in 79.6% of patients in the everolimus and 84% of patients in the placebo arm.

> **Evaluator comment:** The frequency of protocol violations of any type was high in both studies but that of major violations was low. However the FDA Briefing Document[19] states *"The (FDA) method used to categorize major and minor protocol violations differs from that of the applicant."* The FDA document gives the incidence

[19] NDA 22334 ODAC Briefing Document for Afinitor NDA 22334, available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM250378.pdf

of major protocol violations in C2324 PNET as 11.1% and 5.4% in the everolimus and placebo arms respectively; and in C2325 Carcinoid, 13.0% and 9.4% respectively, figures that are substantially higher than those of the sponsor. The TGA adopted EU guideline[20] gives examples of protocol violations but does not define what constitutes a major protocol violation, although this can be regarded as one that could affect the primary endpoint of the study (see *List of questions*, below).

Baseline data

C2324 PNET: Demographic characteristics were relatively well balanced between the two treatment groups. Median age was 58.0 years, slightly more males (227 [55.4%] patients) were enrolled compared to females (183 [44.6%] patients), and most patients (78.5%) were Caucasian. A slightly higher proportion of patients receiving placebo were Caucasian. The number of patients of Japanese ethnicity in the study was 42 (10.2%) with 23 and 19 in the everolimus and placebo arms respectively. There were, overall, more patients in the everolimus group who were aged 65 years or more relative to placebo (29.5% compared with 24.6%, respectively). None of these differences were considered to be clinically relevant.

Disease history was balanced in each arm of the study. The majority (401 [97.8%]) of patients had a primary lesion in the pancreas. Of the remaining 9 patients, 7 had a primary lesion assessed as "other" and were deemed medically eligible. The final 2 patients were mis-randomised or had a protocol deviation. Gastrinoma, glucagonoma, VIPoma, insulinoma or somatostatinoma were reported in 24.1% of patients. More than 80% of the tumours were well-differentiated (341 (83.2%] patients). The majority of patients (398 [97.1%]) were WHO PS 0 or 1. Also, 70.5% of patients were randomised within 3 months of progression.

Tumour characteristics were also balanced. Liver involvement was present in > 90% of patients; metastatic disease was also present in the pancreas (42.9% of the patients), lymph nodes (34.4%), lung (14.1%), and bone (10.2%). A higher proportion of patients in the placebo group had bone involvement relative to everolimus (29 [14.3%] patients versus 13 [6.3%] patients).

C2325 Carcinoid: The study report states "Notable imbalances were evident at baseline for several important prognostic factors including gender, primary tumour site, WHO PS, number of organs involved, and prior use of chemotherapy", and later gave this as a reason for the lack of convincing statistical difference between the two arms of the trial. Given this issue, the 'demographic characteristics' are reproduced below in Table 7, 'disease characteristics at baseline' in Table 8, and 'prior antineoplastic therapy' in Table 9.

[20]CPMP/ICH/363/96 (September 1998) *Note for Guidance on Statistical Principles for Clinical Trials.* http://www.tga.gov.au/pdf/euguide/ich036396en.pdf

Table 7. Demographics baseline - Study C2325 Carcinoid

Demographic characteristic	Everolimus plus depot octreotide N=216	Placebo plus depot octreotide N=213	All patients N=429
Age (years)			
n	216	213	429
Mean (standard deviation)	60.1 (10.72)	59.4 (11.13)	59.8 (10.92)
Median	60.0	60.0	60.0
Range	22 to 83	27 to 81	22 to 83
Age group (n [%])			
< 65 years	143 (66.2)	143 (67.1)	286 (66.7)
≥ 65 years	73 (33.8)	70 (32.9)	143 (33.3)
Gender (n [%])			
Female	119 (55.1)	89 (41.8)	208 (48.5)
Male	97 (44.9)	124 (58.2)	221 (51.5)
Race (n [%])			
Caucasian	204 (94.4)	199 (93.4)	403 (93.9)
Black	5 (2.3)	7 (3.3)	12 (2.8)
Asian	1 (0.5)	1 (0.5)	2 (0.5)
Other	6 (2.8)	6 (2.8)	12 (2.8)

Source: PT-Table 14.1-3.1

Table 8. Tumour characteristics - Study C2325 Carcinoid

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 [a]			
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)

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

Table 8 (continued). Tumour characteristics - Study C2325 Carcinoid

Characteristic	Everolimus plus depot octreotide N=216	Placebo plus depot octreotide N=213	All patients N=429
Number of organs involved (n [%]) [a]			
1	61 (28.2)	57 (26.8)	118 (27.5)
2	63 (29.2)	69 (32.4)	132 (30.8)
3	41 (19.0)	55 (25.8)	96 (22.4)
≥ 4	50 (23.1)	30 (14.1)	80 (18.6)
Organ type involved (n [%]) [a]			
Liver	198 (91.7)	196 (92.0)	394 (91.8)
Lymph nodes	80 (37.0)	85 (39.9)	165 (38.5)
Lung	64 (29.6)	52 (24.4)	116 (27.0)
Bone	35 (16.2)	24 (11.3)	59 (13.8)
Abdominal mass	16 (7.4)	16 (7.5)	32 (7.5)
Peritoneum	13 (6.0)	19 (8.9)	32 (7.5)
Pancreas	12 (5.6)	18 (8.5)	30 (7.0)
Pelvic mass	11 (5.1)	7 (3.3)	18 (4.2)
Mediastinum	11 (5.1)	6 (2.8)	17 (4.0)
Spleen	9 (4.2)	9 (4.2)	18 (4.2)
Ascites	7 (3.2)	11 (5.2)	18 (4.2)
Other	64 (29.6)	58 (27.2)	122 (28.4)
Types of lesions (n [%]) [b]			
Target and non-target	162 (75.0)	156 (73.2)	318 (74.1)
Target only	53 (24.5)	55 (25.8)	108 (25.2)
Number of target lesions			
n	215	211	426
Mean (standard deviation)	4.2 (2.15)	4.0 (1.89)	4.1 (2.02)
Median	4.0	4.0	4.0
Range	1 to 10	1 to 9	1 to 10
Number of target lesions (n [%])			
1 to 2	55 (25.5)	49 (23.0)	104 (24.2)
3 to 5	112 (51.9)	118 (55.4)	230 (53.6)
6 to 10	48 (22.2)	44 (20.7)	92 (21.4)
Number of non-target lesions			
n	215	211	426
Mean (standard deviation)	1.6 (1.70)	1.5 (1.44)	1.6 (1.57)
Median	1.0	1.0	1.0
Range	0 to 10	0 to 7	0 to 10
Number of non-target lesions (n [%])			
0	53 (24.5)	55 (25.8)	108 (25.2)
1 to 2	114 (52.8)	116 (54.5)	230 (53.6)
3 to 5	41 (19.0)	36 (16.9)	77 (17.9)
6 to 10	7 (3.2)	4 (1.9)	11 (2.6)

[a] Organs as per target and non-target lesion locations observed at baseline by investigator
[b] Types of lesions at baseline by local investigator assessment

Table 9. Prior anticancer therapy - Study C2325 Carcinoid

Prior therapy	Everolimus plus depot octreotide N=216 n (%)	Placebo plus depot octreotide N=213 n (%)	All patients N=429 n (%)
Any prior antineoplastic therapy [a]	**216 (100.0)**	**211 (99.1)**	**427 (99.5)**
Any prior surgery	**216 (100.0)**	**211 (99.1)**	**427 (99.5)**
Biopsy	138 (63.9)	159 (74.6)	297 (69.2)
Other	161 (74.5)	151 (70.9)	312 (72.7)
Any prior medications [b]	**99 (45.8)**	**82 (38.5)**	**181 (42.2)**
Therapy type			
Chemotherapy	75 (34.7)	55 (25.8)	130 (30.3)
Immunotherapy	27 (12.5)	20 (9.4)	47 (11.0)
Targeted therapy	15 (6.9)	16 (7.5)	31 (7.2)
Hormonal therapy	0	2 (0.9)	2 (0.5)
Other	21 (9.7)	26 (12.2)	47 (11.0)
Any prior radiotherapy	**52 (24.1)**	**58 (27.2)**	**110 (25.6)**

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

Evaluator comment: The study used no stratification so imbalances are not surprising. The pre defined subgroups from the selection criteria were gender, PS, primary tumour site and histological grade. In addition to these subgroups, imbalances in the number of organs involved with tumour and in the prior use of chemotherapy were considered in the study report. The possible effect of the imbalances on the study endpoints needs to be considered. The best available information on the factors affecting the prognosis of NETs was the analysis of 35,825 cases from the SEER registry. From that study, possible effects on the analysis were as follows:

Prespecified covariates; gender: Female patients in C2325 Carcinoid formed 55.1% of the everolimus group. For well to moderately differentiated tumours, females had a longer median survival than males (HR 1.2 for males, multivariate analysis; Yao *et al*, 2008[21]). The imbalance would therefore favour a better survival for the everolimus patients. However with only a 5% difference in numbers, the 20% increase in median survival would have only a small effect (1%).

WHO PS: The pre treatment PS of patients in the everolimus arm was PS 0, 54.6%; PS 1, 38.9%; PS 2, 6.5%; and in the placebo arm 65.7%, 29.1% and 4.7% respectively. While the individual groups PS 0 and 1 were unbalanced, their combination was similar. No data were provided to show the survival of patients with PS 0 was significantly longer than those with PS 1. PS was not a variable in the analysis of Yao *et al*., 2008.

Additional covariates - histological grade: The everolimus and placebo arms had 76.9% and 82.2% well differentiated (G1) and 17.6% and 14.1% moderately differentiated (G2) NETs. Compared to poorly differentiated tumours (G3/G4), Yao *et al*., 2008 found the latter patients had a significantly shorter median survival. However this grade of NET was excluded from the present study. Median survival of patients with G1 and G2 metastatic tumours also depends on the histopathology of the tumour. Those with G1 metastatic tumours with adenocarcinoma elements (mixed tumours) did worse that those with G2 mixed tumours. The number of tumours with mixed histopathology was not given in the present study, so no conclusion can be made about the effect on the survival of patients in either arm.

Primary tumour site: The main difference was for those NETs originating in the lung with15.3% in the everolimus arm compared with 5.2% in the placebo arm. Yao *et al*., 2008 found that the median survival of patients with NETs differed for patients with localised, regional or metastatic disease, and depended as well on the organ of origin. In the present study (C2325 Carcinoid), all patients had metastatic disease. In the Yao *et al*., 2008 analysis, the median survival for patients with primary tumour site in the lung, pancreas, or small intestine (gastric and colon not given for reasons of space) was 17 months, 27 months, and 26 to 65 months, respectively. Therefore the additional 10% of patients in the everolimus arm with NETs originating in the lung would have a decreased survival of about 50% each, or 5% overall for the everolimus arm, a small effect.

Other potential prognostic factors (not included in the adjusted analyses) -

Number of organs involved: More patients in the everolimus arm had $\geq$ 4 organs involved with tumour (23.1% compared with 14.1%). These data were obtained from the sites of local investigator-determined target and non-target lesions. If the sites of IRC-determined target and non-target lesions were used, the number of

[21] Yao JC, Hassan M, Phan A, *et al*. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumours in 35, 825 cases in the United States. *J Clin Oncol* 2008; 26: 3063-72.

patients with ≥ 4 organs involved with tumour (17.6% everolimus, 15.0% placebo) was similar. The number of organs involved was not a variable in the analysis of Yao *et al*., 2008.

Prior use of chemotherapy: More patients received prior chemotherapy and immunotherapy (34.7%+12.5%) in the everolimus arm than in the placebo arm (25.8%+9.4%). In oncology practice, it is usual that patients pretreated with chemotherapy do not show as much benefit from further treatment as previously untreated patients. However, this is not absolute and no evidence was provided for NETs, relatively rare and slow growing tumour, that this was the case.

Conclusion: From the above, the evaluator concluded that the effect of the imbalances on survival would not be significant, and that any significant effect on PFS would also be unlikely. This is supported by the results of the sponsor's adjustment for the above covariates in calculating the HR for OS, all of which remained not statistically significant. The values for the unadjusted HR was1.22 (95% CI: 0.91, 1.62), for the HR adjusted for baseline covariates, 1.06 (0.79, 1.43), and adjusted for baseline and additional covariates, 1.04 (0.77, 1.40).

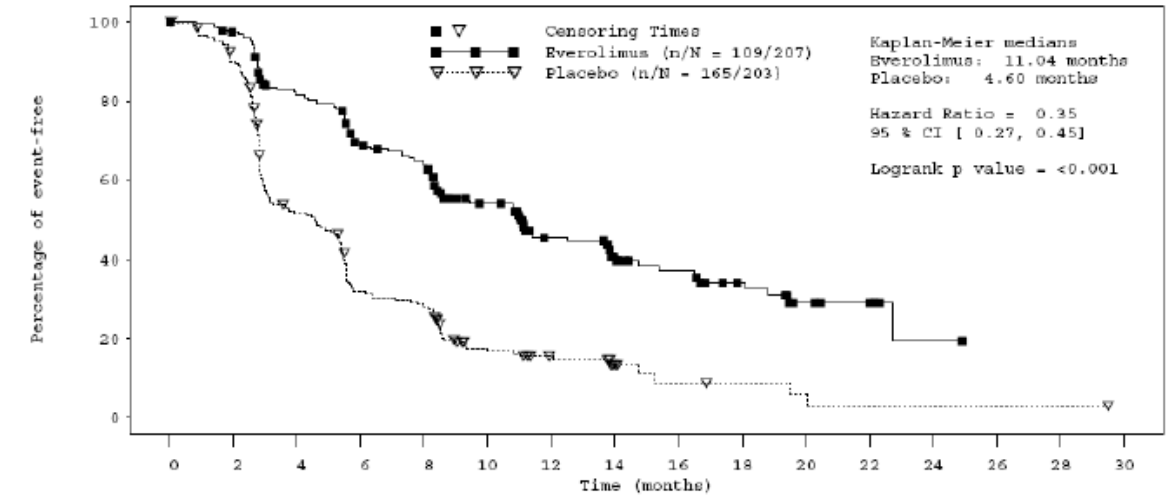
Results for the primary efficacy outcome

In both pivotal studies, assessments of the primary endpoint were made by an IRC, local investigators and an IAC. The results of each assessment differed, and the analyses and discussion of these differences form a large part of the trial reports for both studies, especially C2325 Carcinoid. In this section of the evaluation report, the evaluator emphasises the results of the primary endpoints, as selected by the sponsor, noting that these were not agreed to by the FDA. In the C2324 PNET trial, the primary endpoint was assessed by the local investigators and in the C2325 Carcinoid trial, by the IAC. The other results will be presented briefly for information and support or otherwise.

C2324 PNET: One hundred and nine patients (52.7%) in the everolimus arm had a PFS event (95 with progressive disease and 14 deaths). The number was significantly less (p = <0.001)[22] than the 165 (81.3%) patients with a PFS event (158 with progression, 7 deaths) in the placebo arm. The HR was 0.35 [95% CI 0.27, 0.45]. The numbers censored were 98 (47.3%) in the everolimus arm and 38 (18.7%) in the placebo arm. The median values for the PFS in these arms were 11.04 [8.41, 13.86] months and 4.60 [3.06, 5.39] months respectively. The Kaplan-Meier plot is shown in Figure 3.

[22] 'p value is obtained from the stratified one-sided log-rank test.

Figure 3. Kaplan-Meier plot PFS – Study C2324 PNET



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

- p-value is obtained from the stratified one-sided log-rank test.
- Hazard-Ratio is obtained from stratified unadjusted Cox model.

Censored data: The most frequent reason for censoring in both treatment groups was the absence of disease progression at the time of the analysis cut-off date. The above difference in the incidence of censored events in each arm reflected the higher frequency of disease progression in the placebo arm (81% compared with 53%). The relative proportions (using the total number of censored patients as denominator) of individual censoring reasons were similar between the treatment arms.

> **Evaluator comment:** A different censoring pattern from that used by local investigators above was seen when assessments were done by the IAC review and IRC review. The most frequent reason for censoring in the placebo group (and more so in the everolimus group) was 'new cancer therapy added'. The notable increase (relative to PFS by local investigator) was caused by cross-over to open label everolimus. Sensitivity analyses in each case, gave the results following, and indicated that the conclusions of the primary analysis were robust.

Other estimates of the primary endpoint: Based on assessments by the IAC, the results for the HR ratio were 0.34 [0.26-0.44] and for median PFS in the everolimus and placebo arms, 11.40 months [10.84-14.75] and 5.39 [4.34, 5.55] months respectively. Based on assessments by the IRC, the results for the HR ratio were 0.38 [0.28-0.51] and for median PFS in the everolimus and placebo arms, 13.67 [11.17-18.79] months and 5.68 [5.39, 8.31] months respectively.

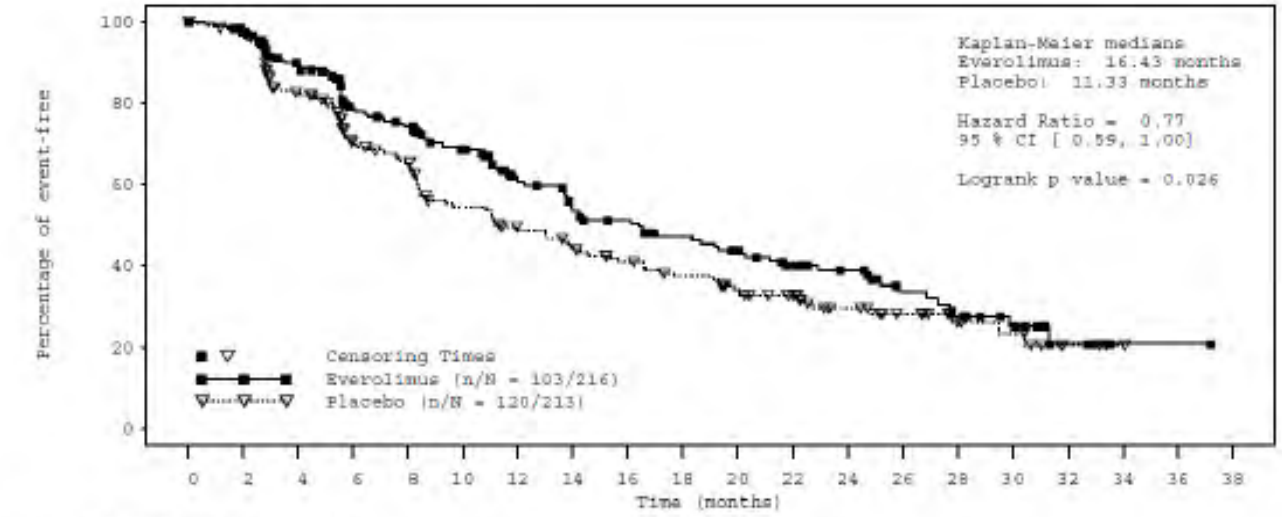
Sub-group analyses based on stratification factors (with or without prior chemotherapy; WHO PS), and on baseline characteristics supported the results of the primary endpoint analysis.

> **Evaluator comments:** The results from the analysis of the primary efficacy endpoint shows everolimus treatment is more effective that placebo, and was supported by the results of the analyses using other methods of assessment and by subgroup analyses.

C2325 Carcinoid: One hundred and three patients (47.7%) in the everolimus arm had a PFS event (69 with progressive disease and 34 deaths) and 120 (56.3%) (101 with progression, 19 deaths) in the placebo arm. The numbers censored were 113 (52.3%) in the everolimus arm and 93 (43.7%) in the placebo arm. The median PFS in these arms were 16.43 [13.67-21.19] months and 11.33 [8.44-14.59] months respectively, with a HR

of 0.77 [95% CI 0.59, 1.00] and a p value of 0.026 for the difference. The predetermined alpha level for significance as adjusted for the two interim analyses was 0.0246. The Kaplan-Meier plot is shown in Figure 4.

Figure 4. Kaplan-Meier plot PFS – Study C2325 Carcinoid



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	34	36	38
Everolimus	216	202	167	129	120	102	81	69	63	56	50	42	33	22	17	11	4	1	1	0
Placebo	213	202	155	117	106	84	72	65	57	50	42	35	24	18	11	9	3	1	0	0

Censored data: In the primary analysis, 113 patients (52.3%) were censored in the everolimus arm and 93 (43.7%) in the placebo arm.

> **Evaluator comment:** The comments on censored data in C2324 PNET (see above) apply here also, except the numbers were comparable because of the similarity of disease progression in each arm.

Other estimates of the primary endpoint

Based on assessments by the local investigators, the results for the HR ratio were 0.78 [0.62-0.98] and for median PFS in the everolimus and placebo arms, 11.99 months [10.61-16.13] and 8.61 [8.08-11.14] months respectively. The p value reached statistical significance with a value of 0.018. Based on assessments by the IRC, the results for the HR ratio were 0.93 [0.71-1.22] and for median PFS in the everolimus and placebo arms, 14.88 [12.22-19.38] months and 13.90 [9.66-19.09] months respectively.

Eight sub-groups were analysed based on baseline characteristics. Of the 19 p values given, 3 had values less than 0.0246, although that value was not adjusted for the eight multiple analyses.

> **Evaluator comment:** On the whole the additional analyses confirm the primary result that no statistical difference was demonstrated in this study to show a difference between everolimus treatment and placebo (in this case, Somastatin LAR). In all cases except for the HR in the local investigators analysis, the CI was wide and included unity.

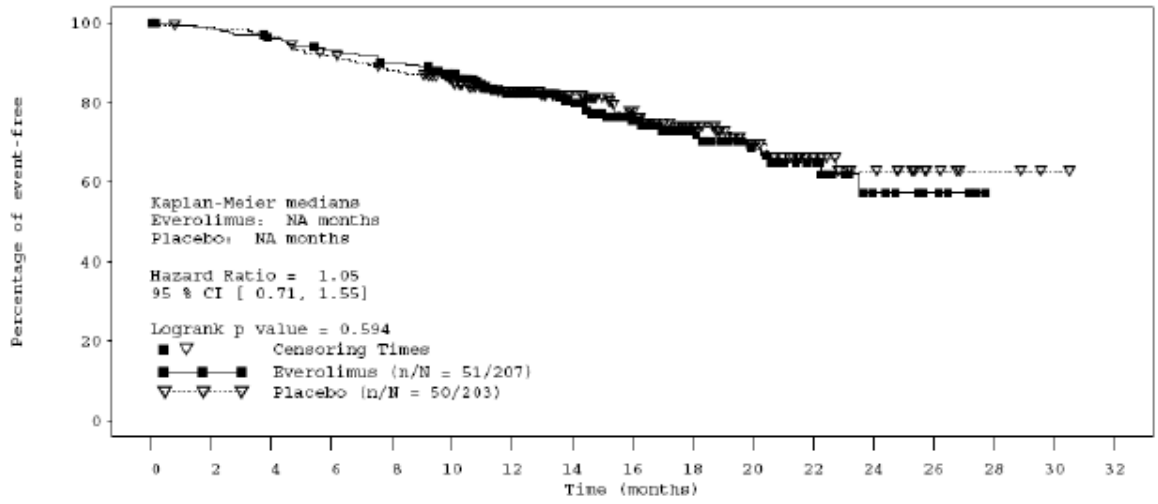
Results for other efficacy outcomes

C2324 PNET

Overall survival: No statistically significant difference was observed between the two treatment groups with an HR of 1.05 (95% CI: 0.71, 1.55; p = 0.594) [see Figure 5, below]. Cross-over occurred for 148 (72.9%) of the 203 patients initially randomised to placebo prior to the data cut-off date. Considering placebo patients who had disease progression

and were thus eligible for cross-over, 148 out of 163 patients (90.8%) were selected to cross-over to open label treatment. Further confounding the OS is subsequent antineoplastic therapies after discontinuation of the study medication. There were 37.7% of patients in the everolimus group and 28.6% in the placebo group who received subsequent antineoplastic therapy after end of study treatment (double blind or open label phase). The most common antineoplastic therapy was chemotherapy. There were a total of 101 deaths at the time of the data cut-off and the median OS was not reached for either treatment group. The estimated 12 month survival rates were 82.3% (95% CI: 76.0, 87.0) with everolimus treatment and 82.6% (95% CI: 76.5, 87.3) for placebo.

Figure 5. Kaplan-Meier plot OS – Study C2324 PNET



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

- p-value is obtained from the stratified one-sided log-rank test.
- Hazard-Ratio is obtained from stratified unadjusted Cox model.

Objective response rate: Local investigator assessment: Response as per investigator, based on RECIST, was reported in 4.8% (95% CI: 2.3, 8.7) of patients who received everolimus and 2.0% (95% CI: 0.5, 5.0) of placebo-treated patients. All responses were partial responses (PRs). Of the 4 placebo-treated patients with a PR, only one was confirmed by the adjudicated central review and this patient received concomitant depot octreotide therapy. Disease stabilisation as best overall response was 72.9% with everolimus treatment and 50.7% with placebo treatment. The overall Disease Control Rate (DCR = CR + PR + stable disease, where CR is 'complete response') was 77.7% with everolimus treatment compared with 52.7% for placebo. Progressive disease was the best overall response for 14.0% of everolimus-treated patients and 41.9% of patients receiving placebo.

Overall response rate (ORR) as assessed by IAC and IRC: From the IAC assessment, the ORR was 2.9% (95% CI 1.1, 6.2] for patients in the everolimus arm and 0.5% [0.0, 2.7] for the placebo arm. From the IRC assessment, the ORR was 2.4% [0.8, 5.5] and 0.5% [0.0, 0.27]. Overall DCRs of 81.6% versus 59.6% for everolimus and placebo treatments were found for IAC assessments and 83.1% versus 67.0% for IRC assessments.

> **Evaluator comment:** All CIs are wide and overlap for each of the two arms in all the analyses. While the DCRs point to a possible higher incidence of DCR in the everolimus arm compared to placebo, consistent with the effect on PFS, this has not been convincingly shown in these statistics and assessments. A consistent assessment of stable disease given the demonstrated differences in the IAC, local investigator and IRC results would be a difficult task.

Time to Response and Duration of Response: The number of responders (10 and 4 patients) was too small to allow a meaningful comparison.

C2325 Carcinoid

Overall survival: No statistically significant difference was evident in terms of overall survival, the HR being 1.22 (95% CI: 0.91, 1.62; p = 0.908). Cross-over of patients initially randomised to placebo to active treatment with everolimus at the time of disease progression was likely to have confounded this result. Cross-over occurred for 124 of the 213 patients (58.2%) initially randomised to placebo and for 124 of 146 patients (84.9%) who progressed and were thus eligible for cross-over. The imbalance in important baseline prognostic factors in favor of placebo is also likely to have confounded the result. The median survival was 26.25 [CI 23.75, not applicable [NA]] in the everolimus arm and 33.18 [30.03, NA] months in the placebo arm.

> **Evaluator comment:** Of note is that the median survival of patients in the placebo arm was longer than that of patients in the everolimus arm. The sponsor attributed this to the imbalance referred to in baseline characteristics but as discussed in *Baseline data*, above this is unlikely. Together with the overlap of CIs, the longer OS in the placebo arm more likely represents a similar statistical result to that in the everolimus arm.

Objective response rate as assessed by IAC: Response as per IAC assessment, based on RECIST, was observed in only 2.3% of patients (95% CI: 0.8%, 5.3%) receiving treatment with everolimus, although disease stabilisation was evident in 84.3% of patients. All responses were PRs. In comparison, the objective response rate among patients receiving placebo was 1.9% while 80.8% experienced stable disease. Of note, progressive disease was the best overall response for 4.2% of everolimus-treated patients and 12.2% of patients receiving placebo. No statistically significant difference was observed relative to placebo in the proportion of patients experiencing an objective response.

Objective response rate as assessed by local investigator and IRC: Objective response rates as per local investigators (3.2% versus 2.3%) and IRC (1.9% versus 1.4%) gave similar results.

Time to response and duration of response: The number of responders was too low (5, 4 patients) to allow analysis.

Other efficacy studies

Study C2239. An open label, stratified, single-arm Phase II study of everolimus in patients with advanced pancreatic NET after failure of cytotoxic chemotherapy

Method

This was a global multi center, open label, stratified, expanded two-stage study of everolimus in patients with advanced pancreatic NET after failure of cytotoxic chemotherapy. Patients were stratified according to whether or not they had received prior treatment with Sandostatin LAR Depot.

- Stratum 1 patients (100 patients planned) who were not receiving regular Sandostatin LAR Depot therapy. These patients were to receive everolimus monotherapy at 10 mg/day.
- Stratum 2 patients (44 patients planned) who had received at least three consecutive months of Sandostatin LAR Depot therapy prior to enrollment. These patients were to receive everolimus 10 mg/day in addition to continuing their entry dose of Sandostatin LAR Depot.

Primary objective

The primary objective of the study was to determine the ORR (CR and PR) of everolimus 10 mg/day monotherapy in patients with advanced pancreatic NET after the failure of cytotoxic chemotherapy (Stratum 1) based on the central radiology review.

Number of patients (planned and analysed)

The total number of patients planned was a maximum of 144 patients, depending on interim analyses for futility. The final study population resulted from 186 patients having been screened for a total of 115 patients in the FAS for Stratum 1 and 45 patients in the Stratum 2 FAS.

Diagnosis and main criteria for inclusion

Eligible patients were adult male or female patients with histologically proven, advanced pancreatic NET with documented objective progression of disease by RECIST criteria during or after treatment with cytotoxic chemotherapy. The key exclusion criteria were patients who received anticancer therapy within 3 weeks of enrollment or prior therapy with everolimus or other rapamycins and patients who presented with liver disease or severely impaired lung function.

Treatment duration

A treatment cycle was defined as 28 days of consecutive daily treatment with everolimus. Treatment continued until tumour progression.

Results

Stratum 1: The ORR by central radiology review was 9.6% (95% CI: 4.9, 16.5) in 11 patients. All confirmed responses by *central radiology review* were PRs; there was no patient with a CR. The rate of stable disease as best overall response was 67.8%. The median duration of response was 10.64 months with a 95% CI lower limit of 9.79 months. Seven of eleven patients with best overall response of PR were still responding at the time of data cutoff. The ORR by *local investigator assessment* was 10.4% (95% CI: 5.5, 17.5) in 12 patients. The rate of stable disease as best overall response was 61.7%. The median duration of response was 19.19 months (95% CI: 5.32, NA). The median PFS estimate based on *central radiology review* was 9.69 months (95% CI: 8.25, 13.3). The median PFS estimate on *investigator review* was 8.5 months (95% CI: 7.8, 11.8).

Stratum 2: The ORR by *central radiology review* was 4.4% (95% CI: 0.5, 15.1) in 2 patients. All confirmed responses were PRs; there were no patients with CR. The stable disease rate was 80.0%. No patients had progressive disease as best overall response and 15.6% of patients had an unknown best overall response. As only two patients demonstrated a PR, the median duration of response has not been calculated. The ORR by *local investigator assessment* was 11.1% (95% CI: 3.7, 24.1) in 5 patients. The stable disease rate was 68.9%, progressive disease occurred in 11.1% of patients and 8.9% had a best response of unknown. The median duration of response was 19.29 months (95% CI: 10.61, 19.29). The median PFS estimate based on the *central radiology review* was 16.69 months (95% CI: 11.07, NA). The median PFS estimate based on *investigator review* was 15.2 months (95% CI: 9.3, NA).The median OS had not been reached at the time of data cut-off (1 November, 2008). These survival data have not been updated in the present application.

> **Evaluator comment:** The numbers of responders, 2 and 5, in Stratum 2 were too low for the ORRs to be reliable. The ORRs in Stratum 1 had greater numbers of responders and were similar, 9.6% and 10.4%, not showing the differences seen in the pivotal trials between IRC and local investigators assessments. The rates were about 4 times higher than those seen in the Phase III trial C2324 PNET of everolimus treatment of the same tumour, even though the patients in the present trial had failed previous chemotherapy. The better results of Phase II trials

compared to the following Phase III trial are common in cancer research. Given the inconsistencies, the evaluator concludes from this Phase II trial that everolimus has activity in PNET but that the measure of that activity is uncertain from the data presented.

Evaluator's conclusions on clinical efficacy for the requested indication: The treatment of advanced NETs of gastrointestinal, lung or pancreatic origin.

Compliance with TGA adopted guidance documents

As originally designed, the studies complied with the following guidance documents adopted by the TGA:

- Guidelines of Good Clinical Practice (*Note for Guidance on Good Clinical Practice* (CPMP/ICH/135/95) - Annotated with TGA comments
- *'Statistical principles for clinical trials'* (ICH Topic E9; CPMP/ICH/363/96), and *'Choice of control group in clinical trials'* (ICH Topic E10; CPMP/ICH/364/96);
- Committee for Medicinal Products for Human Use (CHMP) *'Guideline on the evaluation of anticancer medicinal products in man'* (CPMP/EWP/205/95/Rev3/Corr2), and *'Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man: methodological considerations for using progression free survival (PFS) as primary endpoint in confirmatory trials for registration'* (EMEA/CHMP/EWP/27994/2008).

Progression free survival has been accepted by regulatory agencies as a valid outcome measure (see above references). However the CPMP document states *"Independent review and confirmation of best tumour response and progression should be undertaken if PFS is the primary endpoint"* (CPMP/EWP/205/95/Rev3/Corr2). Whether the two pivotal studies comply after the sponsor changed the protocols by altering the method of assessments of the primary and other endpoints, changes not agreed to by the FDA, has been discussed above (see *Regulatory concerns about the changes to the study design*).

Adequacy of the study designs

The adequacy with respect to the use of controls, randomisation, blinding, and subsequent conduct of the two pivotal trials was acceptable. It was also accepted that the determination of OS would be confounded because of the cross-over of patients on the placebo arms with progressive disease to treatment with everolimus and after that with other anticancer therapy. For this reason, PFS remained the primary endpoint of the two studies.

An issue in the study design was that the two studies included only patients with well or moderately differentiated NETs, whereas the indication covers all grades of differentiation. This may require a change to the wording [of relevant parts] in the PI.

No specific data were collected in support of long term efficacy other than those generated in the individual studies. Open label extensions to the controlled Phase III trials provided safety data over the longer term.

Clinical relevance of the outcomes measured

Progression free survival without supporting OS data has been accepted by regulatory agencies as a valid outcome measure of possible patient benefit (see above references to guideline documents), although OS data were still required. However regulatory agencies retain the right to assess each case on its own merits with respect to the nature of the cancer treated and the conditions of the individual trials. In the case of NETs, the clinical relevance of prolonging PFS has to take into account the relatively long survival of patients with well or moderately differentiated NETs. Patients with metastatic well and moderately differentiated NETs had a median survival of 33 months from data in the SEER registry

(Yao *et al*., 2008). The median survival of patients in C2324 PNET had not been reached, and in the placebo arm of the C2325 Carcinoid trial it was 33 months. The increases in the PFS claimed for everolimus treatment in the C2324 PNET and the C2325 Carcinoid trials were 6.4 months and 5.1 months respectively, noting that the second value did not reach statistical significance. The clinical relevance of these increases in PFS will therefore need to be considered overall, with safety and other data in the risk-benefit assessment. Also to be considered is the lack of alternative treatment in this disease, supported by an expert's opinion, submitted with the sponsor's letter of application.

Efficacy in subpopulations

Subgroup analyses of the primary PFS endpoint in Study C2324 PNET confirmed the consistency of the observed treatment effect across major demographic subgroups, including age (< 65 years, ≥ 65 years), gender and race, and stratification factors of prior chemotherapy and WHO PS score. No subpopulations with significant liver or renal impairment were included in the studies.

Interpretation of the results in the context of other current evidence

Sunitinib (Sutent) was approved in February 2011 by the TGA for the treatment of unresectable, well differentiated PNETs. Sunitinib inhibits the phosphorylation of multiple receptor tyrosine kinases (TOKs) whereas everolimus inhibits a key serine-threonine kinase (mTOR). However, the subsequent biological effects are similar. The pivotal trial of Sutent used PFS as the primary endpoint and showed an increase of PFS from 5.5 months to 11.4 months, a similar result to that in the C2324 PNET trial. In the Sutent trial the median survival had not been reached at the time of data analysis. The results for the effect on the PFS in the pivotal trial of Sutent support the similar results for the C2324 PNET trial with everolimus, noting that only patients with well-differentiated cancers were included in the Sutent trial.

Different conclusions from the sponsor's Clinical Overview

The sponsor's *Clinical Overview concludes that "Substantial evidence of the efficacy of everolimus in advanced NET is provided by two adequate and well-controlled Phase III trials"* in spite of then stating that the second study, C2325 Carcinoid, failed to meet its primary PFS endpoint. The evaluator concludes instead that the second trial failed to demonstrate significant efficacy of everolimus in treating non-pancreatic NETs.

A further conclusion, not made in the sponsor's *Clinical Overview*, is the clinical outcomes in each of the pivotal trials were inconsistent. In C2324 PNET patients in the placebo arm experienced disease progression in a median of 4.6 months and in C2325 Carcinoid in a median of 11.3 months. This indicates that pancreatic NETs have a worse prognosis than the non-PNETs in Study C2325 Carcinoid. This is also consistent with the shorter period of the PFS (11 months) in the C2324 PNET trial compared to that (16.4 months) in the C2325 Carcinoid trial. The PFSs of patients in the Phase II trial, C2239 were not comparable because of differences in the patient population with drug resistant, retreated disease.

Supplementary statistics evaluation - conclusion

Because of the multiple statistical issues, the TGA sought independent expert advice on the statistical methods used in Study C2325 Carcinoid. The evaluator concluded the following:

> The original statistical plan, amendments to plan, and statistical analyses are valid and reasonable. However, the results of this trial are difficult to interpret for at least three reasons:
>
> (i) Ascertaining the precise date of progression in this patient group was difficult
>
> (ii) Progression events accrued more slowly than anticipated.
>
> (iii) Cross-over (switching) means the results for OS are not valid.

Therefore, the sponsor's characterisation of the trial results as *"demonstrating that everolimus, in conjunction with depot octreotide, provides important benefits for this patient population"* is subject to uncertainty.

In terms of strength of evidence, the IPCW results (to adjust for informative censoring) are roughly similar to results from a non-randomised observational study, adjusted for potential selection bias.

From a statistical point of view, the issue is not whether the statistical methods are valid (they are). The key statistical issue is which results should be used in a decision for registration. The IPCW results are interesting, but are appropriately labelled as exploratory in the clinical study report.

The key result for TGA consideration is HR for PFS = 0.77, p = 0.026; which narrowly failed to reach statistical significance at the pre-specified threshold adjusted for the interim analyses (0.0246).

Safety

Studies providing evaluable safety data

The following studies provided evaluable safety data: C2324 PNET, C2325 Carcinoid and C2239 as shown in Table 10 below. Table 10 also shows the safety endpoints used.

Table 10. Number of patients - safety

Study	Study design, objectives, and population	Safety endpoints	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	Toxicity assessment documented by NCI CTCAE Reporting of AEs, SAEs Routine laboratory evaluations	204 + 153 (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 tumor	Toxicity assessment documented by NCI CTCAE Reporting of AEs, SAEs Routine laboratory evaluations	215 + 128 (open-label phase following crossover from placebo)
C2239	Open-label phase-II study Safety and efficacy in patients with advanced pancreatic NET after failure of cytotoxic chemotherapy	Toxicity assessment documented by NCI CTCAE Reporting of AEs, SAEs Routine laboratory evaluations	Stratum 1: 115 Stratum 2: 45
	Total		**858** [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

Safety populations analysed

In all trials, the Safety Analysis Set was defined as all patients who received any study drug and had at least one post baseline safety assessment. In each of the pivotal C2324 PNET and C2325 Carcinoid trials, the patients in the double blind treatment phase were analysed separately from those who crossed over from the placebo arms to receive everolimus in the open phase of the studies. The safety data from the Phase II study was also presented separately. In addition, the *Summary of Clinical Safety* pooled the data of all patients who received everolimus in the three studies, that is, all the patients shown in the above table, leaving a pooled population of 850. A Safety Update had been agreed with the FDA and was also provided for data cut-offs at 3 June 2010 for Study C2324 PNET and 2 July 2010 for Study C2325 Carcinoid. The additional data was from 8 patients, which raised the total number to the 858 shown in the above table. As the safety results from the

additional 8 patients were consistent with previous results, with no new findings evident, the data on the 850 patients will be mainly used for safety evaluation, with use of the updated data where relevant.

Definitions

In these studies, an *AE* was defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) occurring after signing of the informed consent form, and included events reported within the 28 days following the discontinuation of treatment. A *Serious Adverse Event (SAE)* was defined as any adverse drug experience that resulted in one of the following outcomes: death, life-threatening event, in-patient hospitalisation or prolongation of existing hospitalisation, a persistent or significant disability/incapacity or a congenital anomaly/birth defect. Furthermore, important medical events that may not result in death, be life threatening, or require hospitalisation may also be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardise the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above. A *clinical notable* AE was an AE resulting from signals observed during the conduct of the program of potential safety concern.

Identification and timing of AEs

Adverse events were identified by non-directive questioning of the patient at each visit during the study. Adverse events could also be detected when volunteered by the patient during or between visits or through physical examination, laboratory test results, or other assessments. A consistent approach to the collection of AEs was adopted across studies. Adverse events reported during the open label phase of the pivotal Phase III trials were captured in the pooled everolimus dataset and are included in the pooled data in the following sections. Where C2324 PNET and C2325 Carcinoid study data are presented in the following sections, they are from the double blind treatment phases of those studies. Unlike routine safety assessments, SAEs were monitored continuously and had special reporting requirements.

The time to the first onset of selected AEs was recorded throughout the period of the two trials.

> **Evaluator comment:** The safety data from the double blind treatment phases of the pivotal trials form the main data presented and cover a duration of drug exposure equal to that of the double blind treatment phase; 37.8 weeks for patients in the everolimus arm and 16.1 weeks for patients in the placebo arm of C2324 PNET and 37 weeks and 36.6 weeks for patients in the everolimus arm and placebo arm respectively, for Study C2325 Carcinoid. When their disease progressed patients who crossed over from the placebo arms and then had everolimus treatment had shorter periods of exposure to the drug. For the 149 patients in the C2324 PNET trial, the median duration of exposure was 28.9 weeks, and for the 124 patients in C2325 Carcinoid the median duration was 26.3 weeks.

Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- General AEs were assessed by monitoring and recording of all treatment-emergent AEs and SAEs. Adverse events were reported on case report forms (CRFs) using investigator verbatim terms and subsequently coded using the Medical Dictionary for Regulatory Activities (MedDRA) (and recoded for this summary using MedDRA Version 13.0). MedDRA usage was uniform and consistent in the reporting of AE data. All AEs were graded in accordance with the standard oncology reporting system (the National Cancer Institute's [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 3.0) by investigators who were blinded to therapy in Studies C2324

PNET and C2325 Carcinoid but not across the rest of the program. Information recorded included dates of onset and resolution for an event, details of the grading (severity) and relationship to study medication, action taken, and outcome.

- AEs of particular interest resulted from class effects, and effects found in previous studies.
  - *Class Effects:* Toxicities reported with everolimus therapy in an advanced renal cell cancer population were generally mild to moderate and appeared, in general, to be similar both in type and severity to those occurring in patients treated with temsirolimus. Hyperlipidemia, stomatitis/oral mucositis, skin toxicity (rash and related events), hyperglycemia, pneumonitis and infection are all considered to be class effects. The more common metabolic side effects reported with inhibitors of the mTOR result from inhibitory effects on mTOR-regulated lipid and glucose pathways, while infections stem from the immunosuppressive properties of these agents.
  - *Known safety factors warranting monitoring, special tests, or special studies:* Non-infectious pneumonitis is a recognised side effect of rapamycin and its derivatives, and represents one of the most important clinical issues seen with everolimus therapy. Low grade pneumonitis was initially reported in association with everolimus therapy in two investigator initiated studies. In these trials, CT scans were undertaken every 2-3 months to evaluate tumour response and results suggested a high frequency (up to 75%) of patients with Grade 1 (asymptomatic; evident only radiologically) or Grade 2 events (mild symptoms not interfering with daily activities). An advisory board, including several leading pulmonary/thoracic oncologists, was subsequently convened to help formulate an approach to this issue for the broader everolimus clinical program. As a result, routine chest X-ray or CT-scans have been performed in clinical trials to definitively address this issue. It was believed that adherence to these recommendations would provide comprehensive information on pneumonitis associated with everolimus and its appropriate management.
- Laboratory tests consisted of the regular monitoring of haematology and blood chemistry. Abnormal laboratory values (new or worsening from baseline based on Common Terminology Criteria for Adverse Events (CTCAE) grades) were summarised for haematology and clinical chemistry parameters. Laboratory values were converted to International System (SI) units and analysed using National Cancer Institute (NCI) CTCAE grades (Version 3.0)[23]. Although analyses focusing on shifts from normal to abnormal values were performed, it was considered more informative in advanced cancer populations to describe treatment groups in terms of the proportion of patients experiencing an event graded 1 through 4 in accordance with NCI CTCAE criteria. Clinical laboratory results were presented in post-text tables separately for haematology and clinical chemistry variables.

Pivotal studies that assessed safety as a primary outcome

No studies of this type were submitted.

Dose-response and non-pivotal efficacy studies

No dose-response studies were submitted. The non-pivotal efficacy Phase II study, C2239, enrolled patients with advanced pancreatic NET after the failure of cytotoxic chemotherapy. The study provided the following safety data: toxicity assessment documented by NCI CTCAE reporting of AEs, SAEs and routine laboratory evaluations until disease progression, unacceptable toxicity or death, or discontinuation for any other

[23] http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf

reason. The 160 patients (115 in Stratum 1 and 45 in Stratum 2) in the safety population were those who received at least one dose of study drug and for whom post-baseline safety data were available.

Other studies evaluable for safety only

No studies of this type were submitted.

Patient exposure

Exposure by duration is shown in Table 11 below. In total, 312 patients (36.7%) of the total patient number of 850 from the three studies were exposed to everolimus therapy for a period of 48 or more weeks. Treatment duration (calculated from the date of the first to the last dose of study drug [including treatment interruptions]) was considerably longer for patients receiving everolimus in Study C2324 PNET; the median duration of therapy was 37.8 weeks (range: 1.1-118.1) for patients treated with everolimus compared with 16.1 weeks for those receiving placebo (range: 0.4-132.4). In contrast, no difference was evident in Study C2325 Carcinoid: 37.0 weeks (range: 0.6-162.6) for patients treated with everolimus compared with 36.6 weeks for those receiving placebo (range: 0.4-152.1). The shortened duration of exposure of patients in the placebo arm of C2324 PNET was associated with a reduced cumulative dose of placebo tablets, referred to as "everolimus" in the Tables.

> **Evaluator comment:** It is important to note the difference in the two pivotal studies in the time of exposure of patients in the placebo arms. The markedly shorter treatment time for patients in the placebo arm of the C2324 PNET trial suggests these patients had a shorter time to progressive disease and so less exposure to placebo treatment before cross-over to everolimus treatment in the open label phase of the study. In the C2325 Carcinoid trial, however, patients who were in the placebo arm had a time to disease progression similar to those in the everolimus arm and so had similar times of exposure, consistent with reduced efficacy of everolimus in the C2325 Carcinoid study.

Table 11. Exposure by duration

Exposure	Study C2324		Study C2325		Pooled data
	Everolimus N=204	Placebo N=203	Everolimus N=215	Placebo N=211	Everolimus N=850
Exposure categories (weeks) (n [%])					
< 4	6 (2.9)	9 (4.4)	7 (3.3)	4 (1.9)	31 (3.6)
4 to < 8	8 (3.9)	13 (6.4)	15 (7.0)	8 (3.8)	54 (6.4)
8 to < 12	20 (9.8)	23 (11.3)	12 (5.6)	2 (0.9)	72 (8.5)
12 to < 24	33 (16.2)	71 (35.0)	36 (16.7)	52 (24.6)	154 (18.1)
24 to < 36	26 (12.7)	30 (14.8)	32 (14.9)	35 (16.6)	125 (14.7)
36 to < 48	33 (16.2)	29 (14.3)	24 (11.2)	20 (9.5)	102 (12.0)
48 to < 72	50 (24.5)	23 (11.3)	22 (10.2)	25 (11.8)	142 (16.7)
72 to < 96	16 (7.8)	4 (2.0)	17 (7.9)	21 (10.0)	89 (10.5)
≥ 96	12 (5.9)	1 (0.5)	50 (23.3)	44 (20.9)	81 (9.5)
Duration of exposure (weeks)					
n	204	203	215	211	850
Mean (standard deviation)	40.9 (27.87)	25.4 (20.29)	53.2 (43.79)	52.1 (41.30)	42.6 (33.64)
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**

Patients are counted in only one exposure category
Studies included: C2324, C2325, and C2239

Median dose intensities were 9.8 mg/day (range: 2.4-10.0) and 9.5 mg/day (range: 2.8-10.0) for the everolimus treatment groups in Studies C2324 PNET and C2325 Carcinoid, respectively (Table 12). Mean and median dose intensities were consistent for both the Study C2324 PNET and Study C2325 Carcinoid data and the pooled dataset.

Table 12. Cumulative dose, dose intensity

	Study C2324		Study C2325		Pooled data
	Everolimus N=204	Placebo N=203	Everolimus N=215	Placebo N=211	Everolimus N=850
Cumulative dose (mg) [a]					
n	204	203	215	211	850
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) [b]					
n	204	203	215	211	850
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 intensity (mg/day) (n [%])					
0 to < 5	16 (7.8)	0	15 (7.0)	3 (1.4)	57 (6.7)
5 to < 7	29 (14.2)	5 (2.5)	49 (22.8)	5 (2.4)	146 (17.2)
7 to < 9	26 (12.7)	10 (4.9)	28 (13.0)	7 (3.3)	106 (12.5)
9 to < 11	133 (65.2)	188 (92.6)	123 (57.2)	196 (92.9)	541 (63.6)
≥ 11	0	0	0	0	0

[a] Cumulative dose equals total dose received
[b] Dose intensity equals cumulative dose divided by duration of exposure

Studies included: C2324, C2325, and C2239

Exposure was affected by dose interruptions and dose reductions. The numbers and incidences were as follows:

Dose interruption and/or dose reduction: C2324 PNET- Everolimus arm, n = 120 (59%); placebo, n = 57 (28%). C2325 Carcinoid – Everolimus arm, n = 140 (65%); placebo, n = 74 (35%).

One dose interruption and/or dose reduction: C2324 PNET- Everolimus arm, n = 30 (15%); placebo, n = 30 (15%). C2325 Carcinoid – Everolimus arm, n = 30 (14%); placebo, n = 39 (19%).

Two or more dose interruptions and/or dose reductions: C2324 PNET- Everolimus arm, n = 90 (44%); placebo, n = 27 (13%). C2325 Carcinoid – Everolimus arm, n = 110 (51%); placebo, n = 35 (17%).

> **Evaluator comment:** The number of patients with any interruption and/or dose reduction due to an AE was high in each of the everolimus arms compared to placebo (C2324 PNET everolimus arm 52%, placebo arm 19%; C2325 Carcinoid everolimus arm 55%, placebo 26%).

Adverse events

Adverse events were presented as all AEs (classified by System Organ Class [SOC], and preferred term [PT]), severe AEs (Grades 3 and 4), serious AEs (death and other serious outcomes) and clinically notable AEs, defined as several AEs identified in earlier studies and requiring close follow-up. Any relationship to treatment with everolimus was given separately in most cases.

All adverse events (irrespective of relationship to study treatment)

Pivotal studies

AEs by categories: Table 13 below shows the percentage of patients in each of the pivotal trials who had an AE in the categories shown. The data presented for each study was for the double blind treatment period, while the pooled data includes as well those in the open label phase and in Study C2239 who received everolimus. The table below shows all AEs and those considered to be drug related.

Table 13. Incidence of categories of AEs

Category [a]	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 (%)
Adverse event (AE)	**202 (99.0)**	**198 (97.5)**	**215(100.0)**	**203 (96.2)**	**844 (99.3)**
Suspected to be drug-related	195 (95.6)	151 (74.4)	207 (96.3)	133 (63.0)	809 (95.2)
Grade 3-4 AE	**122 (59.8)**	**79 (38.9)**	**159 (74.0)**	**106 (50.2)**	**588 (69.2)**
Suspected to be drug-related	92 (45.1)	28 (13.8)	97 (45.1)	32 (15.2)	363 (42.7)
Clinically notable AE [b]	**193 (94.6)**	**144 (70.9)**	**208 (96.7)**	**144 (68.2)**	**801 (94.2)**
Suspected to be drug-related	185 (90.7)	85 (41.9)	192 (89.3)	71 (33.6)	738 (86.8)
On-treatment deaths	**12 (5.9)**	**4 (2.0)**	**18 (8.4)**	**11 (5.2)**	**68 (8.0)**
Serious adverse event (SAE)	**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)
Other significant AE					
AEs requiring dose interruption and/or reduction	125 (61.3)	55 (27.1)	148 (68.8)	70 (33.2)	539 (63.4)
AEs requiring additional therapy	197 (96.6)	175 (86.2)	212 (98.6)	185 (87.7)	819 (96.4)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
[b] Clinically notable AE: as a result of signals observed during the conduct of the program, several potential safety concerns were identified

Studies included: C2324, C2325, and C2239

> **Evaluator comment:** The incidence of AEs in all categories was high but similar in the everolimus and placebo arms, whereas that for the other categories was higher in the everolimus arms. The difference was more marked for the incidence of AEs considered to be drug related. The incidence of drug-related AEs was similar in the everolimus arms of each study, but AEs irrespective of treatment had a higher incidence in the second study (C2325 Carcinoid) than in the first study (C2324 PNET). The duration of time patients spent in the everolimus arms of the trials during the double blind phase was calculated to be 2.3 times that of the time patients spent in the placebo arms. A correction for this was made as follows.

Adjustments made for time of drug exposure: The adjustment is complex. It appears to have been designed to determine the incidence of AEs during equal periods when patients took either everolimus or placebo during the blinded phase of the trials. This would allow a comparison of incidence of AEs in each arm and could show if there were an increase in the everolimus arm if the drug caused additional AEs in those patients. Adjustment was done by dividing the sum of each patient's exposure in days by 365.25. The adjusted rate for a given AE was calculated as number of events per 100 subject year exposure (= [n/SYE]*100) and is shown in Table 14, below. It is important to note that the placebo patients did not receive any everolimus in this period but received a placebo tablet and it is the duration of treatment with this placebo tablet that was used in the equation for these patients as the "exposure" factor. This allows the incidence of AEs to be compared over equal periods.

The adjusted AE categories (see Table 14) showed the incidence of drug-related AEs were comparable overall in both arms of C2324 PNET but the Grade 3-4 AEs and clinically notable AEs considered drug-related had a higher incidence in the everolimus arm than in the placebo arm, and comparable to that in the pooled data.

Table 14. Adjusted incidence of AEs

Category	Study C2324		Study C2325		Pooled data
	Everolimus N=204 Adjusted rate	Placebo N=203 Adjusted rate	Everolimus N=215 Adjusted rate	Placebo N=211 Adjusted rate	Everolimus N=850 Adjusted rate
Adverse event (AE)	126.3	200.8	98.1	96.3	121.7
Suspected to be drug-related	122.0	153.1	94.5	63.1	116.6
Grade 3-4 AE	76.3	80.1	72.6	50.3	84.8
Suspected to be drug-related	57.5	28.4	44.3	15.2	52.3
Clinically notable AE [a]	120.7	146.0	94.9	68.3	115.5
Suspected to be drug-related	115.7	86.2	87.6	33.7	106.4

[a] Clinically notable AE: as a result of signals observed during the conduct of the program, several potential safety concerns were identified

Studies included: C2324, C2325, and C2239

> **Evaluator comment:** The interpretation of these results is difficult. The similarity of so called drug-related AEs overall suggests that the classification by investigators of these AEs as drug-related is unreliable, whereas classification by investigators of Grade 3-4 AEs and of clinically notable AEs was reliable, as shown by the differences in those values. Why this is so is not clear.

Cut-off limits for presenting AEs: The AEs from the pivotal Studies C2324 PNET and C2325 Carcinoid were selected in the study report with the following cut-offs, while the complete listings were presented in post-text tables: AEs by SOC, irrespective of relationship to study treatment, all events given: AEs by PT and their grading (severity), irrespective of relationship to study treatment with at least a 10% incidence in one treatment group; and AEs with suspected relationship to study treatment with at least a 5% incidence in either group and a difference between groups by PT.

Cut-offs differed in the two studies for most common Grade 3-4 adverse events by PT irrespective of relationship to study treatment with at least 1.5% incidence in either arm of the C2324 PNET study and at least 2% in the C2325 Carcinoid study; and grading (severity) of adverse events by PT with suspected relationship to study treatment with at least 1% incidence of Grade 3 or 4 events in either arm in C2324 PNET and at least 2% in C2325 Carcinoid.

> **Evaluator comment:** The above cut-off limits are reasonable, although the latter differences make a comparison of the studies more difficult. As well, transfer of safety data to the proposed PI is complicated because the cut-off limits used in the PI are different from the above. In addition, the Council for International Organizations of Medical Sciences (CIOMS) III convention of very common (≥ 1/10), and common (1/100 to < 1/10) for the frequency of AEs referenced in the PIwill require that all incidence figures for AEs with a frequency above 1% need to be checked.

AEs by SOC: Overall, AEs were experienced by 99.0% of patients receiving everolimus and 97.5% of the placebo group in Study C2324 PNET, and by 100.0% of everolimus-treated patients and 96.2% of those receiving placebo in Study C2325 Carcinoid. SOCs 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' (Study C2324 PNET: +43.5%; Study C2325 Carcinoid: +35.2%), 'Respiratory, thoracic and mediastinal disorders' (+36.6% and +23.5%), 'Metabolism and nutrition disorders' (+26.7% and +32.3%), 'Blood and lymphatic system disorders' (+22.4% and +32.7%), 'Infections and infestations' (+21.9% and +19.7%), 'Nervous system disorders' (+21.9% and +12.2%), 'General disorders and administration site conditions' (+19.8% and +14.1%), 'Investigations' (+16.1% and +20.8%), 'Gastrointestinal disorders' (+14.8% and

+18.6%), 'Renal and urinary disorders' (+12.2% and +9.0%), and 'Injury, poisoning and procedural complications' (+10.2% and +5.4%).

Adverse events by preferred term: Those AES with an incidence of 20% or more in both studies, in order of frequency, were stomatitis, diarrhoea, rash, fatigue, peripheral oedema, nausea, headache, pyrexia, decreased appetite, vomiting, decreased weight, abdominal pain, anaemia, cough and epistaxis. Others of importance were thrombocytopenia (14.2%, 15.3%), pneumonitis (13.2%, 8.4%), aphthous stomatitis (12.3%, 12.6%) and hypertension (10.3%, 11.6%) in the C2324 PNET and C2325 Carcinoid trials respectively.

> **Evaluator comment:** These events are consistent with the AEs described in the currently approved Australian PI for Afinitor.

Severe AEs (Grade 3 and 4) irrespective of relationship to treatment

The data were shown as those AEs with an incidence of 10% or more in any one group of the pivotal trials. The order of these PT AEs differed from those above.

C2324 PNET: Of the patients in the everolimus arm, 99% experienced an AE, of which 59.8% were severe (Grade 3, 47.5%; Grade 4, 12.3%). In the placebo arm, 97.5% of patients experienced an AE, of which 38.9% (Grade 3, 31.5%; Grade 4, 7.4%) were severe.

Grade 3 AEs that affected 10 or more patients (5%) in order of frequency were hyperglycemia (7.4%), anaemia (6.9%), diarrhoea (4.9%), hypophosphatemia (4.9%), and stomatitis (4.9%) in the everolimus treatment group and abdominal pain (4.9%) in the placebo treatment group. Other Grade 3 AEs with an incidence between 1.5% and 5% are not shown here. Grade 4 AEs in the everolimus arm were anaemia and hypokalemia (n = 3, 1.5%) and cardiac arrest, hypercalcemia, hypocalcemia, pulmonary embolism and thrombocytopenia (n = 2, 1.0%), hyperglycemia, diarrhoea, fatigue, dyspnoea, confusional state (n = 1, 0.5%); and in the placebo group, hypercalcemia (n = 3. 1.5%), abdominal pain and depressed level of consciousness (n = 2, 1.0%), hyperglycaemia, fatigue, pulmonary embolism, renal failure, confusional state and hyperbilirubinemia (n = 1, 0.5%).

C2325 Carcinoid: Of the patients in the everolimus arm, 100% experienced an AE, of which 73.9% were severe (Grade 3, 55.3%; Grade 4, 18.6%). In the placebo arm, 96.2% of patients experienced an AE, of which 50.3% (Grade 3, 42.2%; Grade 4, 8.1%) were severe.

Grade 3 AEs that affected 10 or more patients (5%) in order of frequency were diarrhoea (13.5%), hypokalaemia (10.7%), fatigue (10.7%), abdominal pain (9.3%), hyperglycemia (6.5%), asthenia (5.1%), dyspnoea (4.7%), and anaemia (4.7%). Other Grade 3 AEs with an incidence between 1.5% and 5% are not shown here. Grade 4 AEs in the everolimus arm were hypokalaemia, dyspnoea, and pulmonary embolism (n = 2, 0.9%), fatigue, hyperglycaemia, anaemia, thrombocytopenia, vomiting, hypophosphataemia, pneumonia, neutropenia, hypocalcaemia and deep vein thrombosis (n = 1, 0.5%).

> **Evaluator comment:** Severe AEs were frequent, comprising 60 to 74% of all AEs in the studies. A reasonable degree of consistency was evident. Differences were seen in C2324 PNET and C2325 Carcinoid in the incidence of Grade 3 or 4 diarrhoea (5.4% compared with 13.5%), abdominal pain (2.9% compared with 9.3%), fatigue (3.0% compared with 11.2%), and hypokalaemia (2.5%). The study report suggested that the increased incidence of Grade 3-4 diarrhoea and hypokalaemia in Study C2325 Carcinoid might be attributed in part to the underlying disease as carcinoid syndrome can cause both these events.

Other studies

Study C2239: This was a Phase II, international, multicenter, open label, stratified, single arm trial designed to evaluate the efficacy and safety of everolimus 10 mg in patients with pancreatic NET whose disease had progressed despite prior treatment with cytotoxic chemotherapy. Stratum 1 (those not receiving Sandostatin LAR) consisted of 115 patients

receiving everolimus 10 mg. Stratum 2 (those receiving Sandostatin LAR) 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. Safety assessment was a secondary objective. Toxicity was documented by reporting AEs and SAEs (according to NCI CTCAE reporting system). Routine laboratory evaluations were performed until disease progression, unacceptable toxicity or death or discontinuation for any other reason. Stratum 1 consisted of 115 patients and Stratum 2 of 45 patients.

Stratum 1 safety results: The Safety population comprised all patients enrolled. The median duration of exposure to everolimus was 251 days (range 4 to 772 days), compared to 264 days for C2324 PNET and 259 days for C2325 Carcinoid. The number of patients exposed to everolimus for more than 52 weeks was 33.9% at the time of the second data-cut (01 November 2008). The most common CTCAE Grade 3 AEs were asthenia and fatigue. In general, these events were in keeping with the expected AE profile of everolimus. Twenty patients (17.4%) experienced a maximum Grade 4 AE irrespective of study drug relationship (compared with C2324 PNET 12.3%; C2325 Carcinoid 18.6%). The most common events were anaemia, abdominal pain and pyrexia. Clinically notable AEs occurred in 93.9% of patients. The most common clinically notable AE grouping was 'Infections/infestations' (all grades) and occurred in 63.5% of patients. Stomatitis/oral mucositis/ulcers (all grades) occurred in 61.7% of patients. Renal events occurred in 10.4% of patients. Pulmonary events occurred in 7.0% of patients. Serious AEs (SAEs) were experienced by 51.3% of patients (compared with C2324 PNET 40.2%; C2325 Carcinoid 56.7%). Abdominal pain, asthenia, and pyrexia, were the most frequent SAEs. Ten deaths (8.7%) were reported on-treatment (compared with C2324 PNET 3.4%; C2325 Carcinoid 5.6%). Six of these ten deaths were considered by the study investigator to be related to the primary disease and/or disease progression. The remaining four patients were complex based on disease burden, general condition at study entry and co-morbid conditions and were potentially toxic deaths on-study.

> **Evaluator comment:** The number of patients exposed to everolimus for more than 52 weeks was 33.9%, similar to C2324 PNET (38.2% > 48 weeks) and less than C2325 Carcinoid (41% > 48 weeks). Sixty-six patients (57.4%) experienced a CTCAE Grade 3 AE irrespective of study drug relationship (compared with C2324 PNET: 59.8%; C2325 Carcinoid: 73.9%). For comparable exposure the rate was similar in this study and Study C2324 PNET but less than in Study C2325 Carcinoid.

Stratum 2 safety results: The Safety population comprised all patients enrolled in this stratum. The median duration of exposure to everolimus was 305 days (range 8 to 795 days). Median exposure to Sandostatin LAR Depot was 246 days, ranging from 28 to 757 days. The number of patients exposed to everolimus for more than 52 weeks was 46.7%. Grade 3 AEs, irrespective of study drug relationship, were experienced by 26 patients. The most prevalent events were dehydration, hypokalaemia and thrombocytopenia. In general, events were in keeping with the expected AE profile of everolimus. Eleven patients experienced a maximum Grade 4 AE irrespective of study drug relationship; no Grade 4 AE occurred in more than 1 patient. All patients had a clinically notable AE. The most common clinically notable AE grouping was 'infections/infestations' (all grades) and occurred in 68.9% of patients. Stomatitis/oral mucositis/ulcers occurred in 48.9% of patients. Renal events occurred in 20.0% of patients. Pulmonary events occurred in 13.3% of patients. An SAE was experienced by 55.6% of patients. Abdominal pain, cardiac failure, dyspnoea and thrombocytopenia were the most frequent SAEs. Two on-treatment deaths (4.4%) were reported in this Stratum, both were considered by the investigator to be related to the primary disease and/or disease progression.

Treatment-related adverse events (adverse drug reactions)

Pivotal studies

Adverse events by SOC: Overall, treatment-related AEs were experienced by 95.6% of patients receiving everolimus and 74.4% of the placebo group in Study C2324 PNET, and by 96.3% of everolimus-treated patients and 63% of those receiving placebo in Study C2325 Carcinoid. The incidence by SOCs of drug-related AEs was not presented in the study reports.

Adverse events by PT: Drug-related events where incidence was 10% or more than placebo were: stomatitis (Study C2324 PNET: +41.6%; Study C2325 Carcinoid: +37.0%), rash (+38.2% and +24.9%), diarrhoea (+23.9% and +11.8%), epistaxis (+17.2% and +4.7%), fatigue (+17.1% and +8.0%), peripheral oedema (+16.7% and +9.7%), anaemia (+14.2% and +10.6%), dysgeusia (+13.3% and +13.4%), decreased appetite (+12.7% and +7.3%), headache (+12.7% and +0.3%), thrombocytopenia (+12.7% and +14.0%), pneumonitis (+12.3% and +8.4%), weight decreased (+11.3% and +11.6%), nail disorder (+10.8% and +2.8%), pyrexia (+10.8% and +1.8%), hyperglycemia (+8.8% and +10.2%), aphthous stomatitis (+7.4% and +11.2%) and dyspnoea (+4.4% and +10.7%). Other events with less than 10% difference are not shown here.

Comparison of the most common AEs irrespective of relationship to treatment by PT with those suspected as being drug-related identified 8 events in the everolimus treatment group where incidences were similar: stomatitis, rash, dysgeusia, thrombocytopenia, pneumonitis, nail disorder, aphthous stomatitis and dry skin.

Severe AEs (Grade 3 and 4) related to treatment with everolimus

The discussion below refers to those AEs with an incidence of 10% or more in any one group of the pivotal trials. The order of these PT AEs differed from that of all grades of AEs.

C2324 PNET: Of the patients in the everolimus arm, 40.2% experienced a severe AE (Grade 3, 40.2%; Grade 4, 4.9%). Grade 3 in descending order of frequency, by PT in 1% or more of patients were: hyperglycemia (5.4%), anaemia (4.9%), stomatitis (4.9%), thrombocytopenia (3.4%) and diarrhoea (3.4%) in the everolimus treatment group; and neutropenia (2.0%), hyperglycemia (1.5%), asthenia, increased alanine aminotransferase (ALT) and increased aspartate aminotransferase (AST) (1.0% each) in the placebo treatment group. Grade 4 events reported in the everolimus arm were anaemia (n = 2, 1.0%), thrombocytopenia and pulmonary embolism (each n = 1, 0.5%); in the placebo group, hyperglycemia (n = 1, 0.5%).

C2325 Carcinoid: Of the patients in the everolimus arm, 45.1% experienced a Grade 3 or 4 AE, of which 40.5% were Grade 3 and 4.7%, Grade 4. In the placebo arm, 15.2% experienced a Grade 3 or 4 AE, of which 14.2% were Grade 3 and 0.9% Grade 4.

The most common Grade 3 AEs, in 1% or more of patients (related to treatment) were fatigue (6.5%), diarrhoea (6.0%), hyperglycemia (5.1%), thrombocytopenia (4.7%), stomatitis (3.7%), neutropenia (2.3%), hypophosphatemia (1.9%), mouth ulceration (1.4%), leukopenia (1.4%), cellulites (1.4%) and pneumonitis (1.4%) in the everolimus arm; and fatigue (2.8%), and diarrhoea (2.4%)in the placebo arm. The following Grade 4 events reported in the everolimus arm each had an incidence of 0.5% (1 patient): lip oedema, hypokalaemia, hypomagnesaemia, thrombocytopenia, neutropenia, herpes zoster, intracranial hematoma, hematoma and carcinoid syndrome; and in the placebo arm cardiac disorder and myocardial infarction (each n = 1, 0.5%).

Clinically notable AEs

Because the following AEs were mainly drug-related, they are presented in this section, although both drug-related and non drug-related AEs are referred to here.

The sponsor's *Summary of Clinical Safety* and the reports of the pivotal studies listed the following AEs as clinically notable: stomatitis/oral mucositis/ulcers, rash and similar events, hematopoiesis decreased/cytopenias, metabolic events, bleeding and thromboembolic events, renal events, pulmonary events, and hepatic events. Infections, intestinal obstruction and/or ileus and cardiac events were later added to this list. Each group of terms was defined as a selection of events similar in nature. However the sponsor's *Clinical Overview* selected only three of these for presentation; stomatitis, infections and non-infectious pneumonitis but gave no reason for the selection. In its briefing document to the ODAC, the FDA presented the following as *"Significant Events"* pneumonitis, opportunistic infections, renal failure and hyperglycaemia.

> **Evaluator comment:** The following clinically notable events are those listed mainly in the *Summary of Clinical Safety* above. The order used is based on the reasonable clinical importance of the event and its incidence in the studies.

Overall, events as listed for the *Summary of Clinical Safety* above were experienced by 94.6% of patients receiving everolimus and 70.9% from the placebo group in Study C2324 PNET and by 96.7% and 68.2% of everolimus and placebo treated patients, respectively, in Study C2325 Carcinoid. All groupings were reported by a higher proportion of everolimus-treated patients with the exception of hepatic events.

1. Infections and infestations

Everolimus is prescribed as an immunosuppressant so this group of AEs is considered here in some detail. Because specific infections were reported in a small number of patients, the PTs "infections" and infestations" were combined.

C2324 PNET: Overall, 'Infection and infestation' events were reported in 114 (55.9%) patients in the everolimus treatment group and in 69 (34.0%) patients in the placebo arm. Of these, 22.5% and 5.9% respectively were drug-related. Drug-related Grade 3 and 4 AEs in the everolimus and placebo arms were 2.5% and 0.5% respectively. When corrected for exposure time, the reported AE rates of all grades were similar between treatment groups but not those for Graded 3-4 AEs (see *Evaluator comment* above).

Specific Grade 3 and Grade 4 infections occurring in two or more everolimus patients were: pneumonia, infection, and *Escherichia* sepsis. Discontinuations in the everolimus group were due to pneumonia (n = 2), bacterial infection, biliary tract infection, *Escherichia* sepsis, infection, pulmonary tuberculosis, and gastroenteritis (each AE n = 1). Atypical infections including (Grades 2 or 3) pulmonary tuberculosis, (Grade 3) bronchopulmonary aspergillosis, and reactivation of hepatitis B were also observed. Both events of pulmonary tuberculosis were determined to be related to study treatment; the bronchopulmonary aspergillosis was determined not be related to study treatment. The patient whose Hepatitis B was reactivated died 2 months after his last dose of everolimus. His death was classed as drug-related and is discussed in the following section on study deaths.

A gradual increase over time in the probability of acquiring an infection was noted with an overall earlier onset in the everolimus treatment group. The median time at which an infection was acquired by everolimus patients was 5.3 months as compared with 9.8 months for placebo patients.

C2325 Carcinoid: Overall, 'Infection and infestation' events were reported in 139 (64.7%) patients in the everolimus treatment group and in 95 (45.0%) patients in the placebo arm. Of these, 19.5% and 6.2% respectively were drug-related. Drug-related Grade 3 and 4 AEs in the everolimus and placebo arms were 4.7% and 0.5% respectively. When corrected for exposure time, the reported AE rates remained different between the groups.

Specific Grade 3 or 4 infections occurring in two or more patients were: pneumonia (Grade 3 [n = 6]; Grade 4 [n = 1]), urinary tract infection (Grade 3 [n = 4]), cellulitis (Grade

3 [n = 4]), gastroenteritis (Grade 3 [n = 2]), lung infection (Grade 3 [n = 2]), and herpes zoster (Grade 3 [n = 1]; Grade 4 [n = 1]). Of the 30 patients diagnosed with Grade 3 or 4 infections, dose interruption or adjustment was implemented for 13; this was evident most commonly for patients with pneumonia (n = 4). Treatment with everolimus was discontinued for 6 patients (2.8%) as the result of an infection.

As in the previous study, the probability of acquiring an infection gradually increased with time. The median time at which an infection was acquired by everolimus patients was 4.4 months and 11.7 months for placebo patients.

2. Stomatitis/oral mucositis/ulcers: C2324 PNET

These AEs were reported more frequently in the everolimus arm, were mostly drug-related, and were Grade 3 in 14 (6.9%) patients. One patient with stomatitis discontinued treatment and 32 required dose adjustment or interruption. About half the cases occurred within the first month of treatment, and slowly increased thereafter.

C2325 Carcinoid: These AEs were reported more frequently in the everolimus arm, were mostly drug-related and were Grade 3 in 14 (6.5%) patients. Of these 14 patients, two continued therapy with no dose adjustment, 10 continued treatment but with a reduced dose and two patients discontinued treatment. About half the cases occurred within the first month of treatment and reached a plateau at about 4 months.

3. Pulmonary events (non-infectious)

Pulmonary events (including pneumonitis and similar events) were diagnosed in 38 and 25 everolimus-treated patients (18.6% and 11.6%) in C2324 PNET and C2325 Carcinoid, respectively and none in the placebo arm of C2324 PNET and 2 patients (0.9%) in the placebo arm of C2325 Carcinoid. The majority was drug-related; 16.7% and 11.6% in the everolimus arms of the two studies, respectively.

Adverse events were graded according to the NCI CTCAE (Version 3.0). The criteria for pneumonitis are as follows: Grade 1, asymptomatic, radiographic findings only; Grade 2, symptomatic, not interfering with Activities of Daily Living (ADL); Grade 3, symptomatic, interfering with ADL; oxygen indicated; Grade 4, life-threatening; ventilatory support indicated; Grade 5, death.

Maximum grading (severity) of pulmonary events (pneumonitis and similar) was as follows for the everolimus treatment groups of the two 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. Oxygen therapy was administered to one of the patients with a Grade 2 event, 6 patients with Grade 3, and the patient with a Grade 4 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.

Dose adjustments were implemented for 18 patients with Grade 2 and 7 patients with a Grade 3 event. Treatment with everolimus was discontinued for 11 patients with a Grade 2 pulmonary event and for 3 patients with a Grade 3 event.

Blinded central review of *baseline* chest CT-scans/X-rays had shown radiological changes suggestive of pneumonitis in approximately 5% of patients from both the everolimus and placebo treatment groups. 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 C2324 PNET and in 40.9% and 12.8% in C2325 Carcinoid, respectively

> **Evaluator comment:** The occurrence of non-infectious pneumonitis as a result of everolimus treatment has been recognised previously and precautions are given in the current Australian PI. The above data show a significant difference in the incidence of asymptomatic pneumonitis, diagnosed by radiology only and pneumonitis reported in the trials as AEs, consistent with a number of Grade 1 cases of pneumonitis diagnosed on radiology and without symptoms and so not reported as AEs.
>
> A check of the primary data for pneumonitis showed that of 28 Grade 1 pneumonitis patient/events, 21 continued on everolimus therapy, 6 had therapy interrupted and 1 stopped therapy. Of 24 Grade 2 patient/events, 4 continued everolimus treatment, 13 interrupted therapy and 7 stopped. Of 6 Grade 3 patient/events, 2 continued treatment, 3 had treat ment interrupted and 1 stopped treatment. One patients with a Grade 4 event surprisingly continued everolimus treatment. Unfortunately the outcome of these events was not presented. The durations of the condition however were given and were relatively short, so presumably recovery occurred in this time. While Grade 1 events were treated in the main consistently, the stopping or changing of everolimus treatment for Grade 2 events was varied and the clinical outcomes not stated. The advice in the Australian PI is that *"Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue Afinitor therapy without dose alteration. If symptoms are moderate, consideration should be given to interruption of therapy until symptoms improve."* The same advice was given in the European SPC and the US PI. The majority of patients with Grade 2 pneumonitis in the studies interrupted or stopped everolimus treatment.

4. Renal events

C2324 PNET: Overall renal events were reported in 12.7% of patients in the everolimus arm, of which 3.9% were Grade 3 and 0.5% Grade 4; and in 5.4% of patients in the placebo arm, one of which was Grade 4. Drug-related events in the everolimus arm were 5.4%, including two Grade 3-4 events of renal failure and renal failure acute. One case of renal failure acute was attributable to the trial drug in the placebo arm. Three drug-related AEs led to discontinuations, two in the everolimus group (renal failure and renal failure acute) and one (renal failure acute) in the placebo group.

C2325 Carcinoid: Overall renal events were reported in 15.3% of patients in the everolimus arm, of which 3.3% were Grade 3 and 0.5% Grade 4; and in 4.3% of patients in the placebo arm one (0.5%) of which was Grade 3. Drug-related events in the everolimus arm were 5.6%, including two Grade 3-4 events of renal failure and renal failure acute and 3 cases in the placebo arm, none of which were Grade 3 or 4. One case of renal failure acute was attributable to the trial drug in the placebo arm. Four drug-related AEs led to discontinuations; 3 in the everolimus group (increased blood creatinine, renal failure and renal impairment) and one (renal failure acute) in the placebo group.

5. Hepatic events

Hepatic events were infrequently reported in the pivotal Phase III studies (Study C2324 PNET: everolimus: 7.4%; placebo: 7.4%; Study C2325 Carcinoid: everolimus: 7.9%; placebo: 5.7%). Differences between treatment groups were minimal. The majority of events were Grades 1 or 2. One case of hepatic failure was considered to be unrelated to drug treatment. Dose adjustment/interruption for hepatic events was infrequent and only 3 patients in each study discontinued treatment with everolimus as a result of a hepatic event.

6. Cardiac events

Although not a predefined clinically notable AE, an imbalance in the incidence of cardiac disorders was noted between the respective treatment groups. More patients (n = 30; 14.7%) in the everolimus arm of C2324 PNET were recorded with this event than in the placebo arm (n = 13; 6.4%), while in C2325 Carcinoid, the figures were 46 (21.4%) and 32 (15.2%) respectively. This prompted an additional review of all events within this SOC. Events were typically reported by single individuals or small numbers of patients and no conclusive trends could be identified. The incidence of cardiac AEs thought to be drug-related in the everolimus arm of C2324 PNET and C2325 Carcinoid were 4.4% and 2.3% respectively and in the placebo arms, 0.5% and 0.9%. Cardiac arrest and cardio-respiratory failure were reported but were not suspected to be drug related and reflect terminal events of other conditions.

7. Rash and similar events

C2324 PNET and C2325 Carcinoid: Rash and similar dermatologic AEs were common among patients receiving everolimus therapy. The proportion of patients experiencing any rash-related AE was 58.3% in the everolimus treatment group and 17.7% in the placebo arm in C2324 PNET and 46.5% and 19.0% for the everolimus and placebo treatment arms, respectively, in C2325 Carcinoid, while those that were drug-related were 52.9% and 12.3% in the everolimus and placebo arms respectively of C2324 PNET and 40.9% and 12.8% respectively in C2325 Carcinoid. Most cases of rash and rash-related events were of low grade, with one case (0.5%) of a Grade 3 drug-related AE in the everolimus arm of C2324 PNET and 2 (0.9%) in the everolimus arm of C2325 Carcinoid.

8. Haematopoiesis decreased/cytopaenias

As the number of AEs reported in these categories was fewer than those derived from clinical laboratory values, these AEs will be discussed in that section.

9. Metabolic events

The incidence of abnormal laboratory values for the same parameters was much higher than the reported incidence of AEs. This was because not all laboratory abnormalities were treatment-emergent. In addition, investigators were not required to report laboratory abnormalities as AEs, and the threshold for reporting laboratory abnormalities varied among investigators. Metabolic events based on abnormal clinical laboratory values will be discussed in that section.

10. Bleeding and thromboembolic events

As anti-angiogenic agents can be associated with an increased risk of hemorrhage, bleeding/thromboembolic events were evaluated carefully. Various PTs, high-level terms, and PT+SOC terms were examined. The incidence of bleeding/thromboembolic AEs was only marginally greater for patients who received everolimus (Study C2324 PNET: 11.3%; Study C2325 Carcinoid: 22.8%) relative to those administered placebo (Study C2324 PNET: 9.9%; Study C2325 Carcinoid: 17.5%). After excluding hemorrhoids, the most common PT within this grouping, the incidence of all other hemorrhagic events and of thromboembolic events, was similar between the respective treatment groups in the two pivotal Phase III studies. Individual events were seen in single patients or only small numbers. Few patients experienced bleeding or thromboembolic events that led to study drug discontinuation. Omitted from the original search for this category were a number of additional thromboembolic events. Among these, pulmonary embolism 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. Although not predefined within this category, minor bleeding in terms of epistaxis was reported by 21.1% and 15.3% of patients from the everolimus treatment group in Study C2324 PNET and C2325 Carcinoid (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.

> **Evaluator comment:** The report authors commented that while cancer is a recognised risk factor for pulmonary embolism, all reported cases were confounded by multiple comorbidities. Patients underwent frequent chest helical CT or MRI resulting in an accurate reporting rate for these events. Of note, several cases were diagnosed in conjunction with pneumonia or pneumonitis.

11. Intestinal Obstruction and/or ileus

Intestinal obstruction and/or ileus events were reported more frequently with everolimus therapy in C2324 PNET (2.9%) and C2325 Carcinoid (9.3%) than in the placebo arms (1% and 6.6%) respectively. Only one event in the everolimus arm of C2324 PNET was reported as drug-related. Such events were mainly attributed to the background disease and represented concurrent morbidity in patients with abdominal interventions.

Discontinuations of therapy due to intestinal obstruction and/or ileus events were infrequent (one patient) as were patients requiring dose adjustment/interruption (5 patients). The probability of this event increased slowly with time up to 36 months, but remained at a low figure.

Special safety topics

90 Day safety update

The application contained a 90 day Safety Update that was agreed with the FDA was to be provided, and included safety and survival data on an additional 8 patients so that the Safety Set increased from 850 patients to 858. The information presented was consistent with data reported previously and no new findings were evident that would require changes to the previous safety assessment or to the prescribing information. As well, no unexpected effects were reported in ongoing studies that would affect the established safety profile of everolimus.

Safety in Japanese patients, a sub-set of patients in C2324 PNET

A separate section was included in the study report of C2324 PNET presenting results for the sub population of Japanese patients, including safety assessment. The assessment was made in the same way as for the main report and compared safety outcomes of everolimus treatment and placebo. The sponsor's *Summary of Clinical Safety*, on the other hand, compared the safety results from Japanese patients with those from Caucasian patients and is used in the following discussion.

The sponsor's *Summary of Clinical Safety* stated that subgroup analysis of AEs by race was not particularly informative as the majority of the patients enrolled (87.4%) were Caucasian. Data were not displayed for 15 patients (1.8%) whose race was recorded as 'Other'. Within the pooled dataset, comparison between a Caucasian and Asian population was possible.

> **Evaluator comment:** These statements required clarification. Thirty nine Asian patients were listed in C2324 PNET and one in C2325 Carcinoid. The sponsor's *Summary of Clinical Safety* states that a comparison of the AEs experienced by the 39 Asian patients with those experienced by the 154 Caucasian patients "was not particularly informative". In the pooled data, the number of Caucasian patients increased to 743 because of the additional of those from the everolimus arm of C2325 Carcinoid (blinded phase), the addition of Caucasian patients from C2239 (Phase II) and from the open label phases of both pivotal studies. On the other hand, the number of Asian patients increased from 39 to 68 by adding those Asian patients who entered the open label phase of C2324 PNET only. While this

increased the numbers in both groups, the uniformity of assessments of AEs would be reduced because of the different trials and countries involved in the pooled data. However, with this caveat, the following is based on the comparison of Caucasian and Asian patients in the pooled data group.

A number of events where the incidence was 1.5 fold greater for one race relative to the other and with an incidence ≥ 10% in the pooled dataset included those more prominent in Caucasians: aphthous stomatitis, urinary tract infection, asthenia, peripheral oedema, cough and back pain; and those more prominent in Asians: nasopharyngitis, dysgeusia, hypertension, hyperglycemia, pyrexia, stomatitis, epistaxis and insomnia.

Evaluator comment: Differences in many of the AEs reported in the two ethnic groups are striking. Some may be explained by differences in medical practice in Asia and other countries in the trials, especially in diagnosis and in patients' complaints about their symptoms, such as musculo-skeletal pain with an incidence in Caucasian patients 4.2 times that in Asian patients. For most AEs there is no consistent pattern that could result from increased exposure to everolimus (see PK section). Nevertheless it would be unwise to ignore striking differences in the more serious AEs, where different medical cultures would not be responsible for their identification. This would include hyperglycaemia, 60%, pneumonitis 89%, and hypertension 95% more frequent in Asian patients than in Caucasian patients. These three AEs are based on laboratory and radiological results and are therefore more reliable than other AEs listed[24]. Unless the sponsor can provide a justification for not doing so, these three events should be described in the PI as occurring more frequently in Asian patients.

Open-label sets

The reports for C2324 PNET C2325 Carcinoid present the safety results, analysed separately for the open label phases of the two pivotal studies. Safety was assessed in the same way as in the blinded periods of the two studies, so these data constitute the equivalent of two more studies, C2324 PNET with 149 patients and C2325 Carcinoid with 124 patients.

Evaluator comment: These data were included in the pooled safety data discussed above, and the separate analyses did not show any significant differences from the safety assessments of the blinded periods of the pivotal trials. Therefore the data from each open-phase period will not be presented here. Relevant comments are given in brief in the following section.

Exposure: In C2324 PNET, the median duration of exposure to everolimus during the open label phase was 28.9 weeks (range: 0.1 to 111.3 weeks), with 33 (22.1%) patients receiving > 52 weeks of everolimus therapy. The median duration of everolimus exposure was shorter during the open label phase compared with that of the double blind phase. In C2325 Carcinoid, median duration of exposure to everolimus during the open label phase of the study was 26.3 weeks (range: 1 to 133) compared to a median duration of 37.0 weeks during the blinded treatment phase.

Adverse events: During the open label phase of the study, the majority of patients experienced one or more AEs. The overall incidence of AEs was similar to that observed for the everolimus treatment group during the double blind treatment phase, as was the incidence of drug-related AEs, severe AEs, clinically notable AEs and serious AEs. In Study C2324 PNET, 'on-treatment' deaths occurred in 11 (7.4%) patients. Of these 11 patients, 8 deaths were due to the underlying malignancy. There were 3 deaths due to causes other

[24] The sponsor commented that these conclusions are based on AEs reported in the electronic case report form, not directly based on the laboratory/scan results. They do not include all AEs and might be dependent on region.

than disease progression, one of which was suspected as being drug-related by the investigator. In Study C2325 Carcinoid, six on-treatment deaths (4.8%) were reported that were not attributed to the underlying malignancy. Causes of death were again consistent with what would be expected in an aging population of patients with advanced NET with carcinoid syndrome

Adverse events by age: The incidence of AEs was generally similar for patients <65 years of age and those aged ≥65 years. Of those AEs reported by 10% or more of patients receiving everolimus in either age groups (from the pooled data), the AEs that had a 40% greater incidence in patients aged 65 or more were dehydration (76%), hypomagnesaemia (64%), musculo-skeletal pain (48%), pneumonitis (45%) and neutropenia (43%). The AEs that had a 40% greater incidence in patients less than 65 years includedupper abdominal pain (100%), headache (92%), anxiety (80%), hemorrhoids (74%), upper respiratory tract infection (URTI; 75%), oropharyngeal pain (68%) and flushing (64%).

> **Evaluator comment:** The differences listed may have been in part random, but the increased incidence in the older age group of dehydration, hypomagnesaemia and pneumonitis is reasonable on clinical grounds and of safety concern as well. This will be further addressed in the review of the proposed PI.[25]

Adverse events by gender: No consistent trends were evident that were considered indicative of an increased risk for an event on the basis of gender. The incidence of most AEs was generally similar for both men and women.

Adverse events and hepatic and renal impairment: No safety data in patients with severe hepatic and renal impairment were submitted. Such patients were excluded from the studies by protocol requirements. As everolimus is eliminated primarily *via* the hepatic route, a special warning is already included in the Australian PI as exposure might be increased in patients with severe hepatic impairment. Elevations of serum creatinine concentration have been observed but these were typically mild. Monitoring of renal function is therefore recommended in these patients.

Other studies

Study C2239 (Phase II)

The most frequent AEs (reported in ≥ 5% of patients) suspected of being related to the study medication as assessed by the investigator by preferred term were stomatitis (45.2%), rash (40.0%), diarrhoea (39.1%), fatigue (31.3%) and nausea (29.6%). Severe (Grade 3-4) AEs were not presented as drug-related, and were presented in *Other studies*, *Adverse events*, above)

> **Evaluator comment:** The safety results in C2239 were similar to those in the pivotal studies. The incidence of severe AEs (Grades 3 and 4) was 74-75% in Studies C2325 Carcinoid and C2239 and 60% in C2324 PNET; and the incidence of on treatment deaths was 8.7% (Stratum 1) and 4.4% (Stratum 2) in C2239, and 8.4% and 5.9%, respectively, in Studies C2325 Carcinoid and C2324 PNET (Table 15). The incidence of the AE grouping of pulmonary events was 13.3% in Stratum 2,and for all AEs in Stratum 1, the incidence of dyspnoea (not further defined) was 16.5%, and in Stratum 2, 22%. SAEs of dyspnoea were 3.5% in Stratum 1 and 6.7% in Stratum 2. With no cause given for dyspnoea, underlying lung disease could constitute a significant adverse event.

[25] Note that details of discussions regarding revisions to the PI are beyond the scope of this AusPAR.

Deaths and other serious adverse events

Pivotal studies

Of the 839 patients participating in Studies C2324 PNET and C2325 Carcinoid (including patients who did not receive study drug), 151 patients (35.7%) and 135 patients (32.5%) from the everolimus and placebo treatment groups, respectively, died. Deaths 'on-treatment' (that is, while receiving study medication or within the initial 28 days of discontinuing therapy) were recorded for 45 patients (5.4%) by the 28 February 2010 and 02 April 2010 data cut-off dates for Studies C2324 PNET and C2325 Carcinoid, respectively (see Table 15). Case narratives for all deaths were provided in the corresponding clinical study reports. Of all receiving treatment with everolimus, 30 (7.2%) died; 15 (3.6%) of those receiving placebo died. Twenty of these 45 on-treatment deaths in Studies C2324 PNET and C2325 Carcinoid were attributed to the underlying malignancy while the remaining 25 were mostly from the solitary events (see Table 16).

Across the broader NET program reported in the pooled dataset, 32 patients (3.8%) died where the primary cause of death was reported to be an AE. Approximately 50% of these deaths were attributed to AEs within the respiratory, thoracic and mediastinal disorders and infections and infestations SOCs. Review of the individual cases identified 4 deaths that were related to pneumonia.

Table 15. On-Treatment deaths

	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	(%)
On-treatment deaths	12	(5.9)	4	(2.0)	18	(8.4)	11	(5.2)	68	(8.0)
Deaths 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)

Studies included: C2324, C2325, and C2239
Source: (PT-Table 2.1-2.1)

Table 16. Deaths On-Treatment due to AEs

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

Source: [PT-Table 2.1-2.1]

No unusual or new clinically significant findings were observed and data relating to deaths were consistent with the established safety profile of everolimus and the clinical condition of patients enrolling in these studies. The nature and timing of these deaths was unremarkable and reflected the natural history of the underlying disease.

Patients who died as a result of events that were considered by the investigator to be related to study treatment are listed in Table 17 below, with relevant data on their treatment history in the study. A potential relationship to study drug could not be excluded for a second patient with a cause of death of 'other unknown' (who was diagnosed with pneumonia and interstitial pneumonitis 3 weeks earlier), although this was attributed by the study investigator to clinical disease progression.

Table 17. Deaths - drug-related

Treatment group Patient number Age/gender/race Treatment duration	Cause of death System organ class MedDRA preferred term	Comments	Relationship
Everolimus [C2324-0103-00020] 33/M/Asian 255 days	Respiratory, thoracic and mediastinal disorders Acute respiratory distress syndrome	Hospitalized on Day 253 with acute respiratory distress syndrome secondary to sepsis (Staphylococcus aureus). Study drug discontinued and antibiotic therapy started. Patient developed disseminated intravascular coagulation, pneumomediastinum, pneumothorax and subcutaneous emphysema. Placed on artificial ventilation and short steroid courses. Disease worsened; patient developed multi-organ failure and died on Day 284.	Suspected
Studies included: C2324, C2325, and C2239			

Of the deaths reported following discontinuation of study drug, one (reactivation of hepatitis B with acute liver failure) warrants further comment. This patient (a 50 year old Asian male) was a known hepatitis B carrier with positive hepatitis B surface antigen but no prophylactic therapy was administered. He was treated with everolimus in C2324 PNET. The drug had been discontinued 2 months before the patient's death. The investigator assessed the hepatic failure and reactivation to be related to study medication.

Safety update

The above data were obtained after cut-off dates of 28 February 2010 for C2324 PNET, and 02 April 2010 for C2325 Carcinoid. This Safety Update had data cut-offs of 03 June 2010 for C2324 PNET and 02 July 2010 for Study C2325 Carcinoid.

In the updated analysis, of 839 patients participating in Studies C2324 PNET and C2325 Carcinoid (including patients who did not receive study drug), 162 patients (38.3%) and 154 patients (37.0%) from the everolimus and placebo treatment groups, respectively, died (Table 18). This reflects an increase of 30 deaths from the original analyses: 12 in Study C2324 PNET and 18 in Study C2325 Carcinoid. Of these additional deaths, all except three were attributed to the underlying malignancy and only one of these three occurred during treatment; this was a case of sudden death (in Study C2325 Carcinoid) that was not suspected to be related to everolimus therapy. An additional 'on-treatment' death was reported in Study C2324 PNET, which was attributed to disease progression.

Table 18. Deaths Up-dated

	Study C2324				Study C2325			
	Original data cut-off		Safety Update		Original data cut-off		Safety Update	
	Everolimus N=207	Placebo N=203	Everolimus N=207	Placebo N=203	Everolimus N=216	Placebo N=213	Everolimus N=216	Placebo N=213
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Deaths	51 (24.6)	50 (24.6)	55 (26.6)	58 (28.6)	100 (46.3)	85 (39.9)	107 (49.5)	96 (45.1)
Studies included: C2324, C2325								

For the two pivotal studies, deaths 'on-treatment' (that is, while receiving study medication or within the initial 28 days of discontinuing therapy) during the double blind phases were unchanged from the original analyses. For the pooled dataset, two additional cases were reported.

> **Evaluator comment:** As stated in the reports of the pivotal studies, the updated death rate of about 38% for all patients over a follow-up period of up to 2 years 10 months was relatively low for patients with malignant disease. Most patients received everolimus, either from the beginning (*ab initio*) or on cross-over, so it is not known how much the slow natural history of the disease contributed to the long survival and how much treatment with everolimus. From historical data, the median survival of patients with PNET was 17 months, whereas in C2324 PNET, the median survival was 29.7 months (updated data), suggesting the extension may have been due to everolimus treatment.

Non-fatal SAEs

An SAE is defined as any adverse drug experience that results in one of the following outcomes:

- death (see above)
- life-threatening event
- in-patient hospitalisation or prolongation of existing hospitalisation
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Furthermore, important medical events that may not result in death, be life-threatening, or require hospitalisation may also be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardise the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Serious adverse events were reported more frequently for patients receiving everolimus (Study C2324 PNET: 40.2% and 24.6% for the everolimus and placebo groups, respectively; Study C2325 Carcinoid: 56.7% and 34.6%). The most frequently reported SAEs in 3% or more of patients receiving everolimus therapy in the pivotal trials, irrespective of relationship to treatment, were in the C2324 PNET trial, hepatobiliary disorders (SOC; 4.4%), pyrexia (3.9%), pneumonitis (3.4%), anaemia (3.4%); and in the C2325 Carcinoid trial, abdominal pain (6.0%), pneumonia (4.2%), diarrhoea (3.7%), dyspnoea (3.7%), hepatobiliary disorders (SOC; 3.7%), small intestinal obstruction, pyrexia and dehydration (3.3% each).

Events within the following SOCs were more frequent among patients receiving everolimus therapy relative to placebo by the percentage shown in brackets : Respiratory, thoracic and mediastinal disorders (Study C2324 PNET: +9.3%; Study C2325 Carcinoid: +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 in the two pivotal Phase III studies (20.3%) 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, compared with only 18 patients (4.3%) from the placebo groups. The most commonly reported treatment-related SAEs were pneumonitis (everolimus: 8 patients [1.9%]; placebo: 0 patients), diarrhoea (6 [1.4%] versus 2 patients [0.5%]), anaemia (6 [1.4%] versus 0 patients), and interstitial lung disease (5 [1.2%] versus 0 patients).

> **Evaluator comment:** The incidence of drug-related SAEs is arguably the best measure of the toxicity of drug treatment used and is important in assessing the risk benefit of the treatment and in advice to prescribers in the PI. A 20% incidence of drug-related SAEs as seen in the pivotal trials is significant toxicity and that of pneumonitis and interstitial lung disease (3.1% combined incidence) of some concern.

Safety Update of non-fatal SAEs: The updated figures were not significantly different from the earlier analyses. SAEs (updated) were reported in 40.7% and 25.6% of patients in the everolimus and placebo arms of C2324 PNET respectively, and 58.6% and 34.6% in C2325 Carcinoid. The incidence of individual SAEs and within organ classes were similar, and of drug-related SAEs the same.

Other studies

Study C2239

Deaths and other SAEs in Study C2239 are discussed in this section, separate from the pivotal studies. The data was also included after pooling with the data from the pivotal studies for all patients who received everolimus.

Deaths: Ten deaths (8.7%) were reported on-treatment. Six of these ten deaths were considered by the study investigator to be related to the primary disease and/or to disease progression. Of the other 4 deaths, one patient developed bilateral hydropneumothorax on Day 214 thought to be possibly due to unconfirmed esophageal perforation. The study investigator did not suspect a relationship between bilateral hydropneumothorax and study medication and did suspect a relationship between the unconfirmed esophageal perforation and study medication. Another patient died of lobar pneumonia with a SAE of gastrointestinal angiodysplasia, and clinically significant events of Grade3 hyperglycemia, Grade 3 anaemia and lobar pneumonia. The study investigator considered the hyperglycemia to be drug-related.

> **Evaluator comment:** The incidence of on-treatment deaths was 8.7%. All these patients received everolimus. This figure compared with a figure of 8.0% for deaths of patients in the pivotal trials (pooled data, see Table 15) in the on-treatment phase, who received everolimus. The incidence of AEs associated with the deaths in C2239 was 1.7% (n = 2), compared to 3.8% in the pivotal trials. While the incidence of on-treatment deaths was greater in this study than in the pivotal trials, the incidence of AEs associated with death was not, indicating that patients in this study were at greater risk of death but most likely because of their more advanced disease rather than from drug-related causes.

Non-fatal SAEs: A total of 51.3% of patients experienced an SAE. Those with a frequency of 3% or more were abdominal pain (7.8%), asthenia (5.2%), pyrexia (5.2%), pneumonia, anorexia, dyspnoea, fatigue and vomiting (each 3.5%), similar to that of the pivotal trials.

Discontinuation due to adverse events

Pivotal studies

C2324 PNET: In the double blind phase, more patients discontinued study treatment due to an AE in the everolimus group (19.1%) than in the placebo group (5.9%). The most frequent reason in the everolimus group was pneumonitis (2.9%) while 1% (n = 2) discontinued because of interstitial lung disease. The most frequent reason for discontinuation in the placebo group was confusional state (1.5%, n = 3). Discontinuations due to the following SOCs were more common with everolimus: 'Respiratory, thoracic, and mediastinal disorders' (+5.9% relative to placebo), 'General disorders and administration site conditions' (+2.4%), and 'Infections and Infestations' (+2.4%). A total of 27 (13.2%) patients in the everolimus group and 4 (2.0%) patients in the placebo group discontinued due to AEs that were suspected to be related to treatment. The most commonly reported AEs (with an incidence of more than 0.5%) suspected to be related to everolimus were pneumonitis (2.9%), interstitial lung disease (1%) and fatigue (1%). In the placebo group, all AEs suspected to be related to treatment were reported only in single patients (0.5%).

C2325 Carcinoid: In the double blind phase, more patients discontinued study treatment due to an AE in the everolimus group (28.4%) than in the placebo group (7.0%). The most commonly reported AEs leading to discontinuation of everolimus therapy were fatigue (2.3% of patients) and diarrhoea, general physical health deterioration, interstitial lung disease and pneumonia (each reported in 1.9% of patients). Discontinuations due to the following SOCs were more common with everolimus: 'Respiratory, thoracic, and mediastinal disorders' (+5.5% relative to placebo), 'General disorders and administration

site conditions' (+5.1%) and 'Gastrointestinal disorders' (+4.6%). A total of 40 (18.6%) patients in the everolimus group and 7 (3.3%) patients in the placebo group discontinued due to AEs that were suspected to be related to treatment. The most commonly reported AEs leading to study drug discontinuation suspected to be related to treatment were diarrhoea (everolimus: 4 [1.9%]; placebo: 0), interstitial lung disease (4 [1.9%] versus 0), fatigue (3 [1.4%] versus 1 [0.5%]), and pneumonitis (3 [1.4%] versus 0).

> **Evaluator comment:** Drug-related AEs led to a higher rate of discontinuation in C2325 Carcinoid (18.6%) compared to that in C2324 PNET (13.3%), while the rate in each placebo arms was similar (2%, 3.3%). The sponsor's *Clinical Overview* attributed this to the 'add-on' effect of treatment with depot octreotide but the only adverse effect of octreotide common to those above is nausea (see Australian PI for Sandostatin LAR). This does not explain the higher incidence of discontinuations in C2325 Carcinoid. Of note is that the rates of discontinuations due to drug-related AEs of the pulmonary system (pneumonitis and interstitial lung disease) were similar in the two studies; C2324 PNET, 3.9% and C2325 Carcinoid, 3.3%.

Open label phase of pivotal studies: Adverse events leading to discontinuation were once again more frequent in Study C2325 Carcinoid. Twenty-eight patients (18.8%) and 29 patients (23.4%), respectively, from Studies C2324 PNET and C2325 Carcinoid experienced AEs that resulted in treatment discontinuation during the open label phase of these studies; events were suspected to be drug related for 17 (11.4%) and 13 (10.5%) of these patients, respectively. The incidence of pneumonitis as a cause of treatment discontinuation in C2324 PNET was 2% (n = 3) while no cases were reported in C2325 Carcinoid.

> **Evaluator comment:** The rate of AEs causing treatment discontinuation was similar in this open label phase as in the double blinded phase of Study C2324 PNET and a higher rate was again present in C2325 Carcinoid. Of note is the unexpected finding that no cases of pneumonitis or interstitial lung disease were recorded as AEs causing discontinuation in C2325 Carcinoid.

Other studies

Study C2239 (Phase II): A total of 17.4% of patients (20 of 115) in Stratum 1 discontinued study drug due to an AE. In total, 2.6% (n = 3) of patients discontinued for asthenia and 1.7% (n = 2) for fatigue. One patient in Stratum 1 had an AE of dyspnoea that led to treatment discontinuation. Other AEs occurred in one patient each, including pneumonia in Stratum 1, and one case of interstitial lung disease in Stratum 2 but no cases of pneumonitis.

> **Evaluator comment:** The rates of discontinuation due to AEs were lower overall in this trial than in the pivotal trials. The occurrence of 1 AE of dyspnoea leading to treatment discontinuation and the absence of any AEs of pneumonitis in a patient population of 115 is surprising. Establishing a cause for the case of dyspnoea would have been helpful.

Laboratory tests

In the sponsor's *Summary of Clinical Safety*, abnormal laboratory values (new or worsening from baseline based on CTCAE grades) were summarised for haematology and clinical chemistry parameters. In the studies, laboratory values had been converted to SI units and analysed using NCI CTCAE grades (Version 3.0) that were derived using a computer program. Although analyses focusing on shifts from normal to abnormal values were performed, it was considered more informative for advanced cancer populations to describe treatment groups in terms of the proportion of patients experiencing an event graded 1 through 4 in accordance with NCI CTCAE criteria. Cross-referencing was

provided to the shift tables but detailed interpretation was not done. Updated safety data (90 days) are included with the original analyses below.

Liver function

Pivotal studies

Laboratory findings associated with abnormal hepatic function were evident for both treatment groups in each of the pivotal studies. Low grade elevations of transaminase concentrations were more common in the everolimus treatment group. The percentages of patients with abnormal values newly occurring or worsening from baseline were as follows.

C2324 PNET: AST: Everolimus arm: All, 47.1%; Grade 3, 3.4%; Grade 4, 0.5%; Placebo arm: All, 29.6%; Grade 3, 3.9%; Grade 4, 0.5%. *SGPT (ALT).* Everolimus arm: All, 38.2%; Grade 3, 2.0%; Grade 4, 0. Placebo arm: All, 23.2%; Grade 3, 1.5%; Grade 4, 0.5%. *Bilirubin (total) increased.* Everolimus arm: All, 8.3%; Grade 3, 1.5%; Grade 4, 0; Placebo arm: All, 11.3%; Grade 3, 1.5%; Grade 4, 0.5%.

C2325 Carcinoid: AST: Everolimus arm: All, 43.7%; Grade 3, 1.4%; Grade 4, 0.5%; Placebo arm: All, 29.9%; Grade 3, 0.9%; Grade 4, 0.5%. *SGPT (ALT).* Everolimus arm: All, 34.0%; Grade 3, 1.4%; Grade 4, 0. Placebo arm: All, 28.4%; Grade 3, 1.4%; Grade 4, 0%. *Bilirubin (total) increased.* Everolimus arm: All, 7.9%; Grade 3, 0%; Grade 4, 0.9; Placebo arm: All, 16.1%; Grade 3, 2.4%; Grade 4, 0.5%.

Open phase: The laboratory findings of abnormal hepatic function were similar to those in the blinded phase of the studies (above).

> **Evaluator comment:** The current Australian PI listed increases in the above laboratory findings with Afinitor under the same headings as above, "All", "Grade 3" and "Grade 4" abnormalities. The incidence of all grades of AST abnormality was given as 25% of patients receiving Afinitor, about half that observed in the pivotal studies here (47% and 44%). The proposed PI changes the way the data are presented and instead is proposed to state *"Increased clinical chemistry parameters include … aspartate transaminases, creatinine, alanine transaminases, and bilirubin"*, with a statement following that the abnormalities were mainly Grade 1 or 2. This, however, does not indicate that such AEs were approximately twice as frequent in the patient population with NETs.
>
> None of the Grade 3 or 4 events above was significantly more frequent in the everolimus arm than in the placebo arm of either trial, so Hy's law does not need to be considered in this case.

Other studies

C2239 (Phase II)

Stratum 1: The incidence of all abnormal laboratory values for increased AST was 61.7% for all grades, 3.5% for Grade 3 and no Grade 4; for increased ALT, 50.4%, 1.7%, 0%; bilrubin (total) increased 12.2%, 0.9%, 0.9% respectively.

Stratum 2: The incidence of increased AST was 60.0%, 2.2%, 0; ALT 42.2%, 2.2%, 0; and bilirubin 20%, 4.4%, 0, respectively.

> **Evaluator comment:** The higher incidence of lower grades of abnormal AST and ALT (about 60%) compared to the pivotal studies (about 45%) may reflect more advanced disease in this patient population.

Ongoing study: Study CRAD001X2102, is an open label, single dose study to assess the pharmacokinetics of oral everolimus in 30 subjects with impaired hepatic function that is ongoing.

Kidney function

Pivotal studies

C2324 PNET: Increases in serum creatinine were seen in 16.2% of patients in the everolimus arm, and were mainly low grade with only 1.0% Grade 3 and 1.0% Grade 4 (updated). In the placebo arm the figures were 9.9%, 0 and 0.

C2325 Carcinoid: Increases in serum creatinine were seen in 30.2% of patients, mainly low grade with 2.3% Grade 3 and 0 Grade 4, respectively, while in the placebo arm the incidence was 12.3%, 0.5% and 0, respectively.

> **Evaluator comment:** The incidence of low grade increases in serum creatinine in Study C2325 Carcinoid was twice that in Study C2324 PNET. In the current Australian PI for Afinitor, the incidence was 50% in patients treated with everolimus and 34% in the placebo group(s). However these data related in part to treatment of patients with renal cell carcinoma and the high incidence in the placebo group may reflect the greater frequency of renal impairment in these patients. In Study C2325 Carcinoid, the incidence was 18% more than placebo, and in the PI 16% reflecting a possible drug effect on renal function. The *Precautions* section of the Australian PI refers to the occurrence of renal failure in patients treated with Afinitor. In the pivotal studies in this application however, only one death in C2324 PNET was due to renal failure and that was not classified as drug-related. These data indicate that drug-associated renal failure is not a major safety issue in the patients with NETs treated with everolimus, although monitoring of renal function is appropriate. The sponsor's *Clinical Overview* stated that patients with creatinine elevations required varied interventions, primarily volume repletion and/or change in potentially nephrotoxic medications.

Other studies

C2239 (Phase II):

Stratum 1: Increases in serum creatinine were seen in 20.9% of patients, and were all low grade with no Grade 3 or Grade 4 events.

Stratum 2: Increases in serum creatinine were seen in 37.8% of patients, 6.7% were Grade 3 and 2.2% were Grade 4 events.

Other clinical chemistry

Pivotal studies

C2324 PNET: The updated data showed that the proportion of patients experiencing Grade 3 or 4 changes for hyperglycemia (16.7% [all grades 70.1%]), hypophosphatemia (10.3% [all grades 37.7%]) and hypokalaemia (4% [all grades 22.5%]) was higher with everolimus than with placebo therapy (Grade 3-4 hyperglycaemia 4.4% [all grades 37.4%]; Grade 3-4 hypophosphatemia 3.0% [all grades 9.4%]; Grade 3-4 hypokalaemia 0 [all grades 5.4%]). Although increases in cholesterol and triglyceride concentrations were reported more often for everolimus (approximately 45% and 30% higher than placebo), the incidence of Grade 3 and 4 toxicity (0 to 0.5%) 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. The etiology of hypophosphatemia associated with everolimus is unknown, although it would appear to be a class effect of rapamycins and their analogs.

> **Evaluator comment:** It is of some concern that the proposed wording of the Australian PI will change the advice that the incidence of all grades of hypophosphatemia was 37% with everolimus compared with 8% in placebo, and of Grade 3 events 8.0% compared with 0 in placebo, to read only that Grade 4

reduction in phosphate occurred in < 1% of patients. This also applies to hyperglycaemia and hypokalaemia and was addressed further in the section on the proposed PI[26].

Other studies

C2239 (Phase II).

Stratum 1: The most common Grade 3 and 4 events with newly occurring or increased values were hyperglycemia (Grade 3, 19.1%; Grade 4, 0.9% [all Grades 77.4%]), alkaline phosphatase (Grade 3, 13.0%; Grade 4, 0.9% [all Grades, 78.3%]) and hypophosphatemia (Grade 3, 13.0%; Grade 4, 0 [all Grades 47.8%]). The incidence of hypokalaemia was Grade 3, 5.2%, Grade 4, 0.9% (all Grades, 26.1%).

Stratum 2: The most common events were hypokalaemia (Grade 3, 15.6%; Grade 4, 0 [all Grades 33.3%])), alkaline phosphatase (Grade 3 13.3%; Grade 4, 0 [all Grades, 80%]) and hyperglycemia (Grade 3, 13.3%; Grade 4, 0 [all grades, 91.1%). The incidence of hypophosphatemia was Grade 3, 11.1%, Grade 4, 0 (all Grades, 71.1%).

> **Evaluator comment:** Comparing the two strata, the incidence of increased alkaline phosphatase is similar while that of hyperglycaemia, hypokalaemia and hypophosphatemia is higher in Stratum 2 than Stratum 1. Patients in Stratum 2 were those receiving octreotide (Sandostatin LAR), which may account for the increased incidence of hyperglycaemia, as noted in the Australian PI for Sandostatin LAR. The reason for increase in the incidence of the other two events is uncertain, but presumably most patients in Stratum 2 had or were having carcinoid syndrome, for which they were receiving Sandostatin and which may have contributed to these metabolic disturbances. The effect on blood glucose of coadministration of everolimus and octrotide should be referred to in the *Precautions* section of the proposed PI for everolimus.

Haematology

Pivotal studies

Nearly all patients reported treatment-emergent changes in laboratory results. Low hemoglobin occurred in 67.2% and 28.1% of patients receiving everolimus and placebo, respectively, in Study C2324 PNET and in 74.4% and 32.7% of patients in Study C2325 Carcinoid. Anaemia was reported as an AE in 23.0% and 9.4% of patients, respectively, in Study C2324 PNET and in 27.9% and 10.4% of patients in Study C2325 Carcinoid.

Thrombocytopenia, leukopaenia, lymphopenia, and neutropenia all continue to be reported more frequently for patients receiving everolimus (both overall and as Grade 3-4 events) relative to the placebo arm (Table 19; findings are as percentage of patients shown in the order of all Grades/Grade 3/Grade 4.).

Table 19. Grading (severity) of newly occurring or worsening abnormal haematology values in the pivotal studies

Study C2324 PNET (safety updated).	Everolimus (n = 204)	Placebo (n = 203)
Haemoglobin decreased	67.2/13.7/1.5	28.1/1.5/0
Platelet count (direct) decreased	44.1/2.5/0.5	7.9/0/0

[26] Note that details of discussions regarding revisions to the PI are beyond the scope of this AusPAR.

Study C2324 PNET (safety updated).	Everolimus (n = 204)	Placebo (n = 203)
White Blood Cells (total) decreased	39.7/2.5/0	7.4/0/0
Absolute lymphocytes decreased –	38.7/12.3/0.5	16.3/3.9/0
Absolute neutrophils (seg+ bands) decreased	27.9/3.4/0.5	14.3/2.0/0
Prothrombin time (INR) increased	3.4/0/0	1.0/0/0
Study C2325Carcinoid (safety updated)	Everolimus (n = 215)	placebo (n = 211)
Haemoglobin decreased	74.4/5.6/0.9	32.7/1.4/0.5
Platelet count (direct) decreased	45.6/2.8/0.9	11.8/0.5/0.5
WBC (total) decreased	52.1/2.8/0	16.1/0/0.5
Absolute lymphocytes decreased	50.7/17.7/0.5	24.6/5.7/0
Absolute neutrophils (seg+ bands) decreased	40.0/4.2/0.5	12. 8/0/0
Prothrombin time (INR) increased	6.0/2.3/0	4.3/1.9/0

Other studies

C2239 (Phase II): The incidence of newly occurring or increasing abnormal haematology values in the two Strata of this study are shown (as n(%) of number in Stratum)in the following Table.

Table 20. Abnormal laboratory values in Study C2239.

	Stratum 1 (n = 115)			Stratum 2 (n = 45)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Hemoglobin decreased	96(83.5)	9(7.80)	2(1.7)	42(93.3)	3(6.7)	0
Absolute lymphocytes decreased	58(50.4)	17(14.8)	3(2.6)	23(51.1)	6(13.3)	0
Platelet count (direct) decreased	40(34.8)	3(2.6)	1(0.9)	19(42.2)	2(4.4)	1(2.2)

	Stratum 1 (n = 115)			Stratum 2 (n = 45)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Absolute neutrophils (seg. + bands) decreased	36(31.3)	4(3.5)	0	18(40)	1(2.2)	0
WBC (total) decreased	48(41.7)	4(3.5)	0	18(40)	0	0
Partial thromboplastin time increased	1(0.9)	0	0	2(4.4)	0	0

Evaluator comment: The decreases seen in this study were similar to those in the pivotal studies.

Electrocardiograph

Pivotal studies

Electrocardiograms were performed at baseline and were subsequently repeated at the study investigator's discretion if there were signs and symptoms of cardiotoxicity. Any findings that were considered abnormal by the investigator were reported as AEs and graded according to NCI CTCAE, Version 3.0. No untoward changes were recorded during the two pivotal studies.

Postmarketing experience

Everolimus (Afinitor) is commercially available in a number of countries for the treatment of patients with advanced renal cell carcinoma and was approved for this indication in Australia on 29 July 2009. Safety related changes have been made four times since. Any relevant changes required that arose from the Periodic Safety Update Report (PSUR) 1 have been made to the Australian PI and will not be considered here.

Afinitor PSUR2

The review period was from 01 October 2009 to 31 March 2010.

Patient exposure

Investigational clinical trials: A total of 1332 patients received Afinitor treatment in Novartis sponsored investigational clinical trials during the review period and 1008 patients received Afinitor treatment in Third Party or Investigator Initiated Trials during the reporting period. During the reporting period there were no Post Marketing Surveillance (PMS) studies.

Market experience: An estimate of patient exposure has been calculated based on the worldwide sales of tablets sold during the review period and the defined daily dose (DDD) of one 10 mg tablet per day. The number of 5 mg tablets sold during the review period was 94,147 and the number of 10 mg tablets sold was 340,857, accordingly, the estimated patient exposure based on product use is 1,063-patient-treatment-years (PTYs). In the

previous PSUR period (PSUR1), the exposure was 537-PTYs. The total combined worldwide cumulative market exposure to Afinitor is 1600-PTYs since the International Birth Date (IBD).

Data classification and presentation

Unlisted adverse reaction: An unlisted adverse reaction is one that is not specifically included as a suspected adverse effect in the Company Core Safety Information (CCSI).

Line listings: All spontaneous, unpublished and published individual reports, as well as reports derived from clinical trials meeting the criteria defined below, were presented in line listings in Appendix 3 of the PSUR. Reports were included in the appropriate line listings according to case level assessments. Thus, as an example, a report with serious and non-serious events was assessed as serious and all reported signs, symptoms and diagnoses, whether considered serious or non-serious, presented only once in the line listing of serious reports. Individual reports were presented in the line listings by MedDRA SOCs in accordance with the TGA adopted EU guideline[27]; refer also[28] . The following types of cases were included in the line listings:

- Spontaneous reports: The spontaneous reports received from health care professionals (HCPs) were presented in the following line listings: serious spontaneous reports; non-serious unlisted spontaneous reports; non-serious listed spontaneous reports; Non-HCP reports; Medically unconfirmed reports received from consumers/non-HCPs.
- Reports from studies and named patient use.

Presentation: Summary tabulations: Aggregate summary tabulations of spontaneous and serious suspected solicited events reported in the PSUR period by MedDRA SOC were presented for HCP and non-HCP reports.

A cumulative summary tabulation with preferred MedDRA terms for all serious unlisted events from spontaneous reports and the serious unlisted suspected events from clinical trial reports included in the safety database until data lock point was presented in an Appendix for HCP and non-HCP reports. The tabulation included all diagnoses as well as related signs and symptoms from individual serious unlisted reports.

Overview: A total number of 518 cases were reported during the review period, including 457 reports received from HCPs and 61 reports received from non-HCPs. Details on the distribution of the cases are presented in Table 21.

[27] CPMP/ICH/288/95ICH Topic E2 C (R1)Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs. http://www.tga.gov.au/pdf/euguide/ich467902final.pdf

[28] Volume 9A of *The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use,* 2008. http://www.tga.gov.au/pdf/euguide/vol9riskmmt.pdf

Table 21. Reported cases by report type

	Serious		Non-serious		Grand Total
Report type	Unlisted	Listed	Unlisted	Listed	
Spontaneous HCP	70	60	22	38	**190**
Suspect Solicited HCP	106	161	0	0	**267**
HCP total	176	221	22	38	**457**
Spontaneous non-HCP	11	13	17	20	**61**
Non-HCP total	11	13	17	20	**61**
Grand total	**187**	**234**	**39**	**58**	**518**

Distribution of reactions by MedDRA SOC: A total of 1886 reactions (1754 HCP+132 non-HCP) were reported in the 518 cases (457 HCP+61 non-HCP).

Analysis of individual case histories: Cases were selected for presentation according to the following criteria: cases with fatal outcome; cases identified as relevant safety findings.

Cases with a fatal outcome: There were a total of 81 fatal spontaneous or suspected solicited cases reported during the review period of this PSUR. Of these, 76 were reported by HCPs and five by non-HCPs. Of the 76 HCP reports, 31 cases involved patients enrolled in clinical trials and 45 were reported spontaneously.

Cases with fatal outcome due to disease progression: Of the 76 HCP case reports with fatal outcome, 28 cases reported malignant neoplasm progression.

Cases with fatal outcome related to Afinitor: Of the 76 HCP case reports with fatal outcome, 48 cases reported a fatal outcome (including spontaneous and solicited reports) that had a possible relationship to Afinitor.

> **Evaluator comment:** The category with most events was 'General Disease' (n = 23), but was composed of assorted events often with insufficient information to assign a cause and was largely unhelpful. In the category 'Respiratory' (n = 10), 5 cases of pneumonia or pneumonitis were clearly associated with Afinitor and another possibly so. The category, 'Infections and Infestations' (n = 3), included 2 cases of pneumonia and a more doubtful case of sepsis. Also noteworthy were two cases of hyperglycemia associated with other medical conditions, and one definite and two doubtful cases of renal failure. The remaining reports were difficult to interpret.

The following events had been identified in the Risk Management Plan (RMP) for Afinitor as Important, Identified and Potential risks for close monitoring in the PSUR:

- *Identified risk:* Non-infectious pneumonitis, severe infections, hypersensitivity reactions (anaphylactic reactions), stomatitis, increased creatinine / renal failure, hyperglycemia/new onset diabetes mellitus and interactions with CYP3A4 and PgP inhibitors/inducers/substrates.
- *Potential risks:* Cardiac failure, wound healing complications, lymphopenia, hypophosphatemia and dyslipidemia.
- *Pharmacological class effect:* Hemorrhages.
- Based on the European Medicines Agency (EMA) assessment report for PSUR1, 'thromboembolic events' were also included for close monitoring.

In the PSUR2, each of the above events was reviewed, including a case-by-case description. A number of such events have been assessed previously in the Australian setting and are

included in the current PI. The following briefly presents the events in the PSUR2 that are relevant to safety aspects of everolimus in the present application.

Pneumonitis and interstitial lung disease: Using these terms, 56 cases were reported (39 clinical trial reports and 17 spontaneous reports (one of which was the non-HCP report) and were presented individually. Of the 11 fatal cases, several were referred to above. As well, there were an additional 9 cases (seven serious, clinical trial, HCP cases and two serious, HCP spontaneous case) reporting other lung disorders, retrieved in the Standard MedDRA Queries (SMQ) 'interstitial lung disease'.

Severe infection: The review focused on cases of severe infections, which resulted in death, were considered life-threatening, were Grade 3 CTCAE or above or developed into further complications. The number of cases totaled 102 reports (17 spontaneous reports of which 12 were HCP and five non-HCP and 85 suspected solicited reports, all HCP) received during the review period. These were described as follows by the type of infection.

Sepsis: There were 10 cases reporting severe sepsis - 3 were spontaneous reports and 7 were clinical trial reports, all from HCPs, with 5 fatal cases.

Pneumonia/respiratory infection: There were 11 reports of severe pneumonia / respiratory infections, 10 of which were reported as clinical trial cases from HCPs and one as spontaneous report from a non-HCP, with 7 fatal cases. There were an additional 32 cases of pneumonia/respiratory infection retrieved in the search. The report states that these cases provided limited information (including severity) so that no conclusions could be drawn (presumably about the relationship to treatment with everolimus).

Other infections: There were 13 cases reporting other types of infections, which were considered severe. Twelve were clinical trial reports from HCPs and one was a spontaneous, HCP report. Three cases were fatal. An additional 30 serious 'other infection' cases were retrieved from the search. The report states that these cases provided limited information (including severity) and no conclusions could be drawn. Of these, 27 were clinical trial cases (all from HCP) and three spontaneous (two HCP and one non- HCP cases).

Hypersensitivity: The review focused on cases that could be interpreted as a hypersensitivity to Afinitor, using selected PTs. This produced 43 HCP and nine non-HCP reports. There were no reports of the PTs 'anaphylactic reaction', 'acute respiratory failure, 'bronchospasm', 'drug hypersensitivity' 'generalised oedema', 'laryngeal oedema', 'lip oedema', 'oropharyngeal swelling', 'periorbital oedema', 'tongue oedema' and 'tracheal obstruction' retrieved in the search.

Stomatitis: A search retrieved 54 reports during the review period, of which 26 were solicited clinical trial HCP reports and 28 (23 HCP and five non-HCP reports) were spontaneous reports. Thirty nine (39) were serious, suspected clinical trial reports and serious spontaneous reports. Six cases were associated with a fatal outcome. Additional cases included 7 non-serious spontaneous cases reported by HCPs, and 8 by non-HCPs.

Renal failure: Of the 64 cases retrieved in the 'increased creatinine' search, 39 reported the diagnosis of 'renal failure' or 'renal impairment'. The serious, HCP renal failure cases were presented in the report, including 4 with fatal outcome. There were two non-HCP cases retrieved in the 'increased creatinine/renal failure' search, both serious cases. Both provided only limited information.

Hyperglycemia/new-onset diabetes mellitus: A search retrieved a total of 73 reports during the review period of which 22 were spontaneous (17 HCP and five non-HCP) and 51 were suspected solicited (clinical trial). There were 6 serious, HCP reports of diabetes mellitus (four clinical trial and two spontaneous report). In two of the cases below, the patient had an underlying condition of diabetes mellitus and in the remaining four cases, no medical history was reported. One case was fatal. There were 9 cases reporting large increases in

glucose or hyperglycemia. These were Grade 3 or above hyperglycemia based on CTCAE grading of > 250–500 mg/dL or > 13.9–27.8 mmol/L. Of these, 8 were clinical trial cases and one was a spontaneous report; all reported by HCPs. One case was fatal.

Cardiac failure: A search retrieved 129 reports received during the review period. There were 10 cases containing the terms 'cardiac failure', 'cardiac failure acute', 'cardiac failure congestive', 'acute / pulmonary oedema' and 'pulmonary congestion'. Of the 10 cases, cardiovascular risk factors for developing cardiac failure or an event associated with cardiac failure were reported in 5 cases (including hypertension in three cases). In addition, there 9 cases reported of pleural or pericardial effusion, 9 cases of cardiac arrhythmia, 2 cases of coronary artery disorders, one case of a murmur and one case of endocarditis.

Hypophosphatemia: A search retrieved four HCP reports (two solicited clinical trial reports and two spontaneous reports).

The reports on lymphopenia, dyslipidemia, hemorrhage, and thromboembolic events are not presented here.

Conclusions of the PSUR2

The report concludes *"No new safety concerns were identified during the review period for the Afinitor PSUR 2. Adverse events relevant to the important identified and potential risks are already listed in the CDS* [Core Data Sheet]. *Cumulative analysis did not reveal any increase in severity, frequency or apparent risk level beyond what has been labeled. The safety profile of Afinitor remains favorable and in accord with the safety information contained within the current CDS."*

> **Evaluator comment:** The above conclusion is supported, except for the implication that the current CDS does not require changes (see section on *Safety issues with the potential for major regulatory impact*, below). The PSUR2 indicates that treatment with everolimus at a dosage of 10 mg daily has significant toxicity. The fatal events listed cannot be quantitated to determine their incidence as drug-related events, but they indicate that pneumonitis, infections, stomatitis and hyperglycaemia are significant and serious toxic effects.

Safety issues with the potential for major regulatory impact

The most important clinical events related to safety issues in the two pivotal studies were drug-related AEs of infection and infestations, pneumonitis, hyperglycaemia and stomatitis. The Australian PI for Afinitor in the treatment of renal cell cancer lists these events under *Precautions*. The present data confirm their importance but since they have previously been recognised, they would have no major regulatory impact. However the proposed PI should provide the safety data on these events as reported in the population of patients with NETs. In the sections that follow, only pneumonitis is considered, while the other issues are addressed in the section on the proposed PI[29].

Other issues that may have regulatory impact include the safety of everolimus in Asian patients, in elderly patients, and the higher toxicity of everolimus in the second pivotal study, C2325 Carcinoid. All are considered in the following sections.

Pneumonitis: The diagnosis and management of Grade 2 pneumonitis associated with everolimus treatment raised issues of consistency that were discussed in the section of *Clinically Notable AEs*, above.

Toxicity in Asian Patients with NETs: The safety data showed significant differences in the toxicity of everolimus between Asian and Caucasian patients with NETs that were not

[29] Details of recommended revisions to the PI are beyond the scope of this AusPAR

accounted for by differences in medical practice, especially for hyperglycaemia, pneumonitis and hypertension, the incidence of which was increased in Asian patients by 60%, 90% and 95% respectively. More details are given in the section on *Special safety topics*, above. As stated in that section, *"Unless the sponsor can provide a justification for not doing so, these three events should be described in the PI as occurring more frequently in Asian patients."*

Elderly patients: The AEs reported by 10% or more patients 65 years of age or over with an incidence 40% greater than in younger patients were clinically significant (see *Special safety topics* above). This added toxicity was not noted in the previous studies in renal cell carcinoma, but that patient population differed from those with NETs in the present studies. Advice on this should therefore be provided in the PI.

Increased toxicity of everolimus in patients with non-pancreatic NETs

As discussed previously, non-fatal drug-related SAEs and discontinuation of treatment because of drug-related AEs were significantly more frequent in Study C2325 Carcinoid, and not explained by the additional treatment with depot octreotide given to patients. NETs not of pancreatic origin behave differently from those of pancreatic origin, as shown by the difference in the survival that relates to the site of origin of the tumour (see section on *Clinical rationale* above), difference in the efficacy outcomes from everolimus treatment, and increased toxicity of everolimus in this patient population. This will be a factor in the risk-benefit assessment analysis of everolimus in treating non-pancreatic cancers.

Hyperglycaemia, hypophosphatemia and hypokalaemia[30]*:* The incidence of Grade 3-4 hyperglycaemia (> 250 mg/dL;13.9 mmol/L) was 12.3% higher in patients receiving everolimus than in patients receiving placebo in the pivotal trials; of hypophosphatemia (Grade 3/4 - < 2 mg/dL; 0.6mmol/L) 7.3% higher; and of hypokalaemia (Grade 3-4 - <3mmol/L) 4% higher. While such AEs are treatable and did not contribute significantly to treatment discontinuation, the prescriber should be made aware of their frequency since clinical laboratory monitoring in general oncology practice is less intense than in clinical trials. For example, symptoms alone rarely alert the physician to the possibility of hypophosphatemia. Recognising that hypophosphatemia can complicate specific clinical conditions allows the physician to make this diagnosis. Weakness, bone pain, rhabdomyolysis and altered mental status are the most common features of persons with symptomatic hypophosphatemia.

Evaluator's overall summary and conclusions on clinical safety

Overall summary

In this section, two aspects of safety are considered. The first is based on the safety data from the pivotal clinical studies submitted, and will be used to assess the risk-benefit of Afinitor treatment for the requested indications. The second is based on drug-related AEs from a number of available sources, including updated safety data from the pivotal trials, data from the Phase II study submitted and from the PSUR2.

Clinical safety in the pivotal studies

Comparison of the incidence of drug-related AEs in the everolimus arm of pivotal Study C2324 PNET with that of AEs in the placebo arm was difficult because the duration of treatment in the blinded section of the study differed significantly (see section on *Pivotal studies that assessed safety as a primary outcome - Patient exposure*). Exposure of patients in the everolimus arms of the trials during the double blind phase was calculated to be

[30] These data are from Study C2324 PNET

2.3 times that of patients from the placebo arms. When this adjustment was made, the incidence of AEs overall was similar in each arm, but that of Grade 3-4 drug-related and clinically notable AEs were higher in the everolimus arm. AEs irrespective of treatment had a higher incidence in the second study (C2325 Carcinoid) than in the first study (C2324 PNET).

AEs by SOCs: Patients treated with everolimus in the blinded sections of each pivotal study had a higher incidence (10% or more greater than that in the placebo arm) in the following organ classes:

- Skin and subcutaneous tissue disorders (Study C2324 PNET: +43.5%; Study C2325 Carcinoid: +35.2%);
- Respiratory, thoracic and mediastinal disorders (+36.6% and +23.5%);
- Metabolism and nutrition disorders (+26.7% and +32.3%);
- Blood and lymphatic system disorders (+22.4% and +32.7%);
- Infections and infestations (+21.9% and +19.7%);
- Nervous system disorders (+21.9% and +12.2%);
- General disorders and administration site conditions (+19.8% and +14.1%);
- Investigations (+16.1% and +20.8%);
- Gastrointestinal disorders (+14.8% and +18.6%);
- Renal and urinary disorders (+12.2% and +9.0%);
- Injury, poisoning and procedural complications (+10.2% and +5.4%).

  Evaluator comment: The sponsor's *Clinical Overview* did not include in its safety conclusions the above data on the frequency of adverse effects by SOCs. The Australian PI lists SOCs for which a specified AE is identified but does not give incidence figures for the SOCs as above.

AEs by PT (drug-related): Drug-related events where the incidence was 10% or more than placebo were: stomatitis (Study C2324 PNET: +41.6%; Study C2325 Carcinoid: +37.0%), rash (+38.2% and +24.9%), diarrhoea (+23.9% and +11.8%), epistaxis (+17.2% and +4.7%), fatigue (+17.1% and +8.0%), peripheral oedema (+16.7% and +9.7%), anaemia (+14.2% and +10.6%), dysgeusia (+13.3% and +13.4%), decreased appetite (+12.7% and +7.3%), headache (+12.7% and +0.3%), thrombocytopenia (+12.7% and +14.0%), pneumonitis (+12.3% and +8.4%), weight decreased (+11.3% and +11.6%), nail disorder (+10.8% and +2.8%), pyrexia (+10.8% and +1.8%), hyperglycemia (+8.8% and +10.2%), aphthous stomatitis (+7.4% and +11.2%), and dyspnoea (+4.4% and +10.7%).

> **Evaluator comment:** The above results were from the blinded phases of the pivotal trials and did not differ in the subsequent open phase. The sponsor's *Clinical Overview* used pooled data that also included the safety results from Study C2239, the Phase II study with a patient population different from that of the pivotal trials. Many of the AEs listed in the sponsor's *Clinical Overview* are the same as above but in a different order of frequency. The Australian PI lists the same AEs as above in both the current and proposed PIs.

Severe AEs (drug-related): Drug-related Grades 3-4 AEs occurred in 40% of patients in C2324 PNET and 45% in C2325 Carcinoid.

In the C2324 PNET trial, those occurring in 1% or more of patients, in order, included; Grade 3: hyperglycemia (5.4%), anaemia (4.9%), stomatitis (4.9%), thrombocytopenia (3.4%), and diarrhoea (3.4%) in the everolimus treatment group; and neutropenia (2.0%), hyperglycemia (1.5%), asthenia, increased ALT and increased AST (1.0% each) in the

placebo treatment group; and Grade 4 events in the everolimus arm: anaemia (n = 2, 1.0%), thrombocytopaenia, pulmonary embolism (each n = 1, 0.5%); and in the placebo group, hyperglycemia (n = 1, 0.5%).

In the C2325 Carcinoid trial, Grade 3 AEs included fatigue (6.5%), diarrhoea (6.0%), hyperglycemia (5.1%), thrombocytopenia (4.2%), stomatitis (3.7%), neutropenia (2.3%), hypophosphatemia (1.9%), mouth ulceration (1.4%), leukopenia (1.4%), cellulites (1.4%), pneumonitis (1.4%) in the everolimus arm; and fatigue (2.8%), and diarrhoea (2.4%)in the placebo arm; and Grade 4 events in the everolimus arm, each with an incidence of 0.5% (1 patient): lip oedema, hypokalaemia, hypomagnesaemia, thrombocytopenia, neutropenia, herpes zoster, intracranial hematoma, hematoma, and carcinoid syndrome; and in the placebo arm cardiac disorder, and myocardial infarction (each n = 1, 0.5%).

> **Evaluator comment:** The sponsor's *Clinical Overview's* presentation of severe drug-related AEs differed from the above, using an incidence of 2% or greater rather than the 1% above, and combined several PTs when these were related, so the incidence figures but not the AEs themselves differed. The Australian PI, current and proposed, used a cut-off frequency of 2%, and shortens the list of Grade 3-4 events to infections, stomatitis, fatigue and pneumonitis. The sponsor's *Clinical Overview*, in contrast lists the most common Grade 3-4 drug-related adverse drug reactions with an incidence ≥ 2% as hyperglycemia, stomatitis, diarrhoea, fatigue, thrombocytopenia, anaemia, neutropenia, hypophosphatemia and asthenia from the pooled data of the three clinical trials, including the open phase periods.

Deaths: Forty-five on-treatment deaths (5.4%) were reported in the pivotal Phase III trials: 30 (7.2%) in patients receiving treatment with everolimus and 15 (3.6%) in placebo-treated patients. Twenty of these 45 on-treatment deaths were attributed to the underlying malignancy (11 from the everolimus treatment group and 9 with placebo). For the remaining 25 (19 with everolimus and 6 with placebo, an AE was the primary cause of death, 4 of Infections and infestations (pneumonia, infection and sepsis). Of these, only one was considered to be drug-related, a death from acute respiratory distress. A second patient however died after discontinuing the drug, of reactivation of hepatitis B infection. This possibility is mentioned in the current Australian PI. It can be concluded that no unusual or new clinically significant findings were observed and data relating to deaths were consistent with the established safety profile of everolimus and the clinical condition of patients enrolling in these studies.

> **Evaluator comment:** Although a number of on-treatment deaths were associated with AEs, these AEs with one exception were not considered to be drug-related.

Important specified clinical events: Based on an incidence of 2% or more of drug-related Grade 3-4 events in the pivotal studies, important clinical safety events in the two pivotal studies C2324 PNET and C2325 Carcinoid were hyperglycemia (5.4%, 5.1%), anaemia (4.9%, 1.4%), stomatitis (4.9%, 3.7%), thrombocytopenia (4.94%, 4.7%), diarrhoea (3.4%,6.0%), fatigue (1.5%, 6.5%) and neutropenia (2.9%, 2.8%).

Discontinuation of treatment: Both studies had high rates of interruption and/or dose reduction due to an AE in the everolimus arm (about 30% higher than placebo). Drug-related AEs were responsible for 13.2% permanent discontinuations in C2324 PNET and 18.6% in C2325 Carcinoid while the rate in each placebo arm was similar (2%, 3.3%). The sponsor's *Clinical Overview* attributed this to the 'add-on' effect of treatment with depot octreotide, but the only adverse effect of octreotide common to those above is nausea (Australian PI for Sandostatin LAR). This does not explain the higher incidence of discontinuations in C2325 Carcinoid. Of note is that the rates of discontinuations due to drug-related AEs of the pulmonary system (pneumonitis and interstitial lung disease) were similar in the two studies – C2324 PNET, 3.9%, C2325 Carcinoid, 3.3%.

Updated safety data: The information presented in the 90 day Safety Update of the pivotal clinical trials was consistent with data originally provided in the application, and no new findings were evident that would require changes to the safety assessment or to the prescribing information.

Safety in Japanese patients, a sub-set of patients in C2324 PNET: These data were discussed under the heading *Safety in Japanese patients, a sub-set of patients in C2324 PNET*, above, and indicated that hypertension was 95% more frequent, pneumonitis 90% more frequent, and hyperglycaemia 60% more frequent in Japanese patients than in Caucasian patients. These three AEs are based on laboratory and radiological results and so are less liable to differences in medical practice. The evaluator recommends that the sponsor provide a justification for not reporting this difference in the proposed Australian PI. This conclusion differs from that of the sponsor's *Clinical Overview*.

Adverse events by age: The incidence in the older age group of dehydration, hypomagnesaemia and pneumonitis was 40% or greater than in patients 65 years or younger. These data are grounds for safety concern and should be included in the PI in relation to these studies. This conclusion differs from that of the sponsor's *Clinical Overview*.

Clinical safety from PSUR

From the PSUR2, the category with most events was 'General Disease' (n = 23), but was composed of assorted events often with insufficient information to assign a cause. In the category 'Respiratory' (n = 10), 5 cases of pneumonia or pneumonitis were clearly associated with Afinitor and another was possibly associated. The other category of concern was 'Infections and Infestations' (n = 3) where 2 cases were of pneumonia and a more doubtful case of sepsis. Also noteworthy were two cases of hyperglycaemia associated with other medical conditions, and one definite and two doubtful cases of renal failure. The remaining reports were difficult to interpret.

Conclusions

The PSUR2 indicates the toxicity of treatment with everolimus at a dosage of 10 mg daily. The fatal events listed cannot be quantitated to determine their incidence as drug-related events, but indicate that pneumonitis, infections, stomatitis, and hyperglycaemia are significant and potentially serious toxic effects. These are the same events presented above as the most significant and highlighted in the sponsor's *Clinical Overview*, the proposed PI and in the RMP. The toxicity was on the whole manageable and was of the degree seen with drugs treating serious malignant diseases for which there are few treatment options.

First round benefit-risk assessment

The requested indication for the use of everolimus is the treatment of advanced neuroendocrine tumours of gastrointestinal, lung and pancreatic origin. Because one pivotal study dealt with NETs of pancreatic origin (Study C2324 PNETs) and the other with those originating in other organs (mainly lung and gastrointestinal tract), and because the efficacy and safety results were different in each study, the studies will be considered separately. The following assessments will be applied to the actual patient populations in the trials, not to a population given the general term "advanced neuroendocrine tumours" as in the requested indication.

First round assessment of benefits

Pivotal Study C2324 PNET: The patient population in this study was a population with progressive, unresectable or metastatic, low or intermediate grade neuroendocrine carcinomas of the pancreas. The benefits of everolimus in treating this population compared to placebo was to reduce the risk of progressive disease by 65% (HR 0.35 [95%

CI 0.27, 0.45]) and to increase the time to disease progression (PFS) by 6.4 months from a median of 4.6 months to 11.04 months. The effect was seen in all subgroups and sensitivity analyses. A benefit on overall survival, as assessed by the HR was not shown, as patients in the placebo arm were also treated with everolimus when their disease progressed. Median OS was not reached but appears to be longer than in untreated patients, as may be expected from the increase in the PFS, although other cases have shown increased PFS with no OS benefit. Objective responses were partial only and the rates low (4.8% in the everolimus arm and 2.0% in the placebo arm).

No quality of life assessments were made and would be complicated because placebo patients crossed over to receive everolimus on disease progression. The additional period free of disease (6.4 months) in patients treated with everolimus would be expected to improve their quality of life by preventing or reducing disease-related symptoms in the absence of progression but quality of life could be reduced by the toxicity of treatment.

Pivotal Study C2325 Carcinoid: The patient population in this study was a population with progressive, unresectable or metastatic, low or intermediate grade neuroendocrine carcinomas of any organ, who had a history of symptoms indicating carcinoid syndrome. Of the total patient population, the primary site of cancer was pancreas in 26 of 429 patients (6.1% with 5.1% in the everolimus group and 7.0% in the placebo group), the majority being small intestine (52.2%) and lung (10.3%). No statistically significant benefits of everolimus in treating this population compared to placebo was shown for the primary endpoint, the PFS assessed by adjudicated central review (IAC), as changed by the sponsor after the second interim analysis. The HR was 0.77 (95% CI 0.59, 1.0), the median PFS was 16.43 (13.67, 21.19) months in the everolimus arm and 11.33 (8.44, 14.59) months in the placebo arm. The p value for the difference was 0.026, whereas the predetermined required alpha value was 0.0246. Further analyses using assessments by the local investigators and the IRC gave conflicting results. The subgroup analyses also indicated no statistically significant effect of everolimus treatment in 16 of 19 analyses. The median overall survival was longer in the placebo arm (33.18 months) than in the everolimus arm (26.25 months) and was not explained by imbalance in patient and disease characteristics as claimed by the sponsor.

Overall, a benefit to the patients treated with everolimus was not demonstrated in this study.

First round assessment of risks

Study C2324 PNET

- The risks of everolimus for the proposed usage are:
- That the benefit described above may not be as found in the study because the RECIST guidelines were not followed when assessing disease progression;
- That overall survival may not be increased by everolimus treatment, although this risk is low when overall survival from historical studies are compared;
- The risk of developing drug-related severe (Grade 3-4) hyperglycaemia, anaemia, stomatitis, thrombocytopenia and diarrhoea ranges from 3.4% to 5.4%;
- The risk of developing drug-related pneumonitis is 12.3% and of drug-related dyspnoea 7.4%. In most cases, the pneumonitis had mild or no symptoms, could be managed clinically and was of short duration;
- The risk of death from treatment was insignificant;
- The risks as stated were the same as those experienced previously in the treatment of large numbers of patients, many with other cancers;

- The risk of discontinuing treatment with everolimus because of a drug-related AE was 13.2%;
- For Japanese patients, the risks of experiencing an adverse event of hypertension was 95% higher, of pneumonitis 90% higher, and of hyperglyacemia 60% higher than in Caucasian patients;
- For patients over 65 years, the incidence of dehydration, hypomagnesaemia and pneumonitis was 40% higher than for patients 65 years or younger. The two former events may be associated with or aggravated by stomatitis and diarrhoea (see dot point one)[31];
- The extension of the disease-free period, the only benefit of treatment, may not be accompanied by a better quality of life because of the above risks.

Study C2325 Carcinoid

- The risks of everolimus for the proposed usage are:
- The risk of developing drug-related Grade 3 AEs including fatigue (6.5%), diarrhoea (6.0%), hyperglycemia (5.1%), thrombocytopenia (4.2%), stomatitis (3.7%), neutropenia (2.3%),) mouth ulceration (1.4%), leukopaenia (1.4%), pneumonitis (1.4%);
- A 9.3% risk of developing drug-related pneumonitis and 12.1% risk of drug-related dyspnoea. In most cases, the pneumonitis had none or mild symptoms and could be managed clinically and was of short duration;
- The risk of death from treatment was insignificant;
- The risks as stated were the same as those experienced previously in the treatment of many patients, including those with cancer;
- The risk of discontinuing treatment with everolimus because of a drug-related AE was 18.6%.

First round assessment of benefit-risk balance

From an assessment of the benefit-risk balance based on Study C2324 PNET for the treatment of pancreatic NETs with everolimus, it is concluded that the benefit of treatment with everolimus outweighs the risks, given that the risks are comparable to those seen in the treatment of cancer patients with moderately toxic drugs, especially when there are few treatment options, as in the present case. The toxic effects are manageable and justified by the significant clinical benefit. This conclusion is contingent on the proposed patient population having the same tumour characteristics as those of patients that were treated in the study.

However, the benefit-risk balance based on Study C2325 Carcinoid is unfavourable for that indication because no convincing benefit was shown for patients treated with everolimus and the toxicity of treatment was greater than that in the other pivotal study. As well, the OS of patients in the placebo arm was longer than in the treatment arm, although this may be a statistical aberration and reflect no difference.

The benefit-risk balance of everolimus is unfavourable given the proposed usage but would become favourable if the changes recommended under *Clinical Summary and Conclusions*, below, are adopted.

[31] The sponsor noted that the data from Study C2324 PNET do not support this statement, as the incidences of these AEs in that study are in fact similar to or lower in those aged < 65 years when compared with those aged ≥ 65 years. TGA later determined that the data supporting this statement are from Study C2325 Carcinoid, where the incidences were, for those aged < 65 and those aged ≥ 65, respectively, 5.6% and 13.7% for pneumonitis, 8.5% and 13.7% for dehydration, and 5.6% and 11% for hypomagnesaemia.

List of questions

Efficacy

The TGA requested the sponsor provide further information in response to the following:

It was noted that in its evaluation of this application, the FDA in the United States used a different definition than that of the sponsor for major protocol deviations. Incidences of major protocol deviations using the FDA definition were higher than those obtained using the sponsor's definition. Please comment on the differences in the definitions used and any impact these may have had in interpretation of study findings.

The sponsor's response is reproduced below:

> Novartis is unaware of the analysis methodology used by the FDA to identify major protocol deviations. Major protocol deviations causing patients to be excluded from the Per-protocol Set in both the pNET and carcinoid studies were defined as follows:
>
> 1. Incomplete documentation of an advanced (unresectable or metastatic) biopsy proven pancreatic NET;
> 2. No radiological documentation of progression of disease within 12 months of randomisation;
> 3. No measurable lesion at baseline (per RECIST);
> 4. WHO PS >2;
> 5. Low-grade or intermediate-grade neuroendocrine carcinoma that was not confirmed;
> 6. Prior therapy with mTOR inhibitors (sirolimus, temsirolimus, everolimus); and
> 7. Chronic treatment with corticosteroids or other immunosuppressive agents.
>
> Of the 410 randomised patients, major protocol deviations occurred in a total of 13 (3.2%) patients: six (2.9%) patients in the everolimus treatment group and seven (3.4%) patients in the placebo group. Of these six patients in the everolimus treatment group, three (1.4%) patients had poorly differentiated carcinoma, one (0.5%) patient had incomplete documentation of an advanced pancreatic NET, one (0.5%) patient had no radiological documentation of disease progression within 12 months of randomization, and one (0.5%) patient had no measurable lesion at baseline (per RECIST). Of the seven patients in the placebo group, six (3.0%) patients had no radiological documentation of disease progression within 12 months of randomization and one (0.5%) patient had poorly differentiated carcinoma.
>
> Analyses on the PFS with both the Full Analysis Set (FAS) and the Per-protocol Set were performed using the Kaplan-Meier methodology:

Population	P value*	Hazard ratio**
Full Analysis Set (FAS)	<0.001	0.35 [0.27, 0.45]
Per-protocol Set	<0.001	0.35 [0.27, 0.45]

> * P value was obtained from the stratified one-sided log-rank test.
>
> ** Hazard ratio was obtained from the stratified unadjusted Cox model.
>
> Overall, the number of major protocol deviations occurred in a small number of patients and did not affect the integrity of the results for study CRAD001C2324.

Clinical summary and conclusions

The clinical evaluator recommended that everolimus be approved for the treatment of progressive, unresectable or metastatic, low or intermediate grade neuroendocrine carcinoma of the pancreas.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a RMP which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of *Ongoing safety concerns* (as specified in the EU Safety RMP version 5), which is shown at Table 22.

Subject to the evaluation of the nonclinical aspects of the Safety Specification (SS) by the Toxicology area of the TGA's Office of Safety Evaluation and the clinical aspects of the SS by the Office of Medicines Authorisation (OMA), the summary of the Ongoing Safety Concerns as specified in the EU Safety RMP version 5 is as follows:

Table 22. Ongoing safety concerns

Important identified risks	Non-infectious pneumonitis
	Severe infections
	Hypersensitivity reactions (anaphylactic reactions)
	Stomatitis
	Increased creatinine/Proteinurea/Renal failure
	Hyperglycemia/new onset diabetes mellitus
	Wound healing complications
	Dyslipidemia
	Hypophosphatemia
Important potential risk	Cardiac failure
	Lymphopenia
	Developmental toxicity
	Reproductive (teratogenicity) toxicity
Important identified interactions	Strong CYP3A4 and PgP inhibitors
	Moderate CYP3A4 and PgP inhibitors

	Strong CYP3A4 and PgP inducers
	CYP3A4 and PgP substrates
Important missing information	Paediatric patients less than 3 years old
	Off-label use in paediatric and adolescent patients
	Pregnant or breast-feeding women
	Hormonal contraceptives
	Patients with renal impairment
	Patients with pre-existing infections (other than systemic invasive fungal infections)
	Patients with CNS metastases
	Patients with HIV, or hepatitis B or C seropositivity
	Patients with bleeding diathesis (haemorrhages)*
	Patients with coagulation disorders (thromboembolism)*
	Patients with uncontrolled or significant cardiac disease
	Patients with impairment of gastrointestinal function
	Patients undergoing chronic treatment with steroids or another immunosuppressive agent
	Patients who have undergone surgery within 2 weeks prior to start of treatment
	Long-term safety
	Race other than Caucasian
	Reactivation of background disease

*Two areas of important missing information 'haemorrhages' and 'thromboembolism' are listed as Important identified risks in the EU Safety RMP version 5. In response to a request for the sponsor to clarify this discrepancy, the sponsor indicated that both 'haemorrhages' and 'thromboembolism' *"are considered identified risks and should have been deleted from the missing information section of the RMP"*. This is considered acceptable.

It was noted that 'pregnant or breast-feeding women' and 'reactivation of background disease' were both listed as Important risks in the *Safety Risk Management Plan Australian Implementation* Version 5.0 and are not areas of "Important missing information" as listed in the EU Safety RMP version 5. In response to a TGA request for clarification the sponsor confirmed that both "pregnant or breast-feeding women" and "reactivation of background disease" are still considered areas of Important missing information as classified in the EU Safety RMP version 5 and that there are no changes to the pharmacovigilance (PV) and

risk minimisation activities proposed for these ongoing safety concerns. This is considered acceptable.

One Ongoing Safety Concern "patients with severe hepatic impairment" (listed as Important missing information in the EU Safety RMP version 4) has been removed from the EU Safety RMP version 5 without adequate justification and the sponsor was requested to clarify. This particular safety concern was identified in the EU Safety RMP version 4 to require an additional PV activity, including investigation in an open label, single dose Study CRAD001X2102 designed to assess the PK of Afinitor in participants with impaired hepatic function.

In the sponsor's response to a TGA request for information, it is stated that the safety concern "patients with severe hepatic impairment" has been removed from the EU Safety RMP version 5 because Study CRAD001X2102 has been completed and the results have addressed the dosage requirements for use in this patient population. The sponsor also stated that "*the proposed changes are currently under various Health Authority reviews. In Australia, Study X2102 will be submitted as part of a future application.....The CSR was submitted to EMA on 28 September 2011*".

A synopsis for the final CRAD001X2102 clinical study report (CSR) has also been provided with the response to the TGA request for information.

In the opinion of the evaluator, it is unclear if Study CRAD001X2102 has presented sufficient data to justify the removal of "patients with severe hepatic impairment" from the list of ongoing safety concerns of the RMP for continued close monitoring. The evaluator also discussed details in the proposed PI on the use of everolimus in hepatic impairment; however, these discussions are beyond the scope of this AusPAR.

Pharmacovigilance plan

It is proposed that routine PV activities including cumulative analysis in the PSUR for all Important identified and Potential risks, Identified interactions and Important missing information except for these areas of Important missing information: hormonal contraceptive use, patients with renal impairment, patients with pre-existing infections (other than systemic invasive fungal infections), Central Nervous System (CNS) metastases, HIV or hepatitis B or C seropositivity, uncontrolled or significant cardiac disease, impairment of gastrointestinal function, undergoing chronic treatment with steroids or another immunosuppressive agent, have undergone surgery within 2 weeks prior to start of treatment, long-term safety, race other than Caucasian and reactivation of background diseases (all requiring only routine PV). The following additional PV activities are proposed (from Safety RMP Version 5) (Table 23).

Table 23. Proposed PV activities. Table continued across two pages.

PV activities	Safety concerns
Targeted follow-up questionnaire/checklist for all serious spontaneous reports, serious reports from post-market surveillance and other programs where data is being handled or solicited, SAE reports from all clinical trials.	Important identified risks: non-infectious pneumonitis severe infections hypersensitivity (anaphylactic reactions) increased creatinine/proteinurea/renal failure Important potential risks: cardiac failure

PV activities	Safety concerns
	developmental toxicity reproductive (teratogenicity) toxicity Important missing information: pregnant or breast-feeding women patients with renal impairment reactivation of background diseases
Ongoing clinical trial CRAD001X2103: open label, two-period, fixed-sequence to investigate the effect of everolimus on orally-administered midazolam (CYP3A4 substrate) PK in healthy participants final data submission: July 2011	Identified interactions: strong CYP3A4 and PgP inhibitors moderate CYP3A4 and PgP inhibitors CYP3A4 and PgP inducers CYP3A4 and PgP substrates
Ongoing clinical trial CRAD001M2301: randomised, double blind, placebo controlled to investigate everolimus as a treatment for SEGA associated with TS complex with a 4-year extension phase post last randomisation to allow a 4-5 years follow-up assessments to include weight, height (pre and post enrolment), changes in hormones and Tanner staging until sexual maturation initial phase data submission: 4th quarter of 2011 extension phase data submission: 2nd quarter of 2014	Important potential risks: developmental toxicity Important missing information: long-term safety
Ongoing clinical trial CRAD001C2485: to investigate everolimus as a treatment of giant cell astrocytomas with tuberous sclerosis complex assessments to include weight, height (pre and post enrolment), changes in hormones and Tanner staging until sexual maturation total number = 28 (Table 1-3, RMP version 5, p. 24) final data submission: 4th quarter of 2014	Important potential risks: developmental toxicity Important missing information: long-term safety

Two other studies have also been included in the PV plan:

- A open label, single dose study (CRAD001X2102) to investigate Afinitor pharmacokinetics in subjects with impaired hepatic function (final data submission July 2011)
- Meta-analysis to evaluate the safety/efficacy to everolimus exposure by using pharmacokinetics data from blood samples collected in ongoing clinical studies (final data submission 5 April 2011)

All the proposed targeted follow-up questionnaires for the safety concerns listed above are considered acceptable. One questionnaire *"Renal impairment or failure"* is proposed to cover the following safety concerns: patients with renal impairment (Important missing information), increase creatinine and renal failure/proteinurea. This strategy is acceptable.

Risk minimisation activities

It is proposed that routine risk minimisation activities, which include the provisions of PI and Consumer Medicine Information (CMI) are sufficient for all the listed safety concerns. The conclusion that no additional risk minimisation activities are required aside from the routine risk minimisation activities is acceptable.

The RMP evaluator recommended several amendments to the proposed PI; details of these are beyond the scope of this AusPAR.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application and the implementation of the EU Safety RMP version 5 (18 May 2011) and Australian RMP Implementation version 5.0 (18 May 2011) and any subsequent updated versions be implemented as a condition of registration.

If this submission is approved, it is recommended that the Delegate considers requesting the sponsor to incorporate the following amendments to the RMP:

Safety specifications

- The re-inclusion of "patients of severe hepatic impairment" as a safety concern for ongoing monitoring because the justification for removal of this safety concern has not been satisfactorily addressed.
- The inclusion of "patients aged 65 years and over" as a new safety concern. The clinical evaluator has identified this patient group as requiring further monitoring.

Risk minimisation activities

- The inclusion of relevant information on adverse events observed with patients of Japanese ethnic background and patients aged 65 years and over in the Australian PI

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The submission included a small amount of updated data relating to formulations of everolimus used in clinical trials, including the formulations used in the pivotal clinical

studies included in this submission. The chemistry evaluator had no objections to registration.

Nonclinical

The submission included only a small amount of new preclinical data. *In vitro* data demonstrated that everolimus reduced the proliferation of pancreatic NET cell lines. Previously evaluated studies in rats demonstrated that everolimus suppressed tumour growth in rats bearing pancreatic NETs. There were no preclinical objections to registration.

Clinical

The clinical evaluator has recommended approval, although with a more restricted indication (NETs of pancreatic origin only) than that proposed by the sponsor.

The submission included three clinical trials:

- Study C2324 PNET ('RADIANT-3'): a Phase III, randomised, double blind, placebo controlled trial in patients with *pancreatic* NETs. This trial has been published[32];
- Study C2325 Carcinoid ('RADIANT-2'): a Phase III, randomised, double blind, placebo controlled trial in patients with NETs and a history of diarrhoea and/or flushing consistent *with carcinoid syndrome*. This study has also been published[33].
- Study 2239: a Phase II open label, single-arm trial in patients in patients with *pancreatic* NETs.

Pharmacokinetics

A limited amount of PK data was collected from the three studies. These demonstrated the following:

- PK parameters in patients with NETs in Studies C2324 PNET and C2325 Carcinoid were generally consistent with those seen for other oncology patients in previously evaluated studies (see Table 1 of this AusPAR);
- Systemic exposure to everolimus appeared to be increased in Japanese subjects compared to other subjects;
- Co-administration of everolimus with octreotide did not appear to affect everolimus trough concentrations, but was associated with an increase in octreotide trough concentrations of approximately 21–47%;

Pharmacodynamics

The sponsor analysed the relationship between trough concentrations of everolimus and efficacy outcomes such as PFS and tumour size. The evaluator considered that the results were inconclusive. An analysis of the relationship between trough concentrations of everolimus and adverse events was also conducted. No relationship was demonstrated.

[32] Yao, JC, Shah, MH, Ito T. *et al*., for the RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group. Everolimus for Advanced Pancreatic Neuroendocrine Tumors. *N Engl J Med* 2011; 364:514-523.

[33] Pavel, ME, Hainsworth, JD, Baudin, E. *et al.,* for the RADIANT-2 Study Group. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo controlled, phase 3 study. *Lancet* 2011; 378: 2005–2012

Efficacy

Evidence for efficacy comes from the two Phase III studies. The evaluator raised one question regarding the definition of major protocol violations (see *List of questions*, above).

Study C2324 PNET enrolled subjects with unresectable or metastatic pancreatic NET, who had evidence of progressive disease. Subjects had low or intermediate grade neuroendocrine carcinoma, with high grade or poorly-differentiated disease being excluded. Concomitant use of somatostatin analogues was permitted but not required.

A total of 410 subjects were randomised (1:1) to receive everolimus 10 mg daily or placebo. The two treatment arms were well balanced with respect to demographics and disease characteristics. The proportion of patients who received concomitant somatostatin treatment was comparable in the two treatment arms (38% versus 40%).

The primary endpoint was PFS. In the initial protocol, this was to be assessed by a central IRC. Investigator-assessed PFS was to be a secondary endpoint. The protocol was subsequently changed to make investigator-assessed PFS the primary endpoint and to introduce an IAC to adjudicate on differences in assessment of disease progression between the IRC and the investigator. PFS by the IRC and PFS by the IAC were made secondary endpoints. Results for the primary efficacy endpoint from Study C2324 are shown in Table 24, Figure 6 and Table 25 below:

Table 24. Analysis of PFS based as per investigator using Kaplan-Meier methodology. Full Analysis Set

Primary endpoint	Everolimus 10 mg N=207	Placebo N=203	P value [1]	Hazard ratio [2] [95% CI]
No. of PFS events (n [%])	109 (52.7)	165 (81.3)	<0.001	0.35 [0.27, 0.45]
Progression	95 (45.9)	158 (77.8)		
Death	14 (6.8)	7 (3.4)		
No. censored (n [%])	98 (47.3)	38 (18.7)		
Kaplan-Meier estimates [95% CI] at:				
3 months	84.0 [78.0, 88.4]	58.5 [51.2, 65.0]		
6 months	69.5 [62.4, 75.5]	31.9 [25.4, 38.5]		
12 months	45.6 [37.7, 53.1]	15.4 [10.5, 21.2]		
18 months	34.2 [25.9, 42.7]	8.9 [4.0, 16.3]		
Median PFS [95% CI] (months)	11.04 [8.41, 13.86]	4.60 [3.06, 5.39]		

CI = Confidence interval; 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.

Figure 6. Kaplan-Meier plot of PFS as per investigator – Full Analysis Set

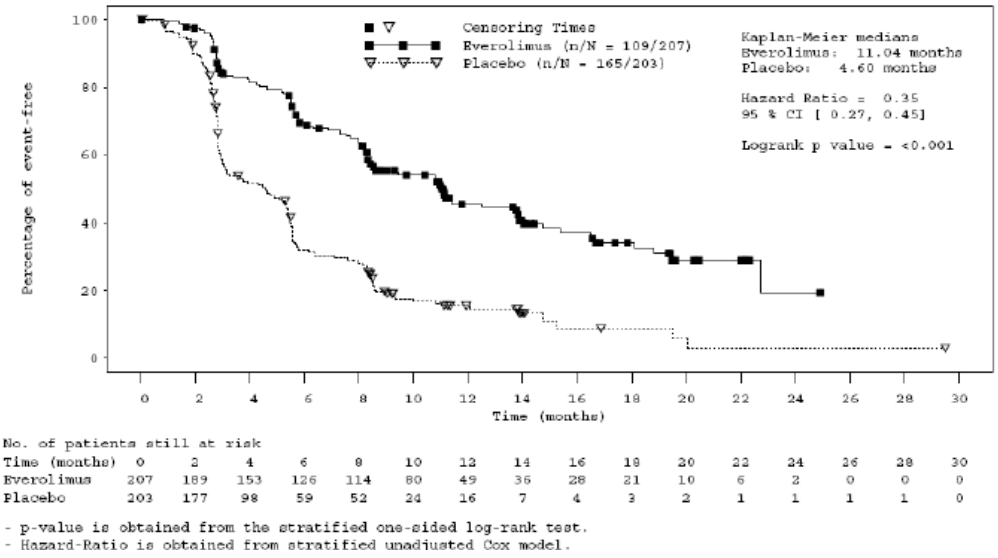


Table 25. Summary of key efficacy results. Full Analysis Set

	Comparison		Median PFS (months) [95% CI]	
Progression-free survival	**P value [1]**	**Hazard ratio [2] [95% CI]**	**Everolimus 10 mg N=207**	**Placebo N=203**
Primary analysis				
Local investigator assessment	<0.001	0.35 [0.27, 0.45]	11.04 [8.41, 13.86]	4.60 [3.06, 5.39]
Supportive analyses				
Adjudicated central radiology review	<0.001	0.34 [0.26, 0.44]	11.40 [10.84, 14.75]	5.39 [4.34, 5.55]
Central radiology review	<0.001	0.38 [0.28, 0.51]	13.67 [11.17, 18.79]	5.68 [5.39, 8.31]

CI = Confidence interval; 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.

Using investigator assessed PFS, treatment with everolimus was associated with a significant prolongation of PFS (HR = 0.35 [95% CI 0.27, 0.45]; p < 0.001) with a prolongation of median PFS by approximately 6.4 months (11.04 versus 4.60). The IRC and IAC assessments gave similar results.

There was no significant difference in overall survival. This was not unexpected; the patients assigned to the placebo arm who experienced progressive disease could cross over to receive treatment with everolimus. There were no significant differences in response rates. Quality of life measures were not examined.

Study C2325 Carcinoid enrolled subjects with unresectable or metastatic carcinoid tumour (originating from any anatomical site), who had evidence of progressive disease. Subjects had low or intermediate grade neuroendocrine carcinoma, with high grade or poorly differentiated disease being excluded. All patients were to be treated with concomitant long acting octreotide (30 mg SC every 28 days).

A total of 429 subjects were randomised (1:1) to receive everolimus 10 mg daily or placebo. There were a number of imbalances between groups in baseline disease characteristics, although the evaluator considered that these were unlikely to have had a significant effect on efficacy outcomes.

In the initial protocol, the primary endpoint was PFS as assessed by a central IRC. Investigator assessed PFS was to be a secondary endpoint. Two interim analyses of the study were conducted. At the second interim analysis, a discrepancy in the PFS results was

noted between the IRC assessment (which showed no significant difference between treatments) and the investigator assessment (which showed a significant difference). The protocol was subsequently changed to introduce an 'independent adjudication committee' (IAC) to adjudicate on differences in assessment of disease progression between the IRC and the investigator. The IAC assessment of PFS was made the primary endpoint.

Results for primary endpoint are shown below. Using IAC assessed PFS, treatment with everolimus was *not* associated with a significant prolongation of PFS (HR = 0.77 [95% CI 0.59, 1.00]; p = 0.0260). The pre-determined alpha level for significance, following adjustment for the two interim analyses, was *0.0246*. The IRC assessment of PFS also failed to demonstrate a significant benefit. However, the investigator assessment of PFS suggested a significant benefit (HR = 0.78 [95% CI 0.62, 0.98]; p = 0.018).

The sponsor considered that the discordant PFS results between the IRC and investigator assessed results at the second interim analysis were due to the phenomenon of 'informative censoring'. The sponsor therefore conducted a further analysis (Cox model with IPCW) to account for this. The analysis was described as exploratory. The efficacy results from Study C2325 Carcinoid, as shown below in Table 26, Figure 7 and Table 27, demonstrated a significant benefit for everolimus treatment.

Table 26. Analysis of PFS as per adjudicated central radiology review using Kaplan-Meier methodology – Full Analysis Set

	Everolimus plus depot octreotide N=216		Placebo plus depot octreotide N=213		p-value [a]	Hazard ratio [b] [95% CI]
No. of PFS events (n [%])	103	(47.7)	120	(56.3)	0.026	0.77 [0.59, 1.00]
Progression	69	(31.9)	101	(47.4)		
Death	34	(15.7)	19	(8.9)		
No. censored (n [%])	113	(52.3)	93	(43.7)		
Kaplan-Meier estimates [95% CI] at:						
4 months	89.9	[84.8, 93.4]	82.6	[76.6, 87.2]		
6 months	78.6	[71.9, 83.8]	70.2	[63.1, 76.2]		
12 months	60.6	[52.6, 67.6]	48.7	[41.0, 56.0]		
18 months	47.2	[38.9, 55.1]	37.4	[29.9, 44.9]		
24 months	39.0	[30.7, 47.3]	29.5	[22.2, 37.2]		
Median PFS [95% CI] (months)	16.43 [13.67, 21.19]		11.33 [8.44, 14.59]			

[a] p-value is obtained from the one-sided log-rank test
[b] Hazard ratio is obtained from the unadjusted Cox model

Figure 7. Kaplan-Meier plot of PFS as per adjudicated central radiology review– Full Analysis Set

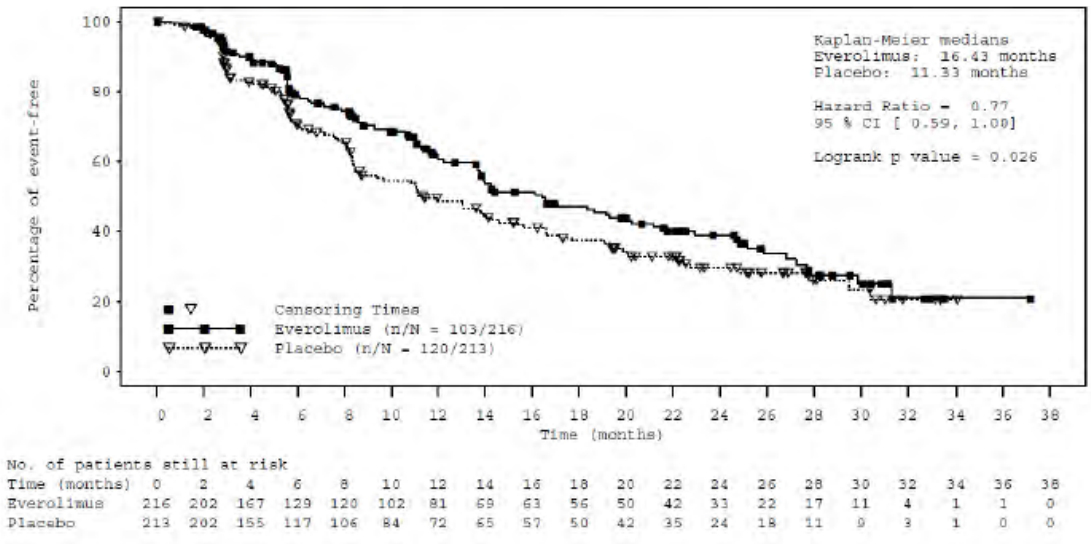


Table 27. Summary of key efficacy results – Full Analysis Set

Progression-free survival Data source	Hazard ratio [95% CI] [a]	p-value [b]	Median PFS [95% CI] Everolimus plus depot octreotide	 Placebo plus depot octreotide
Unadjusted model				
Primary analysis				
Adjudicated central radiology review	0.77 [0.59, 1.00]	0.026	16.43 [13.67, 21.19]	11.33 [8.44, 14.59]
Supportive analyses				
Local investigator	0.78 [0.62, 0.98]	0.018	11.99 [10.61, 16.13]	8.61 [8.08, 11.14]
Central radiology review	0.93 [0.71, 1.22]	0.298	14.88 [12.22, 19.38]	13.90 [9.66, 19.09]
Prespecified adjusted model [c]				
Adjudicated central radiology review	0.76 [0.58, 1.00]			
Local investigator	0.75 [0.59, 0.96]			
Central radiology review	0.94 [0.71, 1.24]			
Prespecified IPCW analysis				
Adjudicated central radiology review	0.60 [0.44, 0.84]	0.0014	13.8	8.3
Central radiology review	0.64 [0.45, 0.90]	0.0054	13.8	8.3

[a] Hazard ratio is obtained from the unadjusted Cox model
[b] p-value is obtained from the one-sided log-rank test
[c] Baseline covariates are age (< 65 years vs. ≥ 65 years), gender (male vs. female), race (Caucasian vs. non-Caucasian), WHO performance status (0 vs. > 0), and prior use of somatostatin analog therapy
IPCW Inverse probability of censoring weights

Due to the multiple statistical issues associated with this trial, the TGA sought independent statistical advice. The evaluator considered that the IPCW analysis should not be used on its own as a basis for regulatory approval as it was exploratory in nature.

There was no significant difference in overall survival. Again, this was not unexpected as patients assigned to the placebo arm who experienced progression could cross over to receive everolimus. There were no significant differences in response rates and quality of life measures were not examined.

Study C2239 was an earlier Phase II single arm trial in patients with pancreatic NETs who had already failed chemotherapy. There were two strata in the study; Stratum 1 included subjects who were not receiving somatostatin treatment, and Stratum 2 included subjects who were receiving somatostatin treatment. The primary endpoint was ORR. As assessed by central radiology review, ORR was *9.6%* in Stratum 1 and *4.4%* in Stratum 2. The evaluator concluded that this study demonstrated some activity for everolimus in pancreatic NET.

Safety

In the three submitted studies, a total of 858 subjects received everolimus. Median duration of exposure was 44.96 weeks, with 337 subjects receiving treatment for a period > 48 weeks. Everolimus treatment was associated with an increase in the incidence of the following events (Table 28).

Table 28. Events with Increased incidence in Everolimus treated patients

	Study 2324 PNET	Study 2325 Carcinoid
Grade 3-4 AEs	59.8% versus 38.9%	74.0% versus 50.2%
Related Grade 3-4 AEs	45.1% versus 13.8%	45.1% versus 15.2%
Serious AEs	40.2% versus 24.6%	56.7% versus 34.6%
Related SAEs	21.6% versus 4.4%	19.1% versus 4.3%
Discontinuation due to AEs	19.1% versus 5.9%	28.4% versus 7.1%
Related discontinuation due to AEs	13.2% versus 2.0%	18.6% versus 3.3%

In Study 2324 PNET, there was an imbalance in the duration of exposure to everolimus or placebo (medians: 37.8 versus 16.1 weeks) and hence the incidence of adverse events might be expected to be higher in the everolimus arm in this trial. However, in Study 2325 Carcinoid, duration of exposure was comparable in the everolimus and placebo arms.

With respect to individual adverse events, everolimus treatment was associated with increased incidences of the following:

- Gastrointestinal toxicity: diarrhoea, stomatitis, nausea, vomiting, decreased appetite;
- Skin toxicity: rash, pruritus, dry skin;
- Respiratory toxicity: dyspnoea, cough;
- Haematological toxicity: anaemia, thrombocytopaenia;
- Metabolic effects: hyperglycaemia, hypokalaemia, hypercholesterolaemia, hypophosphataemia;
- Infections: nasopharyngitis, urinary tract and upper respiratory tract infections;
- Peripheral oedema;
- Fatigue;
- Headache;
- Pyrexia
- Hypertension

The pattern of adverse events observed in the two Phase III studies is consistent with that previously observed for the drug.

There was an excess of deaths due to adverse events in the everolimus group in both of the Phase III trials (7 versus 1 and 12 versus 5). Only one death was suspected to be related to everolimus – a case of acute respiratory distress secondary to sepsis.

Risk management plan

The RMP proposed by the sponsor was considered generally acceptable by the TGA's OPR. The evaluator considered that safety in patients aged >65 years and safety in patients with severe hepatic impairment should be added to the RMP as safety concerns requiring

ongoing monitoring. The Delegate proposed to require these changes to the RMP as a condition of approval.

Risk-benefit analysis

Delegate considerations

Overall risk-benefit

Study C2324 PNET demonstrated a clinically significant efficacy benefit in patients with pancreatic NETs. Median PFS was prolonged by approximately 6 months and the chance of being alive and progression-free at 12 months was increased from 15% to 45%. The prolongation of median PFS compared to placebo seen in this study was comparable to that seen with sunitinib, which was approved by the TGA for use in pancreatic NETs in 2011.

Study C2325 Carcinoid failed to demonstrate a statistically significant efficacy benefit in carcinoid tumours arising from any anatomical site. Although the additional IPCW analysis accounting for the effects of informative censoring suggested there may be a benefit in this patient group, the statistical evaluator considered this should not be used as a basis for regulatory approval as it was exploratory in nature.

In the two Phase III studies, toxicity was significant, with an extra 20% of patients experiencing Grade 3-4 AEs and extra 15-20% experiencing serious AEs or discontinuing treatment due to AEs. There was also a suggestion of an increase in the incidence of fatal AEs in both trials.

Overall the Delegate agreed with the clinical evaluator that a favourable risk-benefit balance can be concluded for the use of everolimus in patients with pancreatic NETs. Study C2325 Carcinoid raises some doubts regarding the efficacy of everolimus in the treatment of NETs originating at anatomical sites other than the pancreas. Given the substantial toxicity produced by the drug, a favourable risk-benefit balance for this patient group cannot be concluded. It is noted that both the FDA and the EMA have restricted approval to use in pancreatic NETs.

In its response to the evaluation reports the sponsor has provided an expert opinion from a group of six Australian oncologists involved in the treatment of patients with NETs. A letter from a patient support organisation (the Unicorn Foundation) was also provided.

The Delegate proposed several recommended changes to the PI; details of the proposed revisions are however beyond the scope of this AusPAR.

Delegate's conclusion and recommendation

The Delegate proposed to approve the application but restrict the indication to use in patients with pancreatic NETs. The advice of the Advisory Committee on Prescription medicines (ACPM) was requested.

Response from sponsor

Novartis welcomes the Delegate's proposal to approve the application and acknowledges the proposal to restrict the indication to pancreatic NETs. Novartis acknowledges that the statistical issues associated with the C2325 Carcinoid trial in patients with non-pancreatic NETs (arising from any anatomical site) as the reason the Delegate proposes to restrict the indication. There is a medical need though, for treatment options for non-pancreatic NETs patients. It is noted that written expert opinions from a group of Australian oncologists involved in the treatment of patients with NETs plus a letter from a patient support

organisation were included in the agenda papers presented to the ACPM. Novartis would welcome the advice of the ACPM in regards to the use of Afinitor for patients with non-pancreatic NETs.

The issues raised by the Delegate in the Delegates overview (DO) are addressed below. For ease of reference, the Delegate's comments are transcribed in italics.

Response to issues raised in the Delegate's overview

Overall risk-benefit

In the two Phase III studies, toxicity was significant, with an extra 20% of patients experiencing Grade 3-4 AEs and extra 15-20% experiencing serious AEs or discontinuing treatment due to AEs. There was also a suggestion of an increase in the incidence of fatal AEs in both trials.

Sponsor's comment:

In Study 2324 PNET, the number of deaths was similar for the two treatment arms (n = 51 in the everolimus arm and n = 50 in the placebo arm), more on-treatment deaths were reported in the everolimus arm (12 versus 4). Cases attributed to AEs were all complex and confounded by the natural history of the disease and concurrent morbidities, with only one of the deaths suspected to be drug related by the investigator.

Also from this study, the frequency of discontinuation attributable to AEs was more evident in the everolimus arm. The most commonly reported AEs leading to discontinuation of therapy was pneumonitis (2.9%), pyrexia (1.5%), elevated AST concentrations (1.0%), fatigue (1.0%), interstitial lung disease (1.0%), and pneumonia (1.0%). The most commonly reported AEs leading to discontinuations were pneumonitis, interstitial lung disease and fatigue. The incidence of these was ≥0.5%.

It is of note, however, that only one fatal AE was attributed to everolimus. The remaining fatal AEs on the everolimus arm were either due to NET disease or not attributed to everolimus. It should be noted that the cross-over design of the studies prevents a thorough assessment of safety in the placebo arm, as most of the patients were crossed over to everolimus within 28 days of progression.

Furthermore, in Study 2324 PNET safety should be interpreted taking into account the longer exposure in the everolimus arm (median 37.8 weeks) versus the placebo arm (median 16.1 weeks), this is clearly shown in the pooled dataset of Table 2-2 of the *Summary of Clinical Safety* addendum (90 day Safety Update), that presents adverse events adjusted by patients exposure.

Table 29. Adverse events adjusted by patients exposure.

Study C2324 PNET				
Category	Original data cut-off		Safety Update	
	Everolimus N = 204 Adjusted rate	Placebo N = 203 Adjusted rate	Everolimus N = 204 Adjusted rate	Placebo N = 203 Adjusted rate
Adverse event (AE)	126.3	200.8	115.9	188.8

Study C2324 PNET				
Suspected to be drug-related	122.0	153.1	111.3	144.9
Grade 3-4 AE	76.3	80.1	71.9	78.2
Suspected to be drug-related	57.5	28.4	53.1	27.7
Clinically notable AE	120.7	146.0	110.2	143.0
Suspected to be drug-related	115.7	86.2	105.6	83.9

The safety and tolerability profile of everolimus in NETs is consistent with prior experience in the oncology setting. The grading of most events is modest, typically Grade 1 or 2 in Study 2324 PNET and Study 2325 Carcinoid. These events have been identified as manageable.

Study C2325 Carcinoid raises some doubts regarding the efficacy of everolimus in the treatment of NETs originating in anatomical sites other than the pancreas. Given the substantial toxicity produced by the drug, a favourable risk-benefit balance for this patient group cannot be concluded.

Sponsor's comment:

Everolimus, in combination with depot octreotide, has provided benefit for this population, despite the study not meeting its primary endpoint. Progression-free survival as per local investigator assessment was below the threshold for statistical significance, and results from the independent adjudicated central assessment (IAC) supported this investigator analysis. Informative censoring proved to be a critical methodological challenge; secondary IPCW analyses correcting for this bias provide evidence for a treatment effect. Tumour shrinkage data and decreases in biomarkers related to tumour burden were consistent and supportive of the primary PFS endpoint.

The safety profile is acceptable and well characterised. The grading of most events was typically Grade 1 or 2, which are generally manageable and not associated with sequelae. Several of the more frequently reported observed AEs are likely to be related partially to the underlying disease or other comorbid conditions. Therefore, overall the results appear to be favourable compared with previous experience in this advanced pre-treated setting.

On treatment deaths were reported for 18 patients in the everolimus arm and 11 patients in the placebo arm. These cases were all complex and confounded by the natural history of the disease and concurrent comorbidities. None of these cases was suspected to be drug related by the study investigator. The frequency of discontinuation attributable to AEs was more evident in the everolimus arm. The most common AE leading to discontinuation were fatigue (2.3%), diarrhoea (1.9%), general physical health deterioration (1.9%), interstitial lung disease (1.9%), pneumonia (1.9%), dyspnoea (1.4%) and pneumonitis (1.4%).

The toxicity is consistent with everolimus in PNET, renal cell carcinoma (RCC) and TS complex-SEGA, which have been evaluated as tolerable. In terms of targeted therapies, it has one of the best tolerability profiles compared to the tyrosine kinase inhibitor class of

drugs. Everolimus therefore has a positive benefit-risk for patients with advanced carcinoid tumours. Its benefit is evident relative to depot octreotide where no other treatment options have been proven as clinically beneficial. This finding is further supported by the Clinical Oncological Society of Australia and the patient support organisation, the Unicorn Foundation.

Although the additional IPCW analysis accounting for the effects of informative censoring suggested there may be a benefit in this patient group [refer to Study C2325 Carcinoid], the statistical evaluator considered this should not be used as a basis for regulatory approval as it was exploratory in nature.

Sponsor's comment:

The IPCW analysis was pre specified in the protocol and was not exploratory in nature. This analysis provided evidence that the primary PFS endpoint as per independent central radiology review (IRC) was confounded by informative censoring. However, although the primary PFS endpoint as per independent central radiology review (IRC) was not statistically significant, results for the secondary PFS endpoint as per investigator assessment were below the threshold for statistical significance.

Revisions to the PI suggested by the TGA were also addressed in the sponsor's response.

Concluding remarks

Novartis welcomes the Delegate's recommendations to approve Afinitor for the indication: *For the treatment of progressive, unresectable or metastatic, well or moderately differentiated neuroendocrine tumours (NETs) of pancreatic origin.*

There remains a medical need for treatments for non-pancreatic NETs patients and Novartis welcomes the advice of the Committee in regards to use of Afinitor in the treatment on non-pancreatic NETs arising from any anatomical site.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered these products to have an overall positive benefit–risk profile for the following indication:

> *The treatment of progressive, unresectable or metastatic, well or moderately differentiated, neuroendocrine tumours (NETs) of pancreatic origin.*

The ACPM agreed with the Delegate regarding the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- a statement in the appropriate sections of the PI and CMI to accurately reflect the lack of efficacy in NETs with the exception of pancreatic origin.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Afinitor, containing everolimus, for the new indication:

For the treatment of progressive, unresectable or metastatic, well or moderately differentiated, neuroendocrine tumours (NETs) of pancreatic origin.

The full indications are now:

For the treatment of patients with advanced renal cell carcinoma after failure of treatment with sorafenib or sunitinib.

Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS) who require therapeutic intervention but are not candidates for curative surgical resection.

For the treatment of progressive, unresectable or metastatic, well or moderately differentiated, neuroendocrine tumours (NETs) of pancreatic origin.

Specific conditions applying to these therapeutic goods

- The implementation in Australia of the everolimus EU Safety RMP version 5 (18 May 2011) and Australian Risk Management Plan (RMP), version 5.0 (18 May 2011) included with the submission, and any subsequent revisions, as agreed with the TGA and its Office of Product Review.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

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Reference/Publication #