21 June 2012

EMA/CHMP/438808/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Afinitor

everolimus

Procedure No.: EMEA/H/C/001038/II/0020

Note

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

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CHMP Type II variation assessment report for Afinitor

Procedure No. EMEA/H/C/001038/II/0020

Marketing authorisation holder (MAH): Novartis Europharm Ltd.

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1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Ltd. submitted to the European Medicines Agency on 10 November 2011 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Afinitor	everolimus	See Annex A

The following variation was requested:

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

The MAH applied for the following indication: "Afinitor is indicated for the treatment of hormone receptor-positive advanced breast cancer, in combination with an aromatase inhibitor, in postmenopausal women previously treated with endocrine therapy." Changes to the SmPC are proposed for sections 4.1, 4.5, 4.8, 5.1 and 5.3 and the PL was proposed to be updated accordingly. In addition, some minor editorial changes to the SmPC were also proposed.

The requested variation proposed amendments to the SmPC, and Package Leaflet.

Rapporteur: Harald Enzmann

1.2. Steps taken for the assessment

Submission date:	10 November 2011
Start of procedure:	20 November 2011
Rapporteur's preliminary assessment report circulated on:	13 January 2012
Co-Rapporteur's preliminary assessment report circulated on:	13 January 2012
Request for supplementary information and extension of timetable adopted by the CHMP on:	16 February 2012
MAH's responses submitted to the CHMP on:	23 March 2012
Rapporteur and Co-Rapporteur's joint assessment report on the MAH's responses circulated on:	4 May 2012
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	24 May 2012
MAH's responses submitted to the CHMP on:	30 May 2012
Rapporteur and Co-Rapporteur's joint assessment report on the MAH's responses circulated on:	18 June 2012

CHMP opinion:	21 June 2012

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/105/2011 on the granting of a class waiver for all medicinal products for the treatment of breast carcinoma.

Scientific Advice

The MAH did not seek scientific advice for the proposed new indication at the CHMP.

2. Scientific discussion

2.1. Introduction

Breast cancer is the most common form of malignancy in women, accounting globally for 23% of all cancers in women and 14% of cancer deaths[1]. Of the estimated 12.7 million new cancer cases worldwide in 2008, 1.38 million were estimated to be new cases of breast cancer[1,2] . In Europe, the estimated incidence of breast cancer in 2008 was 424,800 while the estimated deaths related to breast cancer were 128,700.

A number of breast carcinomas are dependent for their proliferation on 17 beta-oestradiol (E2), which can be synthesized from androstenedione (Δ4A) through the action of aromatase, an enzyme of the cytochrome P450 superfamily. In premenopausal women, the expression of aromatase is found in the granulosa cells of ovarian follicles while in post-menopausal women, the expression of aromatase is in general derived from non-glandular tissue, such as subcutaneous fat[3]. The concentration of oestradiol decreases to levels of about 7pg/ml from a baseline of 110 pg/ml at menopause. In breast carcinoma tissue of post-menopausal women, the concentration of oestradiol is approximately 10 fold the concentration found in plasma[4] . Non-steroidal aromatase inhibitors (NSAIs; letrozole and anastrozole) are generally the treatment of choice for postmenopausal women with oestrogen-receptor (ER+) positive breast cancer[5,6,7,8]. Some patients do not respond to first-line endocrine therapy and patients who initially respond to treatment will eventually relapse. Following recurrence or progression on letrozole or anastrozole, the most commonly subsequent treatment includes exemestane and fulvestrant. In clinical practice, the use of chemotherapy is usually reserved for patients with high tumour burden or for patients that demonstrate an aggressive disease progression or symptomatic visceral disease.

The PI3K/Akt/mTOR pathway is activated in a broad range of cancers, including breast cancers. The p70 ribosomal S6 kinase (S6K), a substrate of mTORC1, (S6K1), directly phosphorylates the activation domain AF-1 of the ER, which leads to ligand-independent receptor activation[9,10]. The activation of the mTOR pathway is thought to be a driving factor for endocrine resistance in breast cancer. The evidence for this proposed mechanism of resistance is based on the finding that PI3K/Akt/mTOR pathway is constitutively activated in aromatase inhibitor (AI)-resistant and long-term oestrogen deprived breast cancer cells[11,12,13]. Coadministration of everolimus and AI in breast cancer cells was found to reverse resistance in cells that had become AI-resistant[14]. Afinitor (everolimus), a derivative of rapamycin, acts as an inhibitor of mTOR which regulates multiple downstream pathways from PI3K such as protein synthesis, proliferation (including angiogenesis) and cell survival.

Afinitor was granted a marketing authorisation in the European Union (EU) in 2009 for the treatment of patients with advanced renal cell carcinoma (RCC) whose disease has progressed on or after treatment

with vascular endothelial growth factor (VEGF)-targeted therapy. In August 2011 Afinitor was granted an extension of indication for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours (NET) of pancreatic origin in adults with progressive disease.

In this application, the Marketing Authorisation Holder (MAH) applied for the following extension of indication for Afinitor:

"Afinitor is indicated for the treatment of hormone receptor-positive advanced breast cancer, in combination with an aromatase inhibitor, in postmenopausal women previously treated with endocrine therapy."

The final indication approved by the CHMP is as follows:

"Afinitor is indicated for the treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor"

Consequently, the MAH proposed the update of sections 4.1, 4.5, 4.8, 5.1 and 5.3 and of the PL. Additional minor editorial changes to the SmPC were also proposed.

2.2. Quality aspects

No new data related to the pharmaceutical quality were submitted with this variation application, which is considered acceptable.

2.3. Non-clinical aspects

2.3.1. Introduction

The MAH provided a non-clinical overview containing bibliographical references based on published literature and non-clinical studies investigating the effect of everolimus on breast cancer models. The non-clinical pharmacodynamic studies submitted were not performed in accordance with GLP. The environmental toxicity studies were performed in accordance with GLP.

The MAH provided 14 new primary pharmacodynamic studies and an updated ERA to support the application of the new indication.

2.3.2. Pharmacology

Primary pharmacodynamic studies – everolimus in breast cancer models

In vitro models

Everolimus was shown to inhibit a panel of cell lines, including breast cancer cell lines (Report RD-2002-03223, Report RD-2006-02213). Sensitive cell lines to everolimus inhibitor activity had IC50 values <1µM. The results of the anti-proliferative *in vitro* studies are shown in Table 1.

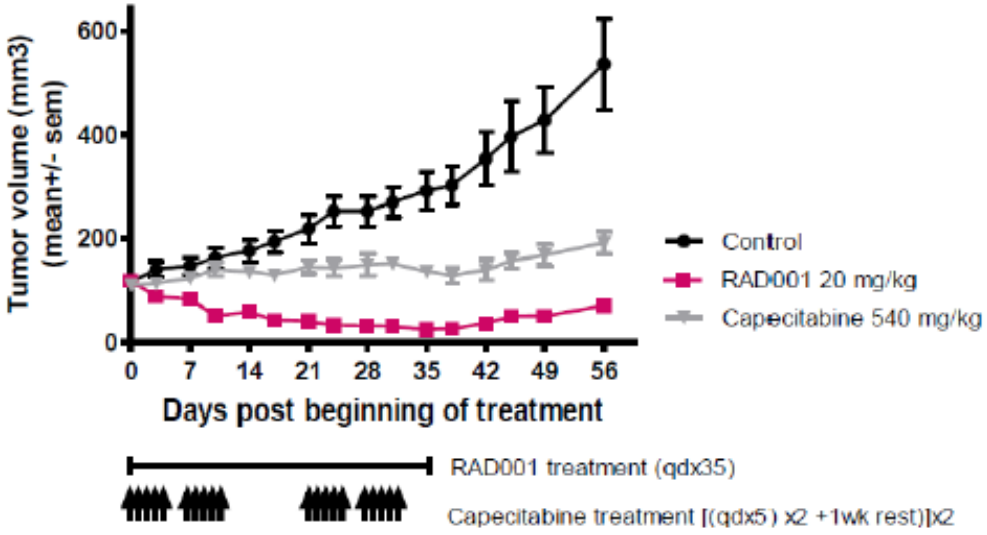
Table 1: Antiproliferative IC50 for RAD001 on human cell lines

Tumor origin	Cell line	IC50 (nM)	Tumor origin	Cell line	IC50 (nM)
Breast	BT549	0.7 ± 0.2 (3)	Lung	A549	2.4 (2)
	ZR-75-1	1.9 ± 1.1 (3)		NCI-H-460	44 ± 20 (3)
	MCF7	0.6 ± 0.1 (3)		NCI-H-1299	10.5 ± 3.1 (3)
	MDA-MB231	7.2 ± 4.1 (3)		NCI-H-596	5 ± 2 (4)
	HCC1395	1.2 ± 1.2 (3)		NCI-H-1650	>2500 (3)
	MDA-MB435	4.5 ± 3.2 (3)		NCI-H-1975	1.3 ± 0.5 (4)
	MDA-MB436	>2500 (3)		NCI-H-838	0.6 ± 0.3 (4)
	MDA-MB468	1.5 ± 0.7 (3)		NCI-H-1838	>2500 (3)
	SKBR3	0.7 ± 0.3 (4)		NCI-H-2122	>2500 (3)
	BT474	0.6 ± 0.1 (4)		NCI-H-226	>2500 (3)
Renal	786-O	0.4 (2)		NCI-H-522	>2500 (3)
	SKRC-01	0.5 ± 0.1 (3)		NCI-H-322M	>2500 (3)
	SKRC-52	0.4 ± 0.2 (3)		NCI-H-23	>2500 (3)
	A-498	2.8 ± 0.7 (4)	Glioblastoma	BS125II.2	3 ± 0.6 (3)
	769-P	0.2 ± 0.1 (4)		BS153	3.9 ± 1.2 (3)
	G402	0.3 ± 0.1 (3)		LN229	21 ± 6 (3)
	RCC4	1.4 ± 0.1 (3)		LN401	1.5 ± 0.3 (3)
	RPTEC	0.3 ± 0.1 (3)		LN428	327 ± 206 (3)
	Caki-1	>2500 (3)		LN751	24 ± 14 (4)
Prostate	DU-145	10.3 ± 2.2 (7)		U87	5.0 ± 0.6 (3)
	PC3M	149 ± 46 (6)	Colon	HCT15	65.2 ± 23 (3)
	LNCap	0.7 (2)		HCT116	4125 ±1853 (3)
Epidermoid	KB -31	1778 ± 800 (7)	Pituitary	GH3 (rat)	2.1 ± 1.8 (3)
	KB-8511	1489 ± 806 (4)	Melanoma	B16 (murine)	0.7 ± 0.2 (3)
			Fibrosarcoma	RIF-1 (murine)	2.6 ± 1.6 (3)

In vivo models

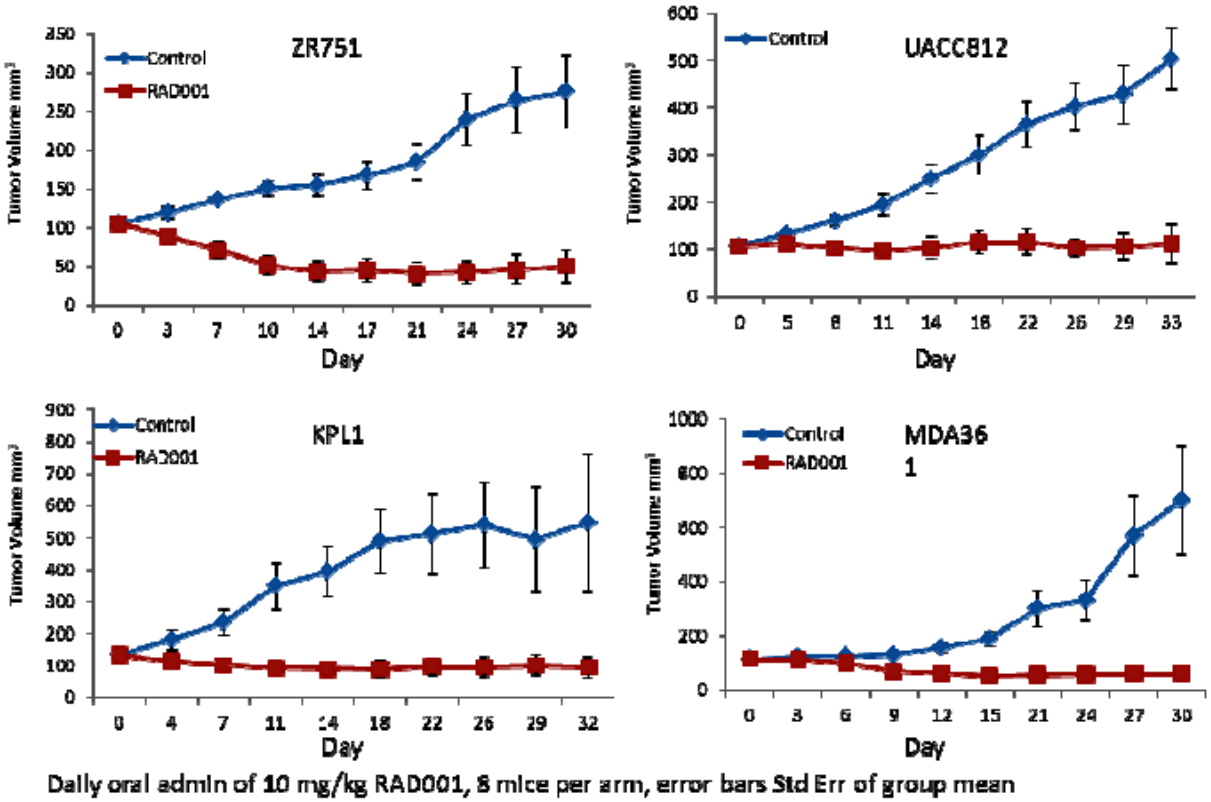
Everolimus was investigated in human breast cancer cell lines *in vivo*. The anti-tumour efficacy of everolimus was compared to other suppressors of cytokine signalling (cyclophosphamide, docorubicin, docetaxel, capecitabine) in a panel of 6 breast cancer xenograft models established after direct transplantation of patients' tumours into nude mice (Report RD-2011-50492). The tumour growth inhibition of the oestrogen-dependent breast cancer model HBCx-3 (XTS-181) had a mean tumour volume regression of -13.5% (Figure 1).

Figure 1: Tumour growth changes in the HBCx-3 breast xenograft model



The anti-proliferative effect of everolimus was evaluated *in vitro* using a panel of molecularly characterized cell lines for different gene mutations or amplifications. The cell lines were divided into three groups based on results of a growth inhibition by everolimus: sensitive (inhibition 80% or greater at 1 µM and an IC50 > 50 nM), intermediate, and resistant cell lines. The most sensitive cell lines were enriched for the ER+ and human epidermal growth factor receptor 2 (HER2) amplified subtypes. The effect of tumour growth inhibition of everolimus in oestrogen-dependent breast cancer models was further verified in four additional cell lines that were oestrogen receptor positive, namely ZR75-1 (ER+, PTENmut; intermediate), UACC812 (ER+, HER+; resistant), MDA361 (ER+, HER2+; resistant), KPL-1 (ER+, PTENwt; resistant) in a xenograft cancer model (Report RD-2011-50447). The results are shown in Figure 2.

Figure 2: Effect of everolimus on tumour volume



The tumour growth inhibition of everolimus was further tested in the MCF-7 human breast carcinoma nude mouse xenograft model (Study RD-2011-50270). Mice were treated orally with everolimus and compared to a pan-PI3K inhibitor, an inhibitor for PI3K/mTOR, and an inhibitor that specifically inhibits the PIK3CA gene product, the p110alpha isoform of the PI3K catalytic subunit. All tested drugs exhibited dose-dependent activities.

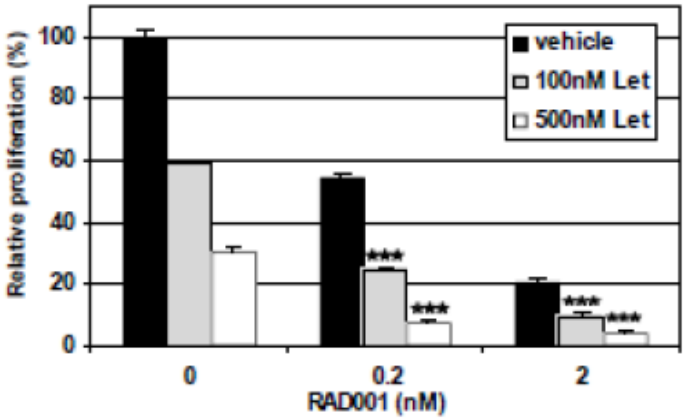
Primary pharmacodynamics studies – everolimus in combination with aromatase inhibitors

In vitro studies

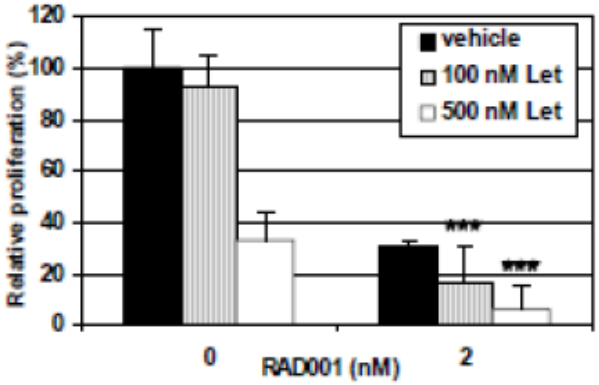
The effect of everolimus/letrozole combinations have been studied in several experiments, e.g. on the proliferation of aromatase-expressing MCF7/Aro cells (Report RD-2003-02908). The results of a proliferation assay are shown in Table 2.

Table 2: Combination effects of everolimus and letrozole

A



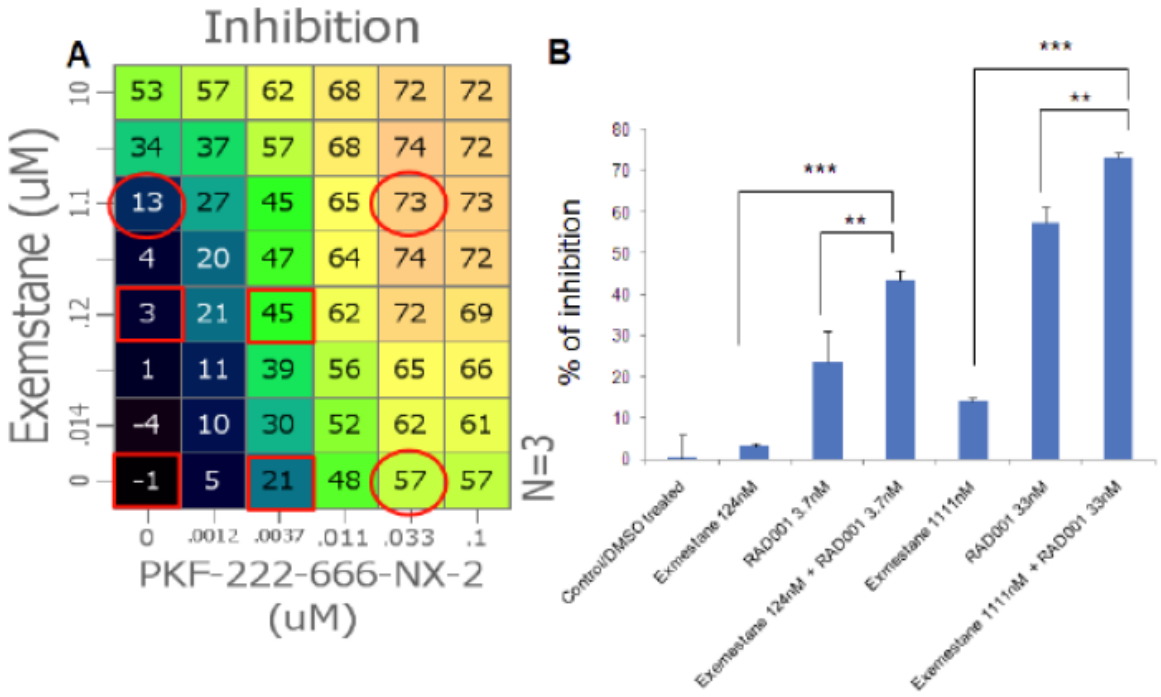
B



MCF7/Aro cells were SD for 3 days. Cells were seeded in 6-well plates and were SD for 2 additional days. Cells were stimulated with 10 nM Δ4A and treated with RAD001 and letrozole (Let) alone or in combination, every other day for 6 days. Cells were counted using a cell counter (A) or relative proliferation was assessed using the YOPRO DNA-binding fluorescent dye assay (B). Mean values (triplicates) +/- standard deviations (shown by error bars) are presented. ***: $p<0.001$; two-way ANOVA.

The effect of everolimus in combination with exemestane was studied *in vitro* in a breast carcinoma cell line that was oestrogen-dependent (Study RD-2011-50532). The data are shown in Figure 3.

Figure 3: Effect of the combination of everolimus with exemestane on Δ4A induced MCF7/Aro cell proliferation



MCF7/Aro cells were treated in 96-well format for 5 days with RAD001 and/or exemestane in the presence of Δ4A. (A) Cell viability was measured using the CellTiter-Glo assay and % inhibition data was displayed numerically as 6 X 8 dose grid. Each data point represents averaged data from 3 wells + standard deviation, and the color spectrum also represents the level of the inhibition. (B) Selected doses from the surface grid were also plotted as bar graphs. Mean values (3 replicas each) + standard deviations (shown by standard deviation bars) were presented. The statistical differences were evaluated using student t-test. (** p<0.01, *** p<0.001)

Ecotoxicity/environmental risk assessment

The MAH submitted an ERA report. A summary of the main results is shown in Table 3. The calculated log K_{ow} was 4.0. The predicted environmental concentration (PEC) based on a daily dose of 10 mg was 0.05 µg/L, which exceeds the trigger value of 0.01 µg/L. A base-data set was submitted for Phase II studies with the exception for the transformation in aquatic sediment systems (OECD 308) which was listed as on-going. Everolimus showed high chronic toxicity to aquatic organisms with growth of *Daphnia magna* being the most sensitive end-point. Everolimus showed low adsorption to sewage treatment plant sludge, and transfer to terrestrial compartments via spreading of sewage sludge was not expected. All other Phase II Tier A PEC/PNEC quotients were below the trigger for Phase II Tier B assessment.

Table 3: Summary of main study results

Substance Everolimus			
CAS-number (if available):918639-08-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	4.0	Potential PBT N
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default	0.05	µg/L	> 0.01 threshold

					Y
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{OC} (sludge) = 1654-3294 K_{OC} (soil) = 50197-2348392			
Ready Biodegradability Test	OECD 301 F	2%			not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	River and pond system, 20°C: $DT_{50, water}$ = 0.29 resp. 0.35 d $DT_{50, sediment}$ = 26.9 resp. 24.4 d $DT_{50, whole\ system}$ =3.1 resp. 2.0 d % shifting to sediment =yes: 25.6 resp. 17.7 % (d 14)			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Daphnia sp. Reproduction Test	OECD 211	NOEC 21d	0.014	µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC 30d	2.1	µg/L	

Discussion on non-clinical aspects

The pharmacology of everolimus was investigated in *in vitro* and *in vivo* breast cancer models. Everolimus was shown to exhibit anti-proliferative activity and anti-tumour activity in breast cancer models. In oestrogen-dependent (ER+) and human epidermal growth factor receptor 2 (HER2)-amplified breast cancer cell lines, administration of everolimus alone displayed anti-proliferative activity. Administration of everolimus as a single agent also showed an anti-tumour effect in breast cancer xenograft models. In an *in vitro* oestrogen-dependent breast cancer model, everolimus in combination with exemestane showed an additive/synergistic inhibition of androstenedione (Δ4A) driven MCF7/Aro cell proliferation compared to everolimus as single agent. The non-clinical data provided in the application were considered acceptable to support the proposed new indication in breast cancer.

The lack of studies on safety pharmacology, pharmacokinetic, toxicity, genotoxicity, carcinogenicity and reproduction toxicity was considered acceptable as the non-clinical data for these studies for everolimus and exemestane are well known in the oncology setting.

Everolimus was considered to pose no significant risk to surface waters, sewage treatment plants and groundwater. However, some pending issues related to the environmental risk assessment will be addressed as noted below.

Conclusion on non-clinical aspects

The non-clinical studies submitted were considered adequate and acceptable for the assessment of non-clinical aspects for the product everolimus in the new clinical indication.

The CHMP recommends the following measures necessary to address the non-clinical issues:

1. The applicant is asked to submit information on the chemical structure of transformation product M4 cited in the transformation study with everolimus in aquatic sediment systems (OECD 308), by 31st May 2013
2. The applicant is asked to provide a fully updated ERA addressing all outstanding concerns and including all three remaining studies, i.e. the study with the sediment-dwelling larvae of the midge species *Chironomus riparius* (OECD 218), the additional algae study (OECD 201) and the planned fish bioconcentration study (OECD 305) by 31st May 2013.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

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

- Tabular overview of clinical studies

Study	Description	Role
CRAD001Y2301	This was a multi-center, double-blind, randomized, placebo-controlled, international phase III study evaluating treatment with everolimus (10 mg daily) versus placebo in combination with exemestane (25 mg daily) in postmenopausal women with locally advanced or metastatic ER positive breast cancer refractory to non steroidal aromatase inhibitors.	Predose and two-hour post-dose concentrations of everolimus and exemestane at Week 4 and estradiol concentrations at baseline and at Week 4 in patients with estrogen positive advanced breast cancer
CRAD001C2222 update	This was a double-blind, placebo-controlled, randomized, multi-center, two-arm, Phase 2 study. Patients with newly diagnosed, previously untreated localized hormone receptor positive breast cancer who have consented to participate in the study and have been shown to be eligible after screening, will be randomized to receive daily treatment with either letrozole 2.5 mg + placebo or letrozole 2.5 mg + RAD001 10 mg for four months prior to undergoing breast-conserving surgery or mastectomy.	Predose concentrations of everolimus and letrozole and the effects of everolimus on predose concentration of letrozole

2.4.2. Pharmacokinetics

To support the indication of Afinitor for the oestrogen-receptor positive (ER+) advanced breast cancer, clinical pharmacology data from a pivotal clinical research study (Study Y2301) and an updated report of the Phase II study C2222 (Study C2222 update) were included in the submission.

Special populations – Metastatic Breast Cancer patients

The CSR for Study C2222 was included in the original submission for the RCC indication. This was a phase 2 double-blind, placebo-controlled, multi-center study in postmenopausal women patients with ER+ early breast cancer. Patients were randomised to receive daily administration of either everolimus 10 mg + letrozole 2.5 mg or placebo + letrozole 2.5 mg for 4 months prior to undergoing breast conserving surgery or mastectomy. The original report included a total of 270 patients. The updated report was based on 251 patients and summarized the results of the end of Stage I analysis, excluding the data for 19 patients enrolled at site 066 due to GCP-related findings at this specific center. These patients were excluded because the site was not able to provide adequate documentation showing that the patients recruited had met the study entry criteria.

Trough blood levels

Pre-dose (Cmin) and 2-hour post-dose (C2h) blood samples for concentration determination of everolimus in blood and exemestane in plasma were collected in up to 88 patients at steady states at Visit 4 in study Y2301. Blood samples for concentration determination of oestradiol were also collected in these patients at baseline and at Visit 4 to evaluate the indirect effect of coadministration of everolimus on the oestradiol level.

Everolimus is rapidly absorbed after oral administration, with a median time to peak blood levels (Tmax) of 1-2 hours post dose. Tmax of exemestane in women with breast cancer was 1.2 hours compared to 2.9 hours in healthy women.

The mean everolimus C_{min} at steady-state was 16.0 ± 9.4 ng/mL (Table 4). The mean C2h of 46.5 ± 18.0 ng/mL observed in this study was within the range of Cmax means observed in previous everolimus studies with the everolimus 10-mg daily dose [59.7 ± 16.9 ng/mL (amended Study C2102 CP report), 76.7 ± 39.3 ng/mL (Study C2240), 56.3 ± 11.8 ng/mL (Study C2324), and 74.8 ± 33.6 ng/mL (Study C2325)].

Table 4: Everolimus blood concentrations [ng/ml] at week 4 – Study Y2301

	Everolimus plus exemestane
Pre-dose (C_{min})	
N	22
Mean ± sd (CV%)	16.0 ± 9.4 (58.3%)
Geometric mean (Geometric CV%)	14.0 (55.3%)
Median (Range)	12.2 (5.7 - 38.6)
2 hours post administration (C_{2h})	
N	24
Mean ± sd (CV%)	46.5 ± 18.0 (38.6%)
Geometric mean (Geometric CV%)	42.5 (50.4%)
Median (Range)	44.0 (8.4 - 79.2)

Everolimus trough concentrations were evaluated in Study C2222. The results are shown in Table 5. The trough concentrations varied from a mean of 25.2 ng/mL at Visit 3 to 9.3 ng/mL at Visit 8.

Table 5: Everolimus trough concentrations – Study C2222

Trough concentration (ng/mL)	Visit 3 (Day 15) N=35	Visit 4 (Month 1) N=59	Visit 8 (EOS) N=40
Mean ± SD	25.2 ± 26.35	13.0 ± 11.73	9.3 ± 11.22
Median (range)	16.0 (0.0-118)	11.8 (0.0-62.0)	7.1 (0.0-60.4)
Geometric mean (CV %)	18 (112)	12 (132)	10 (116)
25^{th} – 75^{th} percentile	10.5-30.2	0.6-18.0	0.0-14.7

Ethnicity

The summary statistics of everolimus and exemestane Cmin and 2-hour post dose concentration (C2h) in postmenopausal women with oestrogen receptor positive breast cancer receiving daily administration of 10 mg everolimus and 25 mg exemestane in Japanese and non-Japanese patients is shown in Tables 6 and 7, respectively.

Table 6: Everolimus blood concentrations in Japanese and non-Japanese patients (ng/ml) at Week 4, at combination with exemestane – Study Y2301

	Japanese	Non-Japanese
Pre-dose (C_{min})		
N	8	14
Mean ± sd (CV%)	15.7 ± 5.6 (35.7%)	16.3 ± 11.2 (68.6%)
Geometric mean (Geometric CV%)	14.8 (38.3%)	13.6 (65.2%)
Median (Range)	15.9 (8.6 – 25.3)	10.5 (5.7 – 38.6)
2 hours post administration (C_{2h})		
N	7	17
Mean ± sd (CV%)	55.7 ± 15.4 (27.6%)	42.7 ± 17.9 (42.0%)
Geometric mean (Geometric CV%)	53.7 (31.3%)	38.6 (54.1%)
Median (Range)	56.6 (30.4 – 74.7)	37.2 (8.4 – 79.2)

Table 7: Exemestane plasma concentrations in Japanese and non-Japanese patients (ng/ml) at Week 4 – Study Y2301

	Japanese patients		Non-Japanese patients	
	Everolimus plus exemestane	Placebo plus exemestane	Everolimus plus exemestane	Placebo plus exemestane
Pre-dose (C_{min})				
n	11	6	23	16
Mean ± sd (CV%)	0.59 ± 0.24 (40.6%)	0.35 ± 0.16 (45.3%)	0.65 ± 0.56 (85.7%)	0.46 ± 0.43 (92.8%)
Geometric mean (Geometric CV%)	0.55 (43.2%)	0.32 (47.9%)	0.53 (64.5%)	0.39 (79.3%)
Median (Range)	0.54 (0.3 – 1.0)	0.34 (0.2 – 0.6)	0.47 (0.2 – 3.0)	0.37 (0.0 – 1.9)
Geometric mean ratio [90% CI] [a]	1.68 [1.15, 2.46]		1.37 [0.96, 1.95]	
2 hours post administration (C_{2h})				
n	11	6	28	16
Mean ± sd (CV%)	21.7 ± 10.6 (49.1%)	11.1 ± 8.6 (77.5%)	23.7 ± 22.6 (95.0%)	14.1 ± 13.1 (92.5%)
Geometric mean (Geometric CV%)	19.3 (56.5%)	6.64 (254%)	15.9 (133%)	11.5 (82.8%)
Median (Range)	21.8 (8.1 – 44.2)	10.3 (0.5 – 22.6)	14.7 (0.5 – 96.8)	9.80 (0.0 – 50.8)
Geometric mean ratio [90% CI] [a]	2.9 [1.28, 6.60]		1.38 [0.84, 2.27]	

[a] Geometric mean ratio of exemestane with everolimus to those without everolimus is calculated using an ANOVA model with treatment as a fixed effect on log-transformed concentration values.

Pharmacokinetic interaction studies

Everolimus is mainly metabolised by the cytochrome 3A4 (CYP3A4) isoenzyme in the liver and to some extent in the intestinal wall and exemestane is metabolised by CYP3A4 and aldoketoreductases. Thus, the effect of everolimus on the metabolism of examestane was investigated in Study Y2301. Average exemestane Cmin and C2h were 45% and 71% higher, respectively, when co-administered with everolimus (Table 8).

Table 8: Exemestane plasma concentrations [ng/mL] at week 4 – Y2301

	Everolimus plus exemestane	Placebo plus exemestane
Pre-dose (C_{min})		
N	34	22
Mean ± sd (CV%)	0.63 ± 0.47 (75.2%)	0.43 ± 0.38 (86.6)
Geometric mean(Geometric CV%)	0.54 (57.3%)	0.37 (70.1%)
Median (Range)	0.49 (0.2 - 3.0)	0.35 (0.0 - 1.9)
Geometric mean ratio [90% CI] [a]	1.45 [1.11, 1.90]	
2 hours post administration (C_{2h})		
N	39	22
Mean ± sd (CV%)	23.2 ± 19.8 (85.5%)	13.3 ± 11.9 (89.4%)
Geometric mean (Geometric CV%)	16.8 (111%)	9.83 (124%)
Median (Range)	15.2 (0.5 - 96.8)	10.3 (0.0 - 50.8)
Geometric mean ratio [90% CI] [a]	1.71 [1.12, 2.59]	

[a] Geometric mean ratio of exemestane with everolimus to those without everolimus is calculated using an ANOVA model with treatment as a fixed effect on log-transformed concentration values.

2.4.3. Pharmacodynamics

Mechanism of action

No studies were submitted addressing the mechanism of action in breast cancer.

Primary and Secondary pharmacology

Exposure-efficacy relationship

According to the applicant, in the absence of sufficient concentration data to perform exposure-response analyses, the effect of everolimus exposure on tumour regression could not be directly ascertained in study Y2301. An analysis was performed to assess the potential impact of dose reductions and interruptions of everolimus by exploring the antitumour activity of patients who received time-averaged doses of <7.5 mg and those who received ≥7.5 mg.

These two time-averaged dose groups were selected to represent and compare the efficacy response in patients with a longer duration of dose reduction versus those with an occasional dose reduction/interruption. Patients in the everolimus plus exemestane arm with time-averaged dose to event of ≥ 7.5 mg had a 24.9% best percentage reduction in target lesion in comparison to a 17.4% reduction for patients with a time-averaged dose < 7.5 mg. Results of the Cox proportional hazard model showed that, in comparison to the placebo plus exemestane arm, patients in the everolimus plus exemestane arm with a time-averaged everolimus dose of < 7.5 mg/day had a PFS HR of 0.37 (95% CI: 0.27, 0.51) and patients with a time-averaged everolimus dose ≥ 7.5 mg/day had a PFS HR of 0.46 (95% CI: 0.37, 0.58).

Table 9: Analysis of PFS based on investigator using Cox Proportional Hazard model by time-average dose of everolimus (FAS) Cut off date: 11 February 2011 - Study Y2301

	>= 7.5 mg/day N=335		< 7.5 mg/day N=150		Placebo N=239		Hazard ratio [95% CI]	Hazard ratio [95% CI]
	No events (%)	No Censored (%)	No events (%)	No Censored (%)	No events (%)	No Censored (%)	>=7.5 mg/day vs. Placebo	< 7.5 mg/day vs. Placebo
Stratified Cox's PH Model	146 (43.6)	189 (56.4)	56 (37.3)	94 (62.7)	157 (65.7)	82 (34.3)	0.46 [0.37,0.58]	0.37 [0.27,0.51]

Oestradiol exposure

Oestradiol concentrations were measured in the study as a biomarker for the activity of exemestane. The results are presented in Table 10.

Table 10: Oestradiol plasma concentrations [ng/ml] at baseline and at week 4 – Study Y2301

	Everolimus plus exemestane	Placebo plus exemestane
At Baseline		
N	41	14
Mean ± sd (CV%)	5.62 ± 3.34 (59.4%)	4.09 ± 1.79 (43.8%)
Geometric mean (Geometric CV%)	4.84 (58.6%)	3.78 (42.3%)
Median (Range)	4.78 (2.1 - 15.5)	3.93 (2.0 - 8.4)
At Week 4		
N	38	15
Mean ± sd (CV%)	3.50 ± 2.55 (72.9%)	5.17 ± 6.92 (134%)
Geometric mean (Geometric CV%)	3.07 (46.5%)	3.43 (90.2%)
Median (Range)	2.71 (2.0 - 15.0)	2.40 (2.1 - 27.2)
Change from baseline at Week 4		
N	27	8
Mean ± sd (CV%)	-2.34 ± 2.40 (-103%)	1.72 ± 9.24 (538%)
Median (Range)	-2.18 (-8.1 - 0.9)	-0.49 (-5.9 - 23.4)

2.4.4. Discussion on clinical pharmacology

Investigation of the effect of exemestane on everolimus plasma concentrations appeared to show no significant effects on the exposure of everolimus as the mean everolimus Cmin or C2h observed in Study Y2301 were consistent with corresponding values observed in previous trials with everolimus 10-mg daily dose. Everolimus, on the other hand, was shown to increase plasma concentrations of exemestane by 45-71%. It is considered that the increase in exemestane plasma concentrations will not have an impact on the safety and efficacy. A new paragraph reflecting the findings was introduced in section 4.5 of the SmPC.

The observed differences in tumour regression data in patients who received time-averaged doses of < 7.5 mg and those who received ≥ 7.5 mg were small and were not considered to be of clinical significance. Thus, the effective dose modification guideline implemented in the study protocol to manage adverse reactions did not compromise the efficacy data.

There was no statistical difference between everolimus Cmin and the change in baseline oestradiol concentration from baseline to week 4. In addition, no major reducing effect of exemestane on estradiol levels was observed. These findings may reflect the fact that estradiol levels had already been suppressed by the last prior therapy which was a NSAI in 74% of study patients and 64% of patients with PK sampling and no further decrease in estradiaol could be measured.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology data from studies Y2301 and updated report for study C2222 submitted by the applicant were adequate for the assessment of everolimus plus examestane pharmacology in the proposed indication. No major effect of exemestane on everolimus exposure is expected. Everolimus was shown to increase plasma concentrations of exemestane by 45-71%. Thus the section 4.5 of the SmPC has been updated as follows:

"Co-administration of everolimus and exemestane increased exemestane Cmin and C2h by 45% and 64%, respectively. However, the corresponding oestradiol levels at steady state (4 weeks) were not different between the two treatment arms. No increase in adverse events related to exemestane was observed in patients with hormone receptor-positive advanced breast cancer receiving the combination. The increase in exemestane levels is unlikely to have an impact on efficacy or safety."

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

- The MAH should commit to further investigate exposure-response relationships for PFS and OS in future studies, with a due date of March 31st 2015.

2.5. Clinical efficacy

2.5.1. Dose response study

No dose response study was submitted.

The selection of the 10-mg continuous daily dose for everolimus was based on a pharmacodynamic model[15] which was supported by results from a clinical pharmacodynamic study in patients with solid tumours[16] and an investigator-initiated, randomised Phase-II study[17] where results showed that the 10-mg daily dose was more efficacious and produced a more sustained suppression of mTOR activity than weekly dosing.

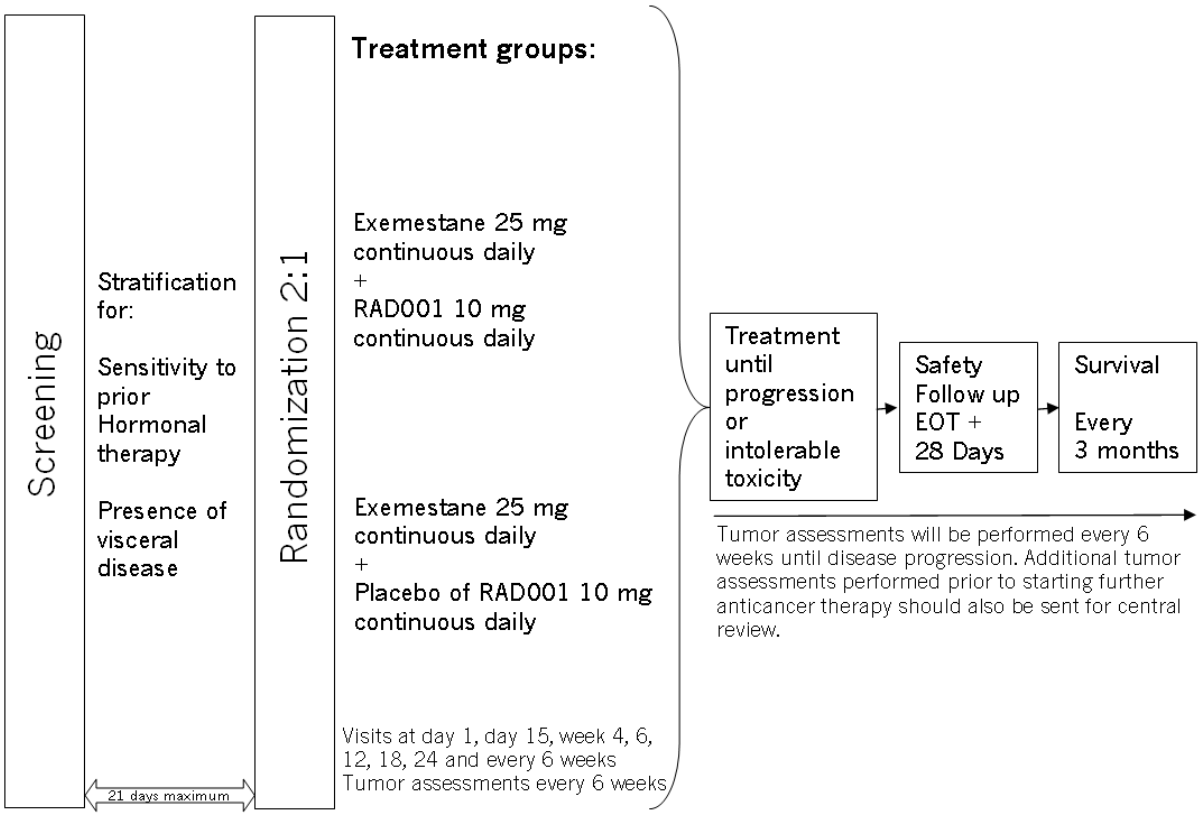
Additionally, the 10-mg daily dose was favoured over a 5-mg dose in a Phase-I study combining everolimus with letrozole in patients with advanced breast cancer[18]. Further supportive evidence was obtained from a 270-patient, randomised Phase-II trial comparing combination therapy with letrozole and everolimus 10 mg daily versus letrozole and placebo as neoadjuvant treatment of 16 weeks duration in postmenopausal women with early breast cancer (Study C2222). Results demonstrated that the response rate by clinical palpation for patients receiving letrozole plus everolimus was higher than that for letrozole plus placebo (68.1% versus 59.1%, respectively)[19].

2.5.2. Main study

CRAD001Y2301: A randomised double-blind, placebo-controlled study of everolimus in combination with exemestane in the treatment of postmenopausal women with oestrogen receptor positive locally advanced or metastatic breast cancer who are refractory to letrozole or anastrozole.

Methods

An overview of the study design is shown below:



Study Participants

Main inclusion criteria

- Adult women with metastatic or locally advanced breast cancer not amenable to curative treatment by surgery or radiotherapy
- Histological or cytological confirmation of ER-positive breast cancer
- Postmenopausal women
- Disease refractory to NSAIs defined as:
    - Recurrence while on or within 12 months of the end of adjuvant treatment with letrozole or anastrozole ***or***
    - Progression while on or within 1 month of the end of letrozole or anastrozole treatment for locally advanced or metastatic breast cancer
- Radiological or objective evidence of recurrence or progression on or after the last systemic therapy prior to randomisation
- Patients must have:
    - At least one lesion that can be accurately measured in at least one dimension ≥ 20 mm with conventional imaging techniques or ≥ 10 mm with spiral computed tomography (CT) or magnetic resonance imaging (MRI) ***or***
    - Bone lesions: lytic or mixed (lytic + sclerotic) in the absence of measurable disease as defined above
    - Adequate bone marrow, liver and liver function (defined in the protocol).

- Fasting serum cholesterol ≤ 300 mg/dL or 7.75 mmol/L and fasting triglycerides ≤ 2.5 ×ULN (on or off statin therapy)
- ECOG performance status ≤ 2.

Key Exclusion Criteria

- HER2-overexpression
- Patients who received ≥ 1 line of chemotherapy for advanced breast cancer
- Previous treatment with exemestane or mTOR inhibitors
- History of CNS metastases
- Patients receiving concomitant immunosuppressive agents (defined)
- Bilateral diffuse lymphangitic carcinomatosis
- Patients with a known history of human immunodeficiency virus (HIV) seropositivity
- Active bleeding diathesis (defined)
- Any severe and/or uncontrolled medical conditions (exemplified)
- Active skin, mucosa, ocular, or gastrointestinal disorders of grade > 1
- Significant symptomatic deterioration of lung function
- Patients being treated with drugs recognized as being strong inhibitors or inducers of the isoenzyme CYP3A

Treatments

Patients in the everolimus and exemestane treatment arm were administered in accordance with a 10-mg oral daily dosing regimen (two 5-mg tablets) in conjunction with exemestane 25 mg orally daily. The placebo group received matching placebo in conjunction with exemestane 25 mg orally daily.

Duration of both treatments was not limited. Treatment should continue until objective tumour progression was determined by the local radiologist (using RECIST), unacceptable toxicity, death, or discontinuation from the study for any other reason.

Objectives

The primary objective was to compare the combination treatment of everolimus and exemestane to exemestane alone with respect to progression-free survival (PFS) in postmenopausal women with oestrogen-receptor (ER)-positive breast cancer that is refractory to non-steroidal aromatase inhibitors (NSAIs).

The main secondary objective was to compare overall survival (OS) between the two treatment arms. Other secondary objectives were:

- to evaluate the two treatment arms with respect to
  - overall response rate (ORR),
  - time to deterioration of Eastern Cooperative Group performance status (ECOG PS),

- safety,
- change in quality-of-life (QoL) scores over time,
- clinical benefit rate (CBR)

- to summarise time to response and duration of response in the two treatment arms;
- to characterise in a subgroup of patients the pharmacokinetics (PK) of everolimus (Cmin, C2h) when administered in combination with exemestane;
- to compare the two treatment arms with respect to pre-dose concentration (Cmin) and concentration at 2 hours post-dose (C2h) of exemestane and to compare in a subgroup of patients the two treatment arms with respect to oestradiol (E2) changes from baseline.

The trial included a biomarker component as an exploratory objective, which included:

- Bone turnover: BSAP, P1NP, and CTX (reported in this submission)
- Angiogenesis: vascular endothelial growth factor and placental growth factor
- Immunohistochemistry: phosphatase and tensin homologue (PTEN), Cyclin D1, Ki-67, and p53

Outcomes/endpoints

Primary Endpoint

The primary endpoint was progression free survival (PFS) as assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 based on local (investigator) radiology review. PFS was defined as the time from the date of randomisation to the date of the first documented progression or death due to any cause. If a patient has not had an event, PFS was to be censored at the date of last adequate tumour assessment.

Secondary Endpoints

The main secondary endpoint was overall survival. OS was defined as the time from date of randomisation to the date of death due to any cause. If a patient was not known to have died, survival was to be censored at the last date of contact.

Other secondary endpoints were clinical benefit rate (CBR), overall response rate (ORR), time to overall response, and duration of overall response, time to deterioration of Eastern Cooperative Group performance status (ECOG PS) and Quality of life (QoL). Clinical benefit rate (CBR) was defined as the proportion of patients whose best overall response was either complete response (CR), a partial response (PR) or stable disease lasting for at least 24 weeks. ORR was defined as the proportion of patients whose best overall response is either CR or PR according to RECIST. Time to overall response (CR or PR) was the time between date of randomisation and first documented response (CR or PR) according to RECIST. Duration of overall response (DoR) applies only to patients whose best overall response was CR or PR. The start date is the date of first documented response (CR or PR) and the end date is the date of event defined as first documented progression of disease or death due to underlying cancer.

ECOG PS categories were defined according to the Table 11.

Table 11: ECOG Performance Status Scale

Score	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Safety was to be assessed by the CTCAE, version 3.0.

Incidence of adverse events, serious adverse events, changes from baseline in vital signs and laboratory results were to be reported.

The EORTC QLQ-C30 questionnaire, along with breast cancer patients' specific module (BR23) was used to collect QoL data. The EORTC scoring manual was be used to transform the raw scores into the domain scores (global heath, functional scales, symptom scales/items).

Sample size

For the sample size it was estimated that the median duration of PFS in the control group (placebo plus exemestane) would be 3.7 months[20] and combination treatment with everolimus and exemestane would result in a 26% reduction in the hazard rate (corresponding to a 35% increase in the median PFS to 5 months). A total of 528 PFS events were required to detect a HR of 0.74 with 90% power using a log-rank test and a 2-look Lan-DeMets group sequential design with an O'Brien-Fleming type boundary at a one-sided cumulative 2.5% level of significance. Assuming recruitment over an 18-month period and that 10% of the patients would be lost to follow-up or would withdraw consent, and a 2:1 randomisation ratio in favour of the combination arm, a total of 705 patients were to be randomised.

Randomisation

Patients were randomised in a 2:1 ratio to receive treatment with either everolimus plus exemestane or placebo plus exemestane.

Based on the expectation that patients previously sensitive to hormonal therapy will respond better to exemestane treatment, while patients with visceral disease will progress more rapidly, randomisation was stratified by:

- Documented sensitivity to prior hormonal therapy (yes versus no)
- Presence of visceral metastasis (yes versus no)

Sensitivity to prior hormonal therapy was defined as either:

- Documented clinical benefit (CR, PR, SD ≥ 24 weeks) to at least one prior hormonal therapy in the advanced setting, or
- ≥ 24 months of adjuvant hormonal therapy prior to recurrence

Blinding (masking)

The study was a double blind study. Patients were assigned to each treatment arm by centralised allocation (i.e., interactive web response system [IWRS]/interactive voice response system [IVRS].

Statistical methods

An interim analysis was to be performed after observing 317 (60%) of the total PFS events as per local assessment. The PFS survival distribution for each treatment group was estimated using Kaplan-Meier methodology. The primary efficacy analysis was the comparison of the survival distributions of two treatment groups using a stratified log-rank test at an overall one-sided 0.025 level of significance (strata information obtained through IXRS used for randomisation). The hazard ratio (HR) for the risk reduction in PFS, along with the two-sided 95% confidence interval (CI), was estimated from a stratified Cox proportional hazards model that accounted for the stratification scheme used at the time of randomisation.

OS was to be statistically evaluated and interpreted only if PFS was significantly different between treatment groups. A hierarchical testing strategy was to be used to control the overall type-I error rate. Up to three OS analyses were planned: these were to be at the time of the interim analysis for PFS, after observing 173 deaths, and after 392 deaths. The type-I error rate was maintained by using an α-spending function described by Lan and DeMets (1983) which approximates O'Brien and Fleming (1979)-type stopping boundaries. Results of the OS interim analyses were not to be disclosed by the IDMC unless found to be statistically significant.

The distribution function of OS was to be estimated using Kaplan-Meier methodology. The two treatment groups were to be compared using a stratified log-rank test at an overall one-sided 2.5% level of significance. A stratified Cox regression was to be used to estimate the OS hazard ratio and the associated 95% CI.

Sensitivity analyses conducted included repeating the primary PFS analysis using different censoring rules and using an unstratified log-rank test to compare the two treatment groups.

Overall response rate (ORR), defined as the proportion of patients with best overall response of either CR or PR, and clinical benefit rate (CBR), defined as the proportion of patients with best overall response of CR, PR, or SD ≥ 24 weeks, were summarised along with the exact 95% CIs calculated using the method described in Clopper and Pearson (1934)[21]. A stratified Cochran-Mantel-Haenszel (CMH) test was used to compare the two treatment groups with respect to ORR and CBR at the one-sided 2.5% level of significance using the same stratification information that was used for randomisation. Response was based on RECIST 1.0. These two endpoints were assessed both as per investigator and independent central review.

QoL scores were analyzed over time using the EORTC QLQ-C30 and breast cancer-specific BR23 questionnaires. Changes from baseline in the sub-scale scores at the time of each assessment were summarised.

Results

Participant flow

Table 12: Patient disposition by treatment (FAS)- Study Y2301

Disposition Reason	Everolimus plus exemestane N=485 n (%)		Placebo plus exemestane N=239 n (%)	
Randomized	**485**	**(100.0)**	**239**	**(100.0)**
Ongoing [a]	**227**	**(46.8)**	**69**	**(28.9)**
Discontinued	**258**	**(53.2)**	**170**	**(71.1)**
Reason for discontinuation [b]				
Disease progression	181	(37.3)	157	(65.7)
Patient withdrew consent	33 [c]	(6.8)	5	(2.1)
Adverse event(s)	32	(6.6)	6	(2.5)
Death	7	(1.4)	1	(0.4)
Protocol deviation	3	(0.6)	0	
New cancer therapy	2	(0.4)	0	
Abnormal laboratory value(s)	0		1	(0.4)

[a] Patients ongoing on study treatment (on at least one study drug) at the time of the data cut-off
[b] Of both treatments or of the second drug if one agent had previously been discontinued
[c] Verbatim reasons for treatment discontinuation included potential adverse effects in 10 patients

Recruitment

The first patient visit was 3rd June 2009, and the study was still ongoing as of the 24th June 2012. Patients were recruited in 196 centres in 24 countries worldwide (Australia, Austria, Belgium, brazil, Canada, Czech republic, Egypt, France, Germany, Hong Kong, Hungary, Italy, japan, Republic of Korea, the Netherlands, New Zealand, Norway, Poland, Spain, Sweden, Thailand, turkey, United Kingdom, USA.

Conduct of the study

Amendment 1 to Clinical Trial Protocol CRAD001Y2301 as of 17 February 2010 clarified that all primary (and secondary) endpoints based on radiological (and photographical when applicable) assessments of tumour burden will be derived using the local (treating centre's) radiologist's/investigator's assessment. The original protocol as of 3 March 2009 stated at this place that efficacy will be assessed via a blinded, independent central review process. PFS as by central review remained an endpoint "for secondary supportive efficacy analyses" following amendment 1.

The study design incorporated a pre-planned interim analysis after observing 60% of this number (corresponding to approximately 317 events). As of the cut-off date for the interim analysis, 359 events (68% of the required number) had occurred as per investigator (at which time 217 central PFS events were recorded as per central review).

As the independent central review of local radiology data formed the basis for the secondary supportive analysis of PFS, the IDMC charter was amended on 11 May 2011 to enable the study to be declared positive for PFS at the time of the interim analysis, if and only if, both local and central PFS analyses were statistically significant in favour of everolimus plus exemestane, using a Lan-DeMets α-

spending function with O'Brien-Fleming type stopping boundaries that were driven by the number of local and central PFS events observed:

- The nominal p-value for the PFS analysis as per investigator was p<0.0065
- The nominal p-value for the PFS analysis as per central review was p<0.0005

Analyses presented in the study report of the submission are based on data collected up to 11 February 2011 (cut-off date for the interim analysis that was performed on 29 June 2011).

Patients in the placebo plus exemestane arm were not allowed to cross over to everolimus at the time of progression. Following progression or after study treatment discontinuation, patients continued to be followed for survival every 3 months until a total of 392 deaths were recorded.

Major protocol deviations are shown in Table 13:

Table 13: Major protocol deviations (FAS) – Study Y2301

Protocol deviation Category	Everolimus plus exemestane N=485 n (%)		Placebo plus exemestane N=239 n (%)	
Any major protocol deviation	9	(1.9)	2	(0.8)
Use of other anticancer agents before documented PD	7	(1.4)	1	(0.4)
ECOG performance status > 2 or ECOG not done at baseline	3	(0.6)	0	
No histologically or cytologically confirmed ER-positive breast cancer	0		1	(0.4)

ECOG Eastern Cooperative Oncology Group; ER Estrogen receptor; PD Progressive disease

Baseline data

The numbers of patients in each of the four strata (presence of visceral metastasis [yes versus no] and sensitivity to prior hormonal therapy [yes versus no]) are presented in Table 14 below. Baseline characteristics are presented in Table 15, 16 and 17.

Overall, 56.1% of patients enrolled had visceral involvement and 84.3% were sensitive to prior hormonal therapy.

Table 14: Randomization stratification (FAS) – Study Y2301

Stratum	Presence of visceral metastasis	Sensitivity to prior hormonal therapy	Everolimus plus exemestane N=485 n (%)		Placebo plus exemestane N=239 n (%)	
1	Yes	Yes	240	(49.5)	119	(49.8)
2	No	No	45	(9.3)	22	(9.2)
3	No	Yes	169	(34.8)	82	(34.3)
4	Yes	No	31	(6.4)	16	(6.7)

Table 15: Patient demographics at baseline (FAS) – Study Y2301

Demographic variable	Everolimus plus exemestane N=485		Placebo plus exemestane N=239		All patients N=724	
Age (years)						
n	485		239		724	
Mean (standard deviation)	62.5	(10.31)	61.2	(9.75)	62.1	(10.14)
Median	62.0		61.0		61.0	
Range	34 - 93		28 - 90		28 - 93	
Age category (years) - n (%)						
< 65	290	(59.8)	159	(66.5)	449	(62.0)
≥ 65	195	(40.2)	80	(33.5)	275	(38.0)
Race - n (%)						
Caucasian	361	(74.4)	186	(77.8)	547	(75.6)
Asian	98	(20.2)	45	(18.8)	143	(19.8)
Black	13	(2.7)	3	(1.3)	16	(2.2)
Pacific islander	2	(0.4)	1	(0.4)	3	(0.4)
Other	11	(2.3)	4	(1.7)	15	(2.1)
Ethnicity - n (%)						
Japanese	71	(14.6)	35	(14.6)	106	(14.6)
Hispanic/Latino	28	(5.8)	10	(4.2)	38	(5.2)
Mixed ethnicity	9	(1.9)	6	(2.5)	15	(2.1)
Chinese	5	(1.0)	0		5	(0.7)
Indian (Indian subcontinent)	1	(0.2)	0		1	(0.1)
Other	371	(76.5)	188	(78.7)	559	(77.2)

Table 16: Tumour characteristics at baseline (FAS) – Study Y2301

Patient and disease characteristics	Everolimus plus exemestane N=485 n (%)		Placebo plus exemestane N=239 n (%)		All patients N=724 n (%)	
Current disease status						
Metastatic	482	(99.4)	239	(100.0)	721	(99.6)
Locally advanced	3	(0.6)	0		3	(0.4)
Metastatic site of cancer						
Bone	369	(76.1)	184	(77.0)	553	(76.4)
Visceral (excluding CNS) [a]	281	(57.9)	143	(59.8)	424	(58.6)
Liver	160	(33.0)	72	(30.1)	232	(32.0)
Lung	140	(28.9)	79	(33.1)	219	(30.2)
Liver and lung	42	(8.7)	25	(10.5)	67	(9.3)
CNS [b]	5	(1.0)	0		5	(0.7)
Other	243	(50.1)	132	(55.2)	375	(51.8)
Number of metastatic sites involved						
1	155	(32.0)	69	(28.9)	224	(30.9)
2	152	(31.3)	81	(33.9)	233	(32.2)
3	103	(21.2)	52	(21.8)	155	(21.4)
4	48	(9.9)	28	(11.7)	76	(10.5)
5	17	(3.5)	6	(2.5)	23	(3.2)
> 5	7	(1.4)	3	(1.3)	10	(1.4)

Patient and disease characteristics	Everolimus plus exemestane N=485 n (%)		Placebo plus exemestane N=239 n (%)		All patients N=724 n (%)	
Type of lesions						
≥ 1 target lesion [c]	338	(69.7)	162	(67.8)	500	(69.1)
≥ 1 bone lesion	146	(30.1)	77	(32.2)	223	(30.8)
Missing	1	(0.2)	0		1	(0.1)

CNS - Central nervous system
[a] Visceral (excluding CNS) includes lung, liver, pleural, pleural effusions, peritoneum, and ascites
[b] CNS includes spinal cord, brain and meninges
[c] Category included 'Target and non-target' and 'Target only' from source table

Table 17: Disease characteristics at baseline(FAS) – Study Y2301

Patient and disease characteristics	Everolimus plus exemestane N=485 n (%)		Placebo plus exemestane N=239 n (%)		All patients N=724 n (%)	
Histology/cytology						
Invasive ductal carcinoma	374	(77.1)	182	(76.2)	556	(76.8)
Invasive lobular carcinoma	64	(13.2)	40	(16.7)	104	(14.4)
Other	39	(8.0)	16	(6.7)	55	(7.6)
Not applicable	8	(1.6)	1	(0.4)	9	(1.2)
Histologic grade						
Well differentiated	57	(11.8)	26	(10.9)	83	(11.5)
Moderately differentiated	186	(38.4)	98	(41.0)	284	(39.2)
Poorly differentiated	89	(18.4)	48	(20.1)	137	(18.9)
Unknown	152	(31.3)	67	(28.0)	219	(30.2)
Missing	1	(0.2)	0		1	(0.1)
Time since most recent recurrence/metastasis						
< 3 months	469	(96.7)	232	(97.1)	701	(96.8)
≥ 3 - < 6 months	11	(2.3)	5	(2.1)	16	(2.2)
≥ 6 months	3	(0.6)	1	(0.4)	4	(0.6)
Missing	2	(0.4)	1	(0.4)	3	(0.4)
ECOG performance status						
0	293	(60.4)	142	(59.4)	435	(60.1)
1	174	(35.9)	84	(35.1)	258	(35.6)
2	9	(1.9)	7	(2.9)	16	(2.2)
Missing [a]	9	(1.9)	6	(2.5)	15	(2.1)
HER2-positive [b]						
No	483	(99.6)	239	(100.0)	722	(99.7)
Missing	2	(0.4)	0		2	(0.3)
ER-positive [b]						
Yes	485	(100.0)	239	(100.0)	724	(100.0)
PgR-positive [b]						
No	122	(25.2)	62	(25.9)	184	(25.4)
Yes	351	(72.4)	173	(72.4)	524	(72.4)
Not assessable	12	(2.5)	4	(1.7)	16	(2.2)

ECOG Eastern Cooperative Oncology Group; ER Estrogen receptor; HER2 Human epidermal growth factor receptor-2; PgR Progesterone receptor
[a] For 13 of these 15 patients, performance status was obtained on the day of, or the day prior to, first study treatment; PS was ≤ 2 in all cases.
[b] As per local pathology assessment

A summary of prior antineoplastic therapy for the two treatment groups is presented in Table 18. Letrozole or anastrozole were administered to all patients at one point during their treatment. Letrozole or anastrozole were the last prior treatment in 74.4% of patients.

Table 18: Prior antineoplastic therapy (FAS) – Study Y2301

	Everolimus plus exemestane N=485 n (%)	Placebo plus exemestane N=239 n (%)	All patients N=724 n (%)
Any prior antineoplastic therapy	**485 (100.0)**	**239 (100.0)**	**724 (100.0)**
Any prior surgery	**451 (93.0)**	**220 (92.1)**	**671 (92.7)**
Any prior radiotherapy	**340 (70.1)**	**164 (68.6)**	**504 (69.6)**
Any non-steroidal aromatase inhibitor (NSAI)	**485 (100.0)**	**239 (100.0)**	**724 (100.0)**
Letrozole only	237 (48.9)	106 (44.4)	343 (47.4)
Anastrozole only	210 (43.3)	114 (47.7)	324 (44.8)
Both letrozole and anastrozole	38 (7.8)	19 (7.9)	57 (7.9)
NSAI setting			
Metastatic only	323 (66.6)	170 (71.1)	493 (68.1)
Adjuvant/neoadjuvant only	137 (28.2)	55 (23.0)	192 (26.5)
Both adjuvant/neoadjuvant and metastatic	20 (4.1)	12 (5.0)	32 (4.4)
Prevention only [a]	5 (1.0)	2 (0.8)	7 (1.0)
Patients with NSAI as last treatment	**361 (74.4)**	**178 (74.5)**	**539 (74.4)**
Metastatic	262 (54.0)	140 (58.6)	402 (55.5)
Adjuvant/neoadjuvant	97 (20.0)	37 (15.5)	134 (18.5)
Prevention [a]	2 (0.4)	1 (0.4)	3 (0.4)
Prior hormonal therapy other than NSAI	**281 (57.9)**	**146 (61.1)**	**427 (59.0)**
Anti-estrogen	276 (56.9)	140 (58.6)	416 (57.5)
Tamoxifen	230 (47.4)	118 (49.4)	348 (48.1)
Fulvestrant	80 (16.5)	39 (16.3)	119 (16.4)
Both tamoxifen and fulvestrant	39 (8.0)	20 (8.4)	59 (8.1)
Toremifene	8 (1.6)	4 (1.7)	12 (1.7)
Raloxifene	0	2 (0.8)	2 (0.3)
Luteinizing hormone releasing hormone analogs	17 (3.5)	11 (4.6)	28 (3.9)
Progestins	8 (1.6)	0	8 (1.1)
Others	6 (1.2)	4 (1.7)	10 (1.4)
Chemotherapy			
Adjuvant/neoadjuvant only	211 (43.5)	95 (39.7)	306 (42.3)
Metastatic only	67 (13.8)	23 (9.6)	90 (12.4)
Both adjuvant/neoadjuvant and metastatic	58 (12.0)	38 (15.9)	96 (13.3)
Other therapy			

	Everolimus plus exemestane N=485 n (%)		Placebo plus exemestane N=239 n (%)		All patients N=724 n (%)	
Targeted therapy	35	(7.2)	11	(4.6)	46	(6.4)
Immunotherapy	0		0		0	
Others	3	(0.6)	2	(0.8)	5	(0.7)
Number of chemotherapy lines received in advanced setting [b]						
1	125	(25.8)	58	(24.3)	183	(25.3)
2	0		0		0	
Number of prior therapies						
1	76	(15.7)	42	(17.6)	118	(16.3)
2	146	(30.1)	71	(29.7)	217	(30.0)
3	133	(27.4)	58	(24.3)	191	(26.4)
4	80	(16.5)	41	(17.2)	121	(16.7)
5	33	(6.8)	19	(7.9)	52	(7.2)
6	13	(2.7)	6	(2.5)	19	(2.6)
7	3	(0.6)	2	(0.8)	5	(0.7)
8	1	(0.2)	0		1	(0.1)
Number of prior therapies in metastatic setting						
None	100	(20.6)	37	(15.5)	137	(18.9)
1	192	(39.6)	112	(46.9)	304	(42.0)
2	128	(26.4)	66	(27.6)	194	(26.8)
3	52	(10.7)	16	(6.7)	68	(9.4)
4	8	(1.6)	7	(2.9)	15	(2.1)
5	3	(0.6)	1	(0.4)	4	(0.6)
6	2	(0.4)	0		2	(0.3)
Number of prior endocrine therapies in advanced setting						
None	107	(22.1)	42	(17.6)	149	(20.6)
1	252	(52.0)	141	(59.0)	393	(54.3)
2	104	(21.4)	46	(19.2)	150	(20.7)
≥ 3	22	(4.5)	10	(4.2)	32	(4.4)

[a] Further review of these cases indicates that these should have been coded as adjuvant
[b] If a chemotherapy regimen was discontinued for a reason other than disease progression and lasted < 21 days, then this regimen did not count as a prior line of chemotherapy

Numbers analysed

The Full Analysis Set (FAS) population consisted of all randomised patients. Four patients (0.6%) were excluded from the Safety Set; all four of these patients (three in the everolimus plus exemestane arm and one in the placebo plus exemestane group) were randomised but subsequently did not receive study treatment (Table 19).

Table 19: Analysis sets by treatment (FAS) – Study Y2301

Analysis populations	Everolimus plus exemestane N=485 n (%)	Placebo plus exemestane N=239 n (%)	All patients N=724 n (%)
Full Analysis Set	485 (100.0)	239 (100.0)	724 (100.0)
Safety Set	482 (99.4)	238 (99.6)	720 (99.4)

The Safety Set population consisted of all patients who received at least one dose of the study treatment and who had at least one valid post-baseline safety assessment. Patients were analysed according to the treatment actually received. For a patient taking at least one dose of the randomised treatment, treatment actually received was considered to be the randomised treatment.

Outcomes and estimation

Primary endpoint: PFS

The results of the primary endpoint PFS in patients treated with the combination of everolimus and exemestane compared to placebo and exemestane treated group are reported in Table 20, 21, 22 and Figure 4. There were three data cut-off updates for PFS. Results from the final PFS analysis for Study Y2301 based on a 15 December 2011 cut-off, corresponded to a median follow-up of 17.7 months.

Table 20: Analysis of PFS as per investigator and central radiology reviews: Final PFS Analysis - Study Y2301

	Final PFS Analysis: 15-Dec-2011 data cut-off			
	Investigator assessment		Central radiology review	
	Everolimus plus exemestane N=485	Placebo plus exemestane N=239	Everolimus plus exemestane N=485	Placebo plus exemestane N=239
Number of PFS events - n (%)	310 (63.9)	200 (83.7)	188 (38.8)	132 (55.2)
Progression	294 (60.6)	198 (82.8)	167 (34.4)	128 (53.6)
Death before progression	16 (3.3)	2 (0.8)	21 (4.3)	4 (1.7)
Censored - n (%)	175 (36.1)	39 (16.3)	297 (61.2)	107 (44.8)
Median PFS [95% CI]	7.82 [6.93, 8.48]	3.19 [2.76, 4.14]	11.01 [9.66, 15.01]	4.14 [2.89, 5.55]
Improvement in median PFS	4.63		6.87	
Hazard ratio [95% CI]	0.45 [0.38, 0.54]		0.38 [0.31, 0.48]	
p-value	<0.0001		<0.0001	

Table 21: Analysis of PFS as per investigator and central radiology reviews: Efficacy Update - Study Y2301

	Efficacy Update: 08-Jul-2011 data cut-off			
	Investigator assessment		Central radiology review	
	Everolimus plus exemestane N=485	Placebo plus exemestane N=239	Everolimus plus exemestane N=485	Placebo plus exemestane N=239
Number of PFS events - n (%)	267 (55.1)	190 (79.5)	155 (32.0)	127 (53.1)
Progression	252 (52.0)	188 (78.7)	139 (28.7)	123 (51.5)
Death before progression	15 (3.1)	2 (0.8)	16 (3.3)	4 (1.7)

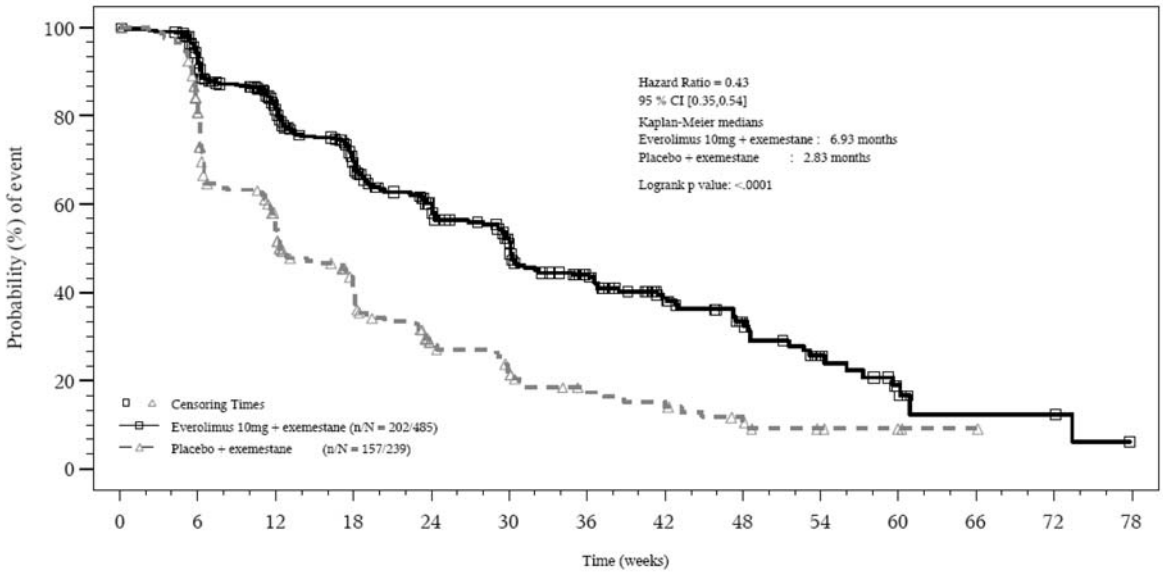
	Efficacy Update: 08-Jul-2011 data cut-off			
	Investigator assessment		Central radiology review	
	Everolimus plus exemestane	Placebo plus exemestane	Everolimus plus exemestane	Placebo plus exemestane
	N=485	N=239	N=485	N=239
Censored - n (%)	218 (44.9)	49 (20.5)	330 (68.0)	112 (46.9)
Median PFS [95% CI]	7.36 [6.93, 8.48]	3.19 [2.76, 4.14]	11.01 [9.56, NA]	4.11 [2.83, 5.55]
Improvement in median PFS	4.17		6.90	
Hazard ratio [95% CI]	0.44 [0.36, 0.53]		0.36 [0.28, 0.45]	
p-value	<0.0001		<0.0001	

Table 22: Analysis of PFS per investigator and central radiology reviews (FAS; data cut-off 11-February-2011) – Study Y2301

Progression-free survival	Investigator assessment		Central radiology review	
	Everolimus plus exemestane	Placebo plus exemestane	Everolimus plus exemestane	Placebo plus exemestane
	N=485	N=239	N=485	N=239
No of PFS events - n (%)	202 (41.6)	157 (65.7)	114 (23.5)	104 (43.5)
Progression	190 (39.2)	156 (65.3)	101 (20.8)	100 (41.8)
Death [a]	12 (2.5)	1 (0.4)	13 (2.7)	4 (1.7)
Censored - n (%)	283 (58.4)	82 (34.3)	371 (76.5)	135 (56.5)
Median PFS (mo)	6.93	2.83	10.58	4.14
Improvement in median PFS (mo)	4.10		6.44	
Hazard ratio [b]	0.43		0.36	
95% CI	0.35, 0.54		0.27, 0.47	
p-value	<0.0001 ($1.4x10^{-15}$)		<0.0001 ($3.3x10^{-15}$)	

mo - Months; PFS - Progression-free survival
[a] Death before progression
[b] Hazard ratio is calculated form the stratified Cox proportional hazard model

Figure 4: Kaplan-Meier plot of PFS as per investigator (data cut-off 11-February-2011) - Study Y2301



Number of Patients still at Risk

Time(weeks)	0	6	12	18	24	30	36	42	48	54	60	66	72	78
Everolimus	485	398	294	212	144	108	75	51	34	18	8	3	3	0
Placebo	239	177	109	70	36	26	16	14	9	4	3	1	0	0

The number of censored events is different between the two treatment groups, for both investigator and independent central review. The reasons for censoring are displayed in Table 23.

Table 23: Summary of censoring reasons – Study Y2301

	Investigator assessment		Central radiology review	
	Everolimus plus exemestane N=485 n (%)	Placebo plus exemestane N=239 n (%)	Everolimus plus exemestane N=485 n (%)	Placebo plus exemestane N=239 n (%)
Total number of censored patients	**283 (58.4)**	**82 (34.3)**	**371 (76.5)**	**135 (56.5)**
Ongoing without PFS event	220 (77.7)	63 (76.8)	212 (57.1)	58 (43.0)
Adequate assessments not available	33 (11.7)	7 (8.5)	47 (12.7)	15 (11.1)
New cancer therapy added	29 (10.2)	9 (11.0)	110 (29.6)	62 (45.9)
Events documented after ≥ 2 missing tumor assessments	1 (0.4)	3 (3.7)	2 (0.5)	0

Several sensitivity analyses were performed to assess the magnitude of investigator bias and of treatment effect. The sensitivity analyses are presented in Table 24.

Table 24: Sensitivity analyses – Study Y2301

Sensitivity analysis	p-value	Hazard ratio [95% CI]	Everolimus plus exemestane	Placebo plus exemestane
			Median PFS (months) [95%CI]	
Primary analysis	<0.0001	0.43 [0.35, 0.54]	6.93 [6.44, 8.05]	2.83 [2.76, 4.14]
Unstratified log-rank test and Cox model	<0.0001	0.44 [0.36, 0.54]	6.93 [6.44, 8.05]	2.83 [2.76, 4.14]
Stratified Cox model, adjusting for baseline covariates [a]	<0.0001	0.40 [0.32, 0.50]	6.93 [6.44, 8.05]	2.83 [2.76, 4.14]
'Actual event' [b]	<0.0001	0.43 [0.35, 0.54]	6.93 [6.44, 8.05]	2.92 [2.76, 4.14]
'Backdating' [c]	<0.0001	0.43 [0.35, 0.53]	6.93 [6.18, 8.31]	2.83 [2.69, 4.07]
'No censoring for antineoplastic therapy' [d]	<0.0001	0.44 [0.36, 0.54]	6.93 [6.18, 7.36]	2.83 [2.76, 4.14]

CI Confidence interval; PFS Progression-free survival
[a] Baseline covariates included in the Cox proportional hazard model are prior chemotherapy (yes versus no), performance status (0 versus 1 or 2), bone only lesions at baseline (yes versus no), time since first diagnosis of metastasis/recurrence to randomization (≤ 6 months versus > 6 months), non-steroidal aromatase inhibitor usage (adjuvant versus metastatic), number of organs involved (1 versus 2 versus ≥ 3), and progesterone receptor status (positive versus negative)
[b] Analysis included the event whenever it occurred even after ≥ 2 missing tumor assessments
[c] Analysis used the date of the next scheduled assessment for events occurring after ≥ 1 missing assessment
[d] Analysis was performed by not censoring patients at start of new antineoplastic therapy

Secondary endpoints

Overall Survival

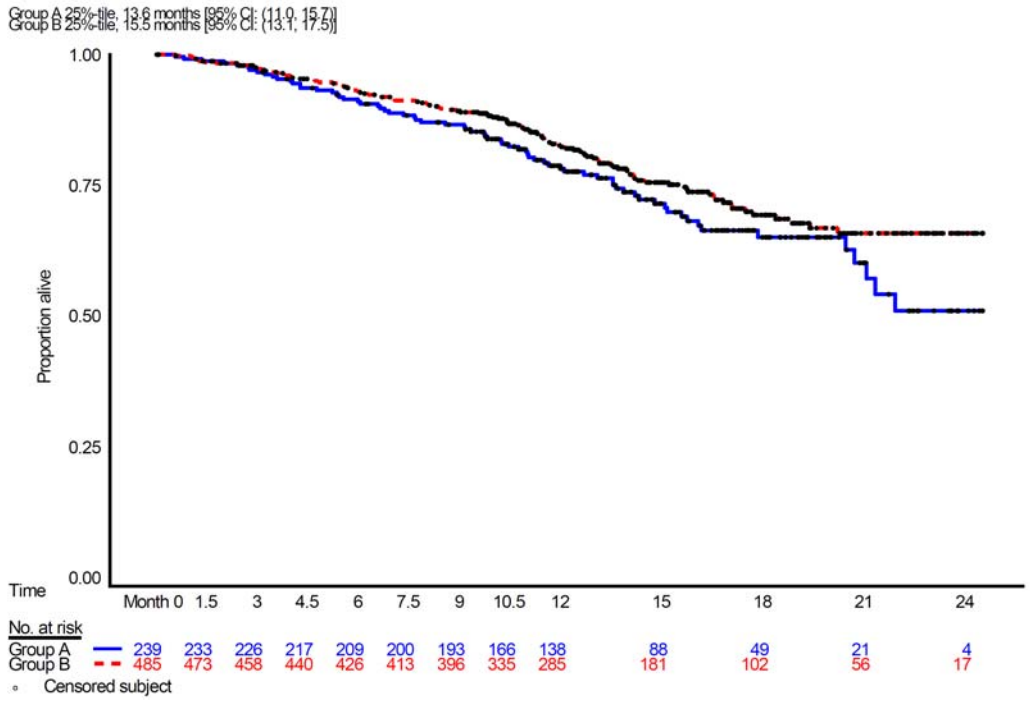
Using the expected number of OS events at the planned conclusion of surveillance for all-cause mortality (i.e., 392 deaths), 170 observed deaths (46% of expected deaths; p-value =0.0010) were required for a second interim analysis of OS. The database at the time of analysis of OS had 182 observed deaths.

The results of the 2nd interim analysis are shown in Table 25 and Figure 5.

Table 25: Overall survival in randomisation strata and among all patients (2nd Interim OS analysis) – Study Y2301

Stratum		Group A	Group B
All patients	No. of patients	239	485
	No. of deaths, n (%)	70 (29)	112 (23)
	No. censored, n (%)	169 (71)	373 (77)
	Median OS [95% CI]	NR [20.7, NR]	NR [NR, NR]
	One-sided p-value	0.046	
	Hazard Ratio [95% CI]	0.77 [0.57, 1.04]	

Figure 5: K-M plot for OS (2nd interim analysis) – Study Y2301



Objective Response Rate

The results of ORR are shown in Table 26 and 27.

Table 26: Best overall response as per investigator – Study Y2301 (FAS)

Best overall response	Everolimus plus exemestane N=485 n (%)	Placebo plus exemestane N=239 n (%)	p-value [a]
Complete response (CR)	2 (0.4)	0	
Partial response (PR)	44 (9.1)	1 (0.4)	
Stable disease (SD)	340 (70.1)	140 (58.6)	
Progressive disease	48 (9.9)	75 (31.4)	
Unknown/too early to evaluate	51 (10.5)	23 (9.6)	
Response analysis			
Objective response rate (ORR) [b]	46 (9.5)	1 (0.4)	<0.0001
95% confidence interval	7.0, 12.4	0.0, 2.3	
Clinical benefit rate (CBR) [c]	162 (33.4)	43 (18.0)	<0.0001
95% confidence interval	29.2, 37.8	13.3, 23.5	

[a] p-value is obtained from the exact Cochran-Mantel-Haenszel test using a stratified version of the Cochran-Armitage permutation test
[b] Objective response rate = proportion of patients with CR or PR
[c] Clinical benefit rate = proportion of patients with CR or PR or SD ≥ 24 weeks

Table 27: Best overall response as per central radiology review (FAS) – Study Y2301

Best overall response	Everolimus plus exemestane N=485 n (%)	Placebo plus exemestane N=239 n (%)
Response analysis		
Objective response rate (ORR) [a]	34 (7.0)	1 (0.4)
95% confidence interval	4.9, 9.7	0.0, 2.3
Clinical benefit rate (CBR) [b]	150 (30.9)	36 (15.1)
95% confidence interval	26.8, 35.3	10.8, 20.2

[a] Objective response rate = proportion of patients with CR or PR
[b] Clinical benefit rate = proportion of patients with CR or PR or SD ≥ 24 weeks

Time to and duration of response

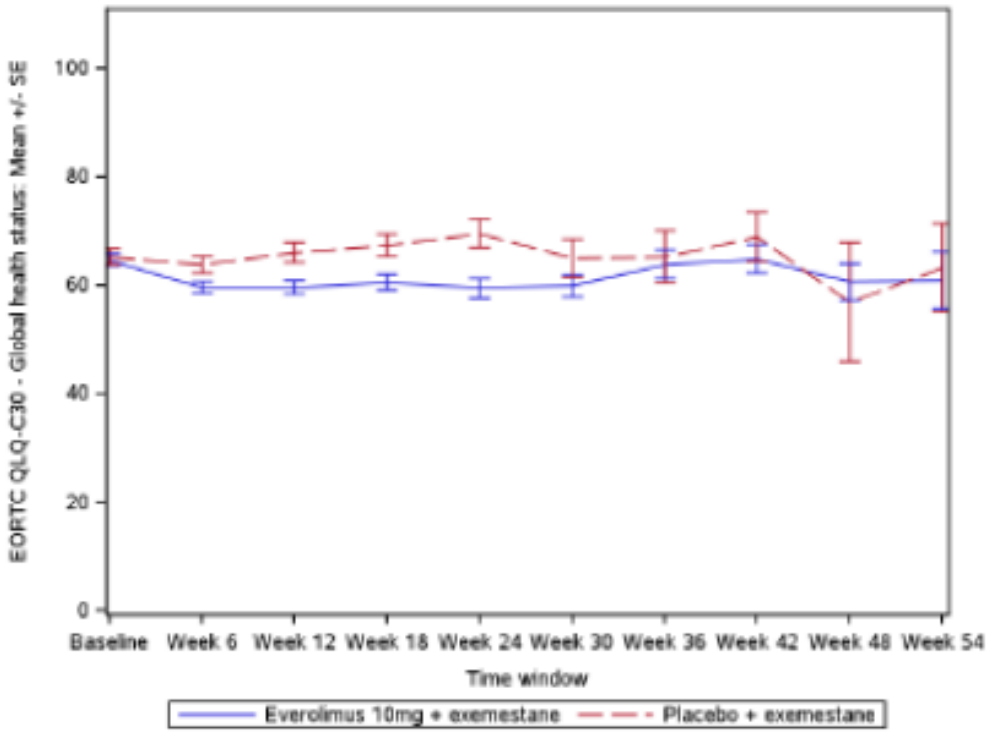
Time to response varied between 5.1 and 37.1 weeks for the exemestane plus everolimus arm and was 7.4 weeks for the single patient with a response in the placebo plus exemestane arm.

Duration of OR varied between 6.0+ and 66.1+ weeks for the everolimus plus exemestane arm and was 12.1+ weeks for the single patient in the placebo plus exemestane arm.

Patient reported outcome

The median times to deterioration (≥ 5%) of global health status/QoL domain score of QLQ-C30 are shown in Figure 6. A mixed effect longitudinal model was fit on the change from baseline in the global health status of QLQ-C30.

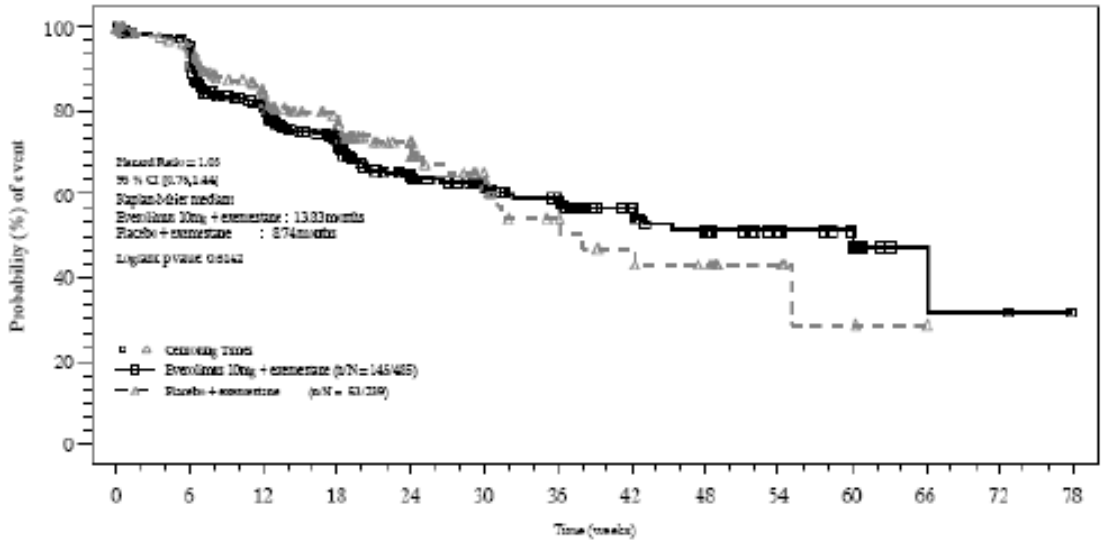
Figure 6: Longitudinal plot of the global health status scale score of the EORTC QLQ-C30 questionnaire – Study Y2301



ECOG performance status

The time to deterioration of ECOG performance status by ≥ 1 point is shown in Figure 7.

Figure 7: K-M plot of time to deterioration in ECOG performance status (FAS) – Study Y2301



Number of Patients still at Risk

Time(weeks)	0	6	12	18	24	30	36	42	48	54	60	66	72	78
Everolimus	405	430	280	211	147	106	78	50	36	21	15	3	2	0
Placebo	139	206	116	88	48	29	16	12	9	5	2	1	0	0

CI Confidence interval; ECOG Eastern Cooperative Oncology Group

Biomarkers

Results for biomarkers were not submitted with the application. The following biomarkers were being evaluated in archival tumour samples collected from approximately 65% of the Full Analysis Set: protein expression of PTEN, pS6, and Ki67 by immunohistochemistry; somatic mutations in PI3KCA, PTEN, and p53 by sequencing; and PI3K amplification.

However, exploratory analyses on bone related biomarkers (bone turnover biomarkers) were submitted. The results are presented in Table 28.

Table 28: Bone-turnover biomarkers: change from baseline over time - Study Y2301

	Original submission: 11-Feb-2011 data cut-off				Safety Update: 08-Jul-2011 data cut-off			
	Everolimus plus exemestane N=485		Placebo plus exemestane N=239		Everolimus plus exemestane N=485		Placebo plus exemestane N=239	
	n		n		n		n	
BSAP (ng/mL)								
Baseline, geomean (geoCV)	450	14.25 (69.7)	227	15.77 (72.2)	453	14.22 (69.6)	228	15.74 (72.1)
Geomean fold change [a] (geoCV)								
At Week 6	385	0.87 (39.9)	183	1.10 (37.5)	403	0.87 (39.3)	190	1.12 (38.0)
At Week 12	273	0.84 (50.4)	109	1.08 (40.7)	331	0.84 (48.3)	126	1.10 (38.8)
P1NP (ng/mL)								
Baseline, geomean (geoCV)	450	50.52 (110.7)	227	59.64 (116.3)	453	50.63 (110.7)	228	59.52 (116.0)
Geomean fold change [a] (geoCV)								
At Week 6	379	0.68 (57.9)	181	1.21 (47.3)	397	0.68 (58.3)	188	1.22 (47.2)
At Week 12	267	0.58 (78.3)	108	1.22 (56.1)	324	0.57 (81.4)	125	1.23 (53.9)
CTX (ng/mL)								
Baseline, geomean (geoCV)	449	0.23 (125.9)	226	0.23 (148.3)	452	0.23 (125.4)	227	0.23 (148.0)
Geomean fold change [a] (geoCV)								
At Week 6	384	0.75 (85.8)	180	1.09 (73.5)	402	0.75 (84.5)	187	1.10 (72.4)
At Week 12	271	0.75 (97.5)	107	1.19 (71.9)	329	0.73 (103.2)	124	1.19 (68.8)

geoCV Geometric coefficient of variation; geomean Geometric mean; geomean fold change Geometric mean of fold change. Fold change is defined as the ratio of post-baseline value to baseline value.

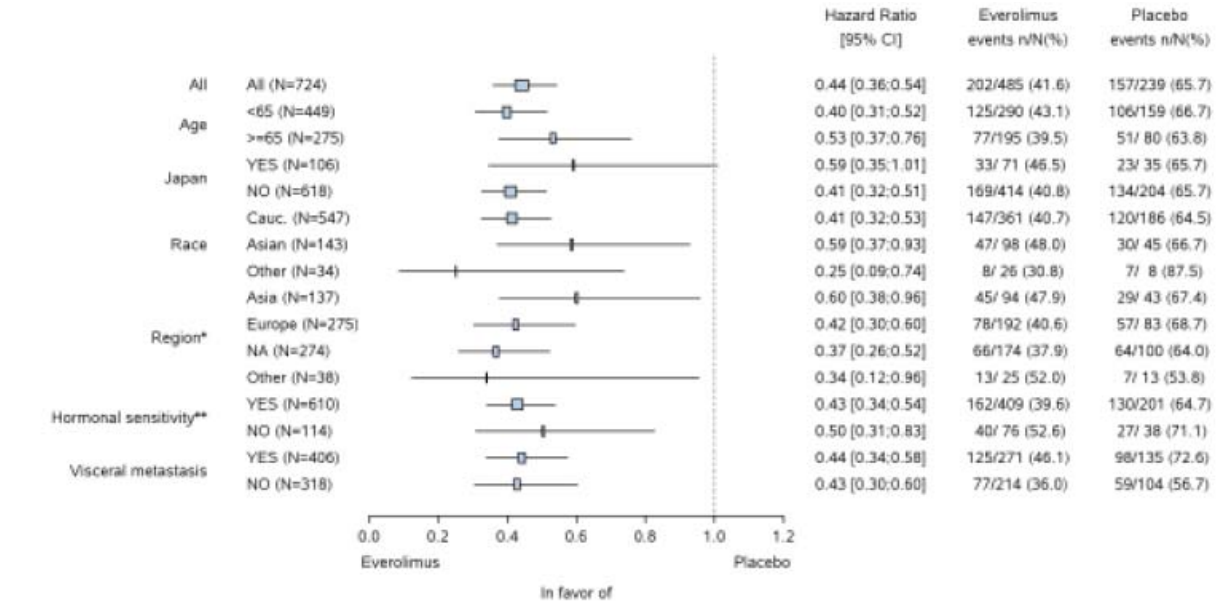
[a] From baseline

Ancillary analyses

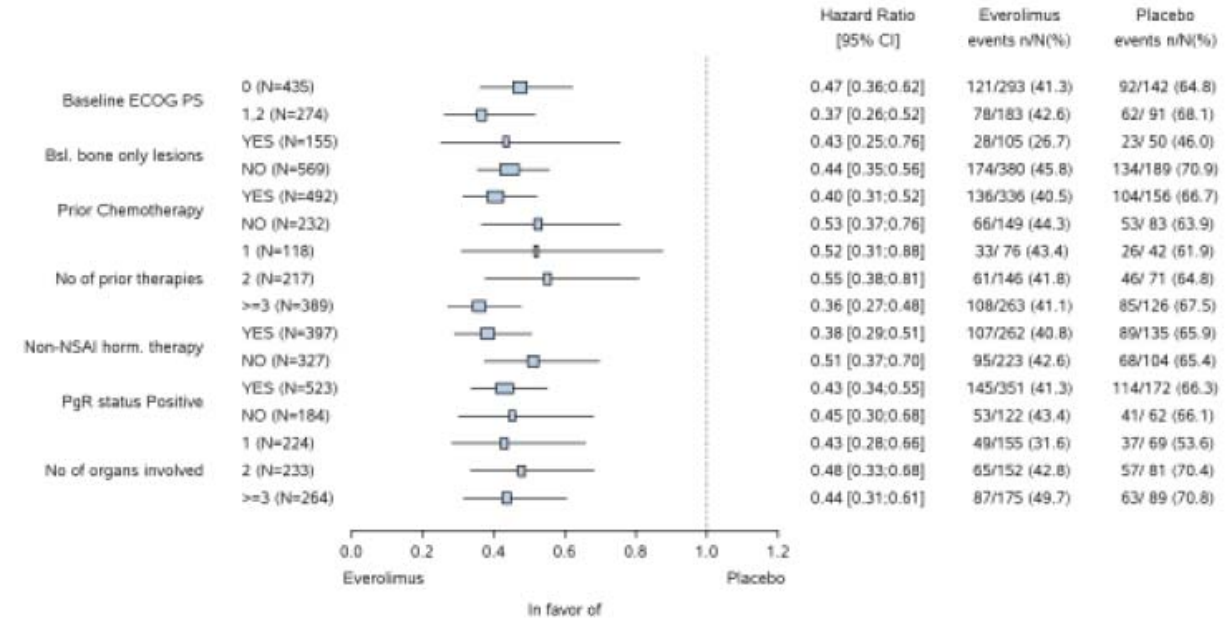
Subgroup analyses

Subgroup analyses were performed to evaluate consistency and robustness of the primary PFS results according to baseline factors, including baseline stratification factors (prior sensitivity to hormonal therapy and presence of visceral disease). The results are shown in Figure 8.

Figure 8: PFS treatment effect for patient subgroups (FAS) - Study Y2301



Region* - NA North America; Hormonal sensitivity** - Sensitivity to prior hormonal therapy
Hazard ratio obtained using unstratified Cox proportional hazard model



Effect of treatment in patients with measurable disease

Table 29 and 30 show the CBR response (ORR: CR+PR; CBR: CR+PR+SD ≥ 24 weeks) and PFS analyses in patients with and without measurable disease at baseline.

Table 29: Best overall response as per investigator for patients with and without measurable disease at baseline (FAS) - Study Y2301

	Efficacy Update: 08-Jul-2011 data cut-off			
	Patients with measurable disease at baseline		Patients without measurable disease at baseline	
	Everolimus plus exemestane	Placebo plus exemestane	Everolimus plus exemestane	Placebo plus exemestane
	N=338	N=163	N=147	N=76
Response analysis				
Objective response rate (ORR)	58 (17.2)	3 (1.8)	0	0
95% CI	13.3, 21.6	0.4, 5.3	NA	NA
Clinical benefit rate (CBR)	154 (45.6)	35 (21.5)	91 (62.3)	26 (34.2)
95% CI	40.2, 51.0	15.4, 28.6	53.9, 70.2	23.7, 46.0
Best overall response				
Complete response (CR)	2 (0.6)	0	0	0
Partial response (PR)	56 (16.6)	3 (1.8)	0	0
Stable disease (SD)	221 (65.4)	88 (54.0)	128 (87.1)	54 (71.1)
Progressive disease (PD)	38 (11.2)	62 (38.0)	11 (7.5)	16 (21.1)
Unknown	21 (6.2)	10 (6.1)	8 (5.4)	6 (7.9)

Table 30: PFS as per investigator for patients with and without measurable disease at baseline (FAS) - Study Y2301

	Efficacy Update: 08-Jul-2011 data cut-off			
	Patients with measurable disease at baseline		Patients without measurable disease at baseline	
	Everolimus plus exemestane	Placebo plus exemestane	Everolimus plus exemestane	Placebo plus exemestane
	N=338	N=163	N=147	N=76
No of PFS events - n (%)	210 (62.1)	139 (85.3)	57 (38.8)	51 (67.1)
Median PFS (mo)	6.80	2.76	11.70	4.70
Improvement in median PFS (mo)	4.04		7.00	
Hazard ratio	0.45		0.37	
95% CI	0.37, 0.56		0.25, 0.54	

Hazard ratio calculated from the unstratified Cox model

Last treatment prior to enrolling in Study Y2301

The CHMP requested to analyse the results of PFS according to patients having received NSAI as the last therapy before enrolling in the study Y2301. There were 361 patients (74.4%) in the everolimus+exemestane and 178 patients (74.4%) in the placebo+exemestane arms whose last therapy prior to enrolling in Study Y2301 was a NSAI. Subgroup PFS analyses for patients having received a NSAI (yes) or other therapy (no) as last treatment before treatment with everolimus/placebo in combination with exemestane are presented in Table 31 for the 11-February-2011 and 08-July-2011 (updated) data cut-offs.

Table 31: Comparison of PFS between patients that received or not NSAI as last treatment prior to study treatment in both treatment group - Study Y2301

	Original submission: 11-Feb-2011 data cut-off	
	Patients with NSAI as last prior therapy	
	Yes	No

	Everolimus plus exemestane N=361	Placebo plus exemestane N=178	Everolimus plus exemestane N=124	Placebo plus exemestane N=61
Number of PFS events - n (%)	146 (40.4)	114 (64.0)	56 (45.2)	43 (70.5)
Median PFS (months)	6.93	2.96	6.93	2.79
Hazard ratio [95% CI]	0.46 [0.36, 0.59]		0.35 [0.23, 0.53]	
Hazard ratio obtained from unstratified Cox proportional-hazards model				

	Efficacy Update: 08-Jul-2011 data cut-off			
	Patients with NSAI as last prior therapy			
	Yes		No	
	Everolimus plus exemestane N=360	Placebo plus exemestane N=178	N=125	Placebo plus exemestane N=61
Number of PFS events - n (%)	190 (52.8)	139 (78.1)	77 (61.6)	51 (83.6)
Median PFS (months)	8.08	3.94	6.93	2.79
Hazard ratio [95% CI]	0.47 [0.38, 0.58]		0.31 [0.22, 0.46]	
Hazard ratio obtained from unstratified Cox proportional-hazards model				

Therapies after treatment discontinuation

Following discontinuation of study treatment, patients in both treatments arms were eligible to receive further antineoplastic therapy, 49.1% (137 of 279) of patients from the everolimus+exemestane arm and 43.9% (83 of 189) of patients from the placebo+exemestane arm received further endocrine therapy.

Table 32: Antineoplastic therapies after discontinuation of study treatment (FAS) - Study Y2301

	Everolimus plus exemestane N=485 n (%)		Placebo plus exemestane N=239 n (%)	
Any post-treatment therapy	**279**	**(57.5)**	**189**	**(79.1)**
Chemotherapy	162	(33.4)	130	(54.4)
Hormonal therapy	137	(28.2)	83	(34.7)
Radiotherapy	24	(4.9)	13	(5.4)
Targeted therapy	13	(2.7)	18	(7.5)
Immunotherapy	2	(0.4)	0	
Surgery	2	(0.4)	0	
Other	8	(1.6)	2	(0.8)
Patients could receive more than one category of post-treatment therapy				

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 33: Summary of Efficacy for trial Y2301

Title: BOLERO2				
Study identifier	Y2301			
Design	Formally double-blind, randomised (2:1) everolimus + exemestane vs. exemestane comparative study in patients with metastatic, ER positive, HER2 non-overexpressed breast cancer refractory to non-steroidal breast cancer.			
	Duration of main phase:	Ongoing		
Hypothesis	Superiority, PFS			
Treatments groups	Everolimus+exemestane	Experimental arm, until disease progression, death or unacceptable toxicity, n=485		
	Exemestane	Control arm, until disease progression, death or unacceptable toxicity, n=239		
Endpoints and definitions	PFS	Conventionally defined. Investigator and independent review.		
	OS	Not reported yet, too low event rate		
	ORR	RECIST 1. Investigator and independent review.		
Database lock	15th December 2011			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	ITT			
Descriptive statistics and estimate variability	Treatment group	Experimental	Control	
	Number of subject	485	239	
	PFS HR Investigator*	0.45		
	95%ci	0.38; 0.54		
	PFS median difference	4.6 months		
	ORR Independent	7%	0.4%	
	95% CI for difference	4; 9%		
Notes	*Independent review HR: 0.38			

Supportive study

Study title: A phase II, double-blind, randomised, placebo-controlled, multicenter study assessing the value of adding RAD001 to letrozole (Femara) as preoperative therapy of primary breast cancer in postmenopausal women.

The study was designed as a double-blind Phase II study to assess clinical response in patients randomised for 16 weeks to treatment with 10 mg everolimus + 2.5 mg letrozole or placebo + 2.5 mg letrozole following surgery. Surgery had to have occured maximum of 1 week after last dose.

There was an open-label extension (depending on risk/benefit assessment) powered for final analysis of predictive biomarkers.

The first patient was enrolled in the study on 22 May 2005 and the last patient completed the study on 4 April 2007.

The results of the study are shown in Table 34, 35 and 36.

Table 34: ORR by ultrasound

	RAD001 + letrozole N=129			Placebo + letrozole N=122			Total N=251		
Tumor response	**n**	**(%)**	**95% CI**	**n**	**(%)**	**95% CI**	**n**	**(%)**	**95% CI**
Complete response	6	(4.7)		0			6	(2.4)	
Partial response	71	(55.0)		58	(47.5)		129	(51.4)	
No change	39	(30.2)		53	(43.4)		92	(36.7)	
Progressive disease	4	(3.1)		6	(4.9)		10	(4.0)	
Not available/not evaluable	9	(7.0)		5	(4.1)		14	(5.6)	
Overall response (CR + PR)	77	(59.7)	(51.2, 68.2)	58	(47.5)	(38.7, 56.4)	135	(53.8)	(47.6, 60.0)
Chi-square test p-value			0.0268						

Tumor response is calculated using tumor change from baseline measurements measured by breast ultrasound.

Response is calculated from the Month 4 assessment. If this is missing than the last non-missing tumor assessment is used.

Patients with missing baseline or having no post-baseline measurements are considered non-evaluable.

The 95% Confidence Intervals are calculated using the normal approximation to the binominal distribution.

Chi-square test without continuity correction (significance threshold: 1 sided p-value ≤ 0.10).

Table 35: ORR by palpation

	RAD001 + letrozole N=129			Placebo + letrozole N=122			Total N=251		
Overall response	**n**	**(%)**	**95% CI**	**N**	**(%)**	**95% CI**	**n**	**(%)**	**95% CI**
Complete response	18	(14.0)		11	(9.0)		29	(11.6)	
Partial response	68	(52.7)		56	(45.9)		124	(49.4)	
No change	32	(24.8)		41	(33.6)		73	(29.1)	
Progressive disease	2	(1.6)		5	(4.1)		7	(2.8)	
Not available/not evaluable	9	(7.0)		9	(7.4)		18	(7.2)	
Overall response (CR + PR)	86	(66.7)	(58.5, 74.8)	67	(54.9)	(46.1, 63.7)	153	(61.0)	(54.9, 67.0)
Chi-square test p-value			0.0283						

Overall response is obtained by investigator reported tumor and nodal response.

Response is calculated from the Month 4 assessment. If this is missing than the last non-missing tumor assessment is used.

Patients with missing baseline or having no post-baseline measurements are considered non-evaluable.

The 95% Confidence Intervals are calculated using the normal approximation to the binominal distribution.

Chi-square test without continuity correction (significance threshold: 1 sided p-value ≤ 0.10).

Table 36: ORR by pathological response

	RAD001 + letrozole N=129			Placebo + letrozole N=122			Total N=251		
Pathological response	**n**	**(%)**	**95% CI**	**n**	**(%)**	**95% CI**	**n**	**(%)**	**95% CI**
Surgery performed	117	(90.7)		116	(95.1)		233	(92.8)	
Surgery not performed	12	(9.3)		6	(4.9)		18	(7.2)	
Complete pathological response	2	(1.6)	(0.2, 5.5)	1	(0.8)	(0.0, 4.5)	3	(1.2)	(0.2, 3.5)
Microscopic residual disease	15	(11.6)		10	(8.2)		25	(10.0)	
Remaining macroscopic disease	100	(77.5)		104	(85.2)		204	(81.3)	
No pathological response recorded	12	(9.3)		7	(5.7)		19	(7.6)	

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The study Y2301 was a phase III pivotal randomised, placebo controlled, blinded, multicentre study. The choice of PFS as a primary endpoint as per investigator (local) assessment and of OS and ORR as secondary endpoints was considered acceptable. The CHMP noted that patients were not allowed to cross-over to everolimus plus exemestane treatment after recurrence or progression of the disease. This avoided any confounding effect from subsequent treatment on both arms.

The choice of the comparator arm of placebo plus exemestane was not considered as the appropriate comparator arm for the study population being treated with everolimus plus exemestane. The CHMP highlighted that everolimus alone would have been a better choice considering that the heavily pre-treated patient population was refractory to aromatase inhibitors. Because of the low response observed in the exemestane treated arm of 0.4% for ORR compared to the expected ORR of 15%, there was the possibility that patients received suboptimal treatment with exemestane. Thus, the CHMP requested the submission of the results of the study BOLERO-6, which compares everolimus treated patients to everolimus plus exemestane treated patients to chemotherapy treatment, as a condition of the marketing authorisation. The CHMP was of the opinion that the study results on the efficacy of everolimus treatment alone may impact the benefit risk of the proposed indication. Thus, the requirement to submit results of this study was included as a condition in Annex II.

Efficacy data and additional analyses

The study reached its primary objective and the final PFS analysis (15 December 2011) showed a statistically significantly higher PFS for everolimus plus exemestane of 7.82 months compared to 3.19 months for placebo plus exemestane (HR:0.45; CI 0.38-0.54; $p<0.0001$) in the analysis of the primary endpoint. Assessment by central radiology review supported the primary analysis of PFS (11.01 vs 4.14 months, respectively, HR 0.38; CI 0.31-0.48; $p<0.0001$). Although the OS data did not reach the stopping boundary and were considered still immature, the secondary endpoints OS and ORR and the sensitivity analyses further supported the results of the primary analysis. The subgroup analyses showed that a benefit in favour of the exemestane plus everolimus could be observed in all subgroups analysed, including for the subgroups stratified according to hormonal sensitivity and the presence or absence of visceral metastases. The low ORR and the lack of suppression of oestrogen was of concern since there was the possibility that exemestane treatment may have been suboptimal and ineffective in both treatment arms. However, because the PFS results were consistent and stable for the three different efficacy analyses, the effect of everolimus plus exemestane was confirmed.

The proportion of patients with non-measurable disease was balanced between the two treatment arms. There were no patients in the non-measurable group with an ORR in either treatment arm and no patients experienced a complete response. The treatment effect in terms of CBR was comparable for patients with and without measurable disease for both the everolimus plus exemestane and placebo plus exemestane arms. The median PFS for patients with measurable disease was slightly shorter than that for patients with non-measurable disease. This is an expected result for patients with visceral involvement who typically have a worse prognosis than patients with bone or soft tissue involvement. There was no difference in PFS between patients either treated or not with NSAI as last treatment prior to enrolment in the study. The observations appear to be consistent with expected treatment-effect results for both treatment groups.

Bone turnover biomarkers such as bone specific alkaline phosphatase (BSAP), aminoterminal propeptide of type 1 procollagen (P1NP), and collagen type 1 cross-linked C-telopeptide (CTX) showed

minor decreases from baseline compared to increases with exemestane; however, CVs are wide in all cases. The results appear to indicate that there were no negative effect on bone turnover from the combination treatment.

The results for Quality of Life and Clinical Performance Status did not show a significant difference between the two treatment arms.

2.5.4. Conclusions on the clinical efficacy

The pivotal trial Y2301 provided satisfactory evidence that the combination of everolimus plus examestane leads to prolongation of PFS in hormone-receptor positive, Her2/neu negative, post-menopausal advanced breast cancer women compared to exemestane alone. The clinical benefit was considered relevant in spite of the low ORR and the immature OS data. There was no comparative data of everolimus plus exemestane with chemotherapy, which is the treatment of choice for patients with more aggressive course of disease characterised by symptomatic visceral disease. Thus, the CHMP considered that the indication should be restricted to patients without symptomatic visceral disease in order to avoid the possibility of undertreatment.

The CHMP considers the following measures necessary to address issues related to efficacy. These measures are included in the RMP:

- CRAD001J2301: A randomised, phase III, double-blind, placebo-controlled multicenter trial of everolimus in combination with trastuzumab and paclitaxel as first-line therapy in women with HER2 positive locally advanced or metastatic breast cancer
- CRAD001W2301: A randomised, phase III, double-blind, placebo-controlled multicenter trial of daily everolimus in combination with trastuzumab and vinorelbine, in pretreated women with HER2/neu over-expressing locally advanced or metastatic breast cancer
- CRAD001Y2301: A randomised, double-blind, placebo-controlled study of everolimus in combination with exemestane in the treatment of postmenopausal women with oestrogen receptor positive locally advanced or metastatic breast cancer who are refractory to letrozole or anastrozole (submission of final OS data)
- Submission of CSR of BOLERO-6, in order to clarify the combined effect of everolimus plus exemestane vs everolimus alone due date 3Q 2017.

The CHMP considers the following measure necessary to address issues related to efficacy. This measure is included as a condition in the Annex II:

- Submission of CSR of BOLERO-6, in order to clarify the combined effect of everolimus plus exemestane vs everolimus alone due date 3Q 2017.

2.6. Clinical safety

The overall safety database in the proposed indication consisted of data from 720 postmenopausal women with hormone-receptor-positive advanced breast cancer, with similar demographic and disease characteristics for the two treatment arms in the pivotal study Y2301: 482 were exposed to everolimus at the recommended 10-mg dose and exemestane, using the proposed recommended 25 mg daily dose regimen, and 238 to examestane alone. In addition, safety data from other ongoing studies with everolimus in the treatment of breast cancer, neuroendocrine tumors, renal cell cancer, tuberous sclerosis, lymphoma, hepatocellular carcinoma, and gastric cancer were reviewed for safety signals.

Patient exposure

As of the data cut-off (11 February 2011), median follow-up was 7.6 months. The median duration of exposure to everolimus was 14.6 weeks (range: 1 to 79); the median duration of exposure to exemestane in the same arm was slightly longer (17.4 weeks, range: 1 to 79). Placebo and exemestane were both administered for a median 12.0 weeks in the control arm (range: 1 to 69). Duration of exposure (Table 37), cumulative dose, dose intensity and relative dose intensity (Table 38) are shown below.

Table 37: Duration of exposure to study drug

	Everolimus plus exemestane			Placebo plus exemestane		
	Everolimus	Exemestane	Any[a]	Placebo	Exemestane	Any[a]
	N=482	N=482	N=482	N=238	N=238	N=238
Exposure categories (weeks)						
< 4	26 (5.4)	14 (2.9)	13 (2.7)	6 (2.5)	5 (2.1)	5 (2.1)
4 - < 8	102 (21.2)	89 (18.5)	90 (18.7)	84 (35.3)	82 (34.5)	82 (34.5)
8 - < 12	57 (11.8)	57 (11.8)	57 (11.8)	27 (11.3)	28 (11.8)	28 (11.8)
12 - < 16	69 (14.3)	72 (14.9)	72 (14.9)	32 (13.4)	30 (12.6)	29 (12.2)
16 - < 20	47 (9.8)	46 (9.5)	46 (9.5)	27 (11.3)	29 (12.2)	29 (12.2)
20 - < 24	35 (7.3)	36 (7.5)	36 (7.5)	14 (5.9)	16 (6.7)	16 (6.7)
24 - < 28	26 (5.4)	32 (6.6)	32 (6.6)	12 (5.0)	11 (4.6)	12 (5.0)
28 - < 32	28 (5.8)	37 (7.7)	37 (7.7)	11 (4.6)	12 (5.0)	12 (5.0)
≥ 32	92 (19.1)	99 (20.5)	99 (20.5)	25 (10.5)	25 (10.5)	25 (10.5)
Duration of exposure (weeks)						
n	482	482	482	238	238	238
Mean (SD)	19.80 (15.562)	21.26 (15.537)	21.28 (15.523)	15.83 (12.676)	16.11 (12.685)	16.17 (12.699)
Median	14.57	17.36	17.36	12.00	12.00	12.00
Range	1.0 - 79.4	1.0 - 79.4	1.0 - 79.4	1.0 - 68.6	1.0 - 68.6	1.0 - 68.6
Total patient-year exposure[b]						
	182.9	196.4	196.5	72.2	73.5	73.8

[a] Corresponding to the longer of the two exposures

[b] Total patient-year exposure is the sum of each subject's exposure in days divided by 365.25.

Table 38: Cumulative dose, dose intensity and relative dose intensity

	Everolimus plus exemestane N=482		Placebo plus exemestane N=238	
	Everolimus	**Exemestane**	**Placebo**	**Exemestane**
Cumulative dose (mg) [a]				
n	482	482	238	238
Mean	1145.95	3674.12	1088.61	2808.19
SD	919.098	2705.482	879.511	2214.319
Median	877.50	2875.00	840.00	2100.00
Range	70.0 - 4520.0	175.0 - 13900.0	70.0 - 4800.0	175.0 - 12000.0
Dose intensity (mg/day) [b]				
n	482	482	238	238
Mean	7.89	24.55	9.64	24.83
SD	2.441	1.706	1.153	1.205
Median	8.96	25.00	10.00	25.00
Range	0.4 - 10.0	6.0 - 25.0	1.3 - 10.0	11.5 - 25.9
Relative dose intensity [c]				
n	482	482	238	238
Mean	0.79	0.98	0.96	0.99
SD	0.244	0.068	0.115	0.048
Median	0.90	1.00	1.00	1.00
Range	0.0 - 1.0	0.2 - 1.0	0.1 - 1.0	0.5 - 1.0
Relative dose intensity - n (%) [c]				
0.00 - < 0.50	76 (15.8)	3 (0.6)	5 (2.1)	1 (0.4)
0.50 - < 0.70	81 (16.8)	3 (0.6)	5 (2.1)	1 (0.4)
0.70 - < 0.90	85 (17.6)	20 (4.1)	14 (5.9)	1 (0.4)
0.90 - < 1.10	240 (49.8)	456 (94.6)	214 (89.9)	235 (98.7)

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

Adverse events

A summary of the adverse events for study Y2301 is presented in Table 39.

Table 39: Summary of AE categories

Category	Everolimus plus exemestane N=482 n (%)	Placebo plus exemestane N=238 n (%)
Any AE	**481 (99.8)**	**210 (88.2)**
AEs suspected to be drug related [a]	462 (95.9)	142 (59.7)
Grade 3-4 AEs	211 (43.8)	61 (25.6)
Suspected to be drug related	164 (34.0)	18 (7.6)
Clinically notable AEs	**450 (93.4)**	**100 (42.0)**
Suspected to be drug related [a]	418 (86.7)	45 (18.9)
All deaths	**51 (10.6)**	**31 (13.0)**
On-treatment deaths [b]	12 (2.5)	4 (1.7)
Any SAE	**110 (22.8)**	**29 (12.2)**
Suspected to be drug-related	52 (10.8)	3 (1.3)
AEs leading to discontinuation [c]	**92 (19.1)**	**11 (4.6)**
Suspected to be drug-related	79 (16.4)	7 (2.9)
Other significant AEs	**450 (93.4)**	**161 (67.6)**
AEs leading to dose interruption and/or reduction	278 (57.7)	29 (12.2)
AEs requiring additional therapy	437 (90.7)	160 (67.2)

[a] Related to either one of the two drugs
[b] On-treatment deaths are deaths which occurred up to 28 days after the discontinuation of study treatment
[c] Of at least one of the two study drugs
AEs occurring more than 28 days after the discontinuation of study treatment are not summarized
Additional therapy includes all non-drug therapy and concomitant medications
The clinically notable adverse event groupings consist of adverse events for which there is a specific clinical interest in connection with everolimus or adverse events which are similar in nature

A list of adverse events (at least 10% incidence) in patients treated with examestane and everolimus is presented Table 40.

Table 40: All-causality AEs with grading with at least 10% incidence

	Everolimus plus exemestane N=482			Placebo plus exemestane N=238		
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Any preferred term	**481 (99.8)**	**176 (36.5)**	**35 (7.3)**	**210 (88.2)**	**49 (20.6)**	**12 (5.0)**
Stomatitis	271 (56.2)	37 (7.7)	0	25 (10.5)	2 (0.8)	0
Rash	174 (36.1)	4 (0.8)	0	14 (5.9)	0	0
Fatigue	158 (32.8)	16 (3.3)	2 (0.4)	62 (26.1)	2 (0.8)	0
Diarrhoea	144 (29.9)	9 (1.9)	1 (0.2)	37 (15.5)	2 (0.8)	0
Decreased appetite	139 (28.8)	5 (1.0)	0	24 (10.1)	0	0
Nausea	130 (27.0)	1 (0.2)	1 (0.2)	63 (26.5)	2 (0.8)	0
Cough	105 (21.8)	3 (0.6)	0	26 (10.9)	0	0
Dysgeusia	99 (20.5)	1 (0.2)	0	11 (4.6)	0	0
Headache	92 (19.1)	2 (0.4)	0	30 (12.6)	0	0
Weight decreased	90 (18.7)	5 (1.0)	0	11 (4.6)	0	0
Dyspnoea	86 (17.8)	19 (3.9)	0	22 (9.2)	2 (0.8)	1 (0.4)
Arthralgia	78 (16.2)	4 (0.8)	0	37 (15.5)	0	0
Anaemia	75 (15.6)	25 (5.2)	3 (0.6)	9 (3.8)	1 (0.4)	1 (0.4)
Epistaxis	73 (15.1)	0	0	3 (1.3)	0	0
Vomiting	69 (14.3)	2 (0.4)	1 (0.2)	26 (10.9)	1 (0.4)	0
Oedema peripheral	66 (13.7)	5 (1.0)	0	14 (5.9)	1 (0.4)	0
Pyrexia	66 (13.7)	1 (0.2)	0	15 (6.3)	1 (0.4)	0
Aspartate aminotransferase increased	61 (12.7)	12 (2.5)	1 (0.2)	13 (5.5)	3 (1.3)	0
Constipation	61 (12.7)	1 (0.2)	0	27 (11.3)	1 (0.4)	0
Hyperglycaemia	61 (12.7)	19 (3.9)	2 (0.4)	5 (2.1)	1 (0.4)	0
Pneumonitis	60 (12.4)	15 (3.1)	0	0	0	0
Thrombocytopenia	58 (12.0)	11 (2.3)	4 (0.8)	1 (0.4)	0	1 (0.4)
Asthenia	56 (11.6)	8 (1.7)	0	6 (2.5)	0	0
Alanine aminotransferase increased	55 (11.4)	14 (2.9)	1 (0.2)	8 (3.4)	4 (1.7)	0
Pruritus	55 (11.4)	1 (0.2)	0	8 (3.4)	0	0
Insomnia	53 (11.0)	1 (0.2)	0	18 (7.6)	0	0
Back pain	51 (10.6)	0	0	19 (8.0)	2 (0.8)	0
Pain in extremity	32 (6.6)	2 (0.4)	0	25 (10.5)	4 (1.7)	0
Hot flush	23 (4.8)	0	0	33 (13.9)	0	0

The event with maximum severity is counted for patients who experienced multiple episodes of an event

Stomatitis, rash, and fatigue were the most common AEs reported with everolimus plus exemestane therapy and are each reported in ≥30% of patients. Epistaxis was the most frequent bleeding event responsible for the high overall bleeding frequencies.

A list of adverse drug reactions is presented in Table 41.

Table 41: Adverse events and grading with suspected relationship to study drug

	Everolimus plus exemestane N=482			Placebo plus exemestane N=238		
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Any preferred term	**462 (95.9)**	**149 (30.9)**	**15 (3.1)**	**142 (59.7)**	**16 (6.7)**	**2 (0.8)**
Stomatitis	269 (55.8)	37 (7.7)	0	25 (10.5)	2 (0.8)	0
Rash	155 (32.2)	4 (0.8)	0	11 (4.6)	0	0
Fatigue	104 (21.6)	10 (2.1)	2 (0.4)	39 (16.4)	0	0
Decreased appetite	93 (19.3)	3 (0.6)	0	13 (5.5)	0	0
Diarrhoea	88 (18.3)	6 (1.2)	1 (0.2)	21 (8.8)	1 (0.4)	0
Dysgeusia	87 (18.0)	1 (0.2)	0	9 (3.8)	0	0
Nausea	82 (17.0)	1 (0.2)	1 (0.2)	36 (15.1)	0	0
Pneumonitis	60 (12.4)	15 (3.1)	0	0	0	0
Weight decreased	52 (10.8)	2 (0.4)	0	5 (2.1)	0	0
Epistaxis	48 (10.0)	0	0	1 (0.4)	0	0
Thrombocytopenia	48 (10.0)	10 (2.1)	1 (0.2)	0	0	0
Hyperglycaemia	45 (9.3)	16 (3.3)	1 (0.2)	4 (1.7)	1 (0.4)	0
Headache	43 (8.9)	0	0	13 (5.5)	0	0
Pruritus	43 (8.9)	1 (0.2)	0	5 (2.1)	0	0
Alanine aminotransferase increased	42 (8.7)	12 (2.5)	0	6 (2.5)	3 (1.3)	0
Anaemia	42 (8.7)	10 (2.1)	2 (0.4)	4 (1.7)	1 (0.4)	0
Aspartate aminotransferase increased	40 (8.3)	11 (2.3)	0	10 (4.2)	1 (0.4)	0
Dyspnoea	40 (8.3)	11 (2.3)	0	6 (2.5)	0	0
Cough	39 (8.1)	2 (0.4)	0	7 (2.9)	0	0
Asthenia	32 (6.6)	5 (1.0)	0	1 (0.4)	0	0
Hypercholesterolaemia	32 (6.6)	1 (0.2)	0	2 (0.8)	0	0
Vomiting	31 (6.4)	1 (0.2)	1 (0.2)	10 (4.2)	0	0
Neutropenia	30 (6.2)	11 (2.3)	0	0	0	0
Dry mouth	29 (6.0)	0	0	8 (3.4)	0	0
Nail disorder	28 (5.8)	0	0	1 (0.4)	0	0
Alopecia	26 (5.4)	0	0	8 (3.4)	0	0
Constipation	26 (5.4)	0	0	10 (4.2)	0	0
Oedema peripheral	26 (5.4)	3 (0.6)	0	4 (1.7)	0	0
Dry skin	24 (5.0)	0	0	2 (0.8)	0	0
Arthralgia	23 (4.8)	1 (0.2)	0	15 (6.3)	0	0
Hot flush	11 (2.3)	0	0	25 (10.5)	0	0

Note: Related to either one of the two drugs

The event with maximum severity is counted for patients who experienced multiple episodes of an event

Serious adverse event/deaths/other significant events

Serious adverse events

Serious adverse events were reported in 22.8% of patients in the everolimus plus exemestance treated group compared to 12.2% of patients in the placebo plus exemestane treated group. The most commonly reported SAEs in the everolimus group were pneumonitis (2.5%), pneumonia (1.5%), anaemia, dyspnoea, pulmonary embolism, pyrexia, and renal failure (all 1.2%).

There were 52 patients (10.8%) in the everolimus plus exemestane group compared with 3 patients (1.3%) in the placebo plus exemestane group that experienced SAEs that were suspected to be

adverse drug reactions. The most commonly serious adverse drug reactions were pneumonitis (everolimus: 12 [2.5%]; placebo: 0), renal failure (5 [1.0%]; 0) and hyperglycemia (4 [0.8%]; 0).

Deaths

From the safety population of 720 patients, 51 patients (10.6%) and 31 patients (13.0%) died in the everolimus plus exemestane compared to placebo plus exemestane treatment groups. A summary of the causes of death is shown in Table 42. In the everolimus+exemestane treated arm, one death (0.2%) was suspected by the investigator to be related to study treatment (after 32 days of treatment); for this patient the primary cause of death was hemorrhage from tumor (right anterior chest wall mass). The remaining 6 deaths were not suspected to be related to study treatment, although 4 were due to events that reflect known risks of everolimus therapy. All 6 of these additional deaths from data cut-off of 08-July-2011 were attributed to the underlying malignancy (4 due to study indication and single cases of metastatic breast cancer and neoplasm progression).

Table 42: On-treatment deaths (Safety Set) - Study Y2301

System organ class/ Preferred term	**Original submission: 11-Feb-2011 data cut-off**		**Safety Update: 08-Jul-2011 data cut-off**	
	Everolimus plus exemestane	**Placebo plus exemestane**	**Everolimus plus exemestane**	**Placebo plus exemestane**
	N=482	**N=238**	**N=482**	**N=238**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Total number of on-treatment deaths	**12 (2.5)**	**4 (1.7)**	**18 (3.7)**	**4 (1.7)**
Study indication as primary cause of death	5 (1.0)	3 (1.3)	9 (1.9)	3 (1.3)
AE as primary cause of death	7 (1.5)	1 (0.4)	9 (1.9)	1 (0.4)
Infections and infestations	**3 (0.6)**	**0**	**3 (0.6)**	**1 (0.4)**
Pneumonia	1 (0.2)	0	1 (0.2)	1 (0.4)
Sepsis	1 (0.2)	0	1 (0.2)	0
Staphylococcal sepsis	1 (0.2)	0	1 (0.2)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (0.2)**	**0**	**3 (0.6)**	**0**
Tumour haemorrhage	1 (0.2)	0	1 (0.2)	0
Breast cancer metastatic	0	0	1 (0.2)	0
Neoplasm progression	0	0	1 (0.2)	0
Nervous system disorders	**1 (0.2)**	**0**	**1 (0.2)**	**0**
Transient ischaemic attack	1 (0.2)	0	0	0
Ischaemic stroke	0	0	1 (0.2)	0
Psychiatric disorders	**1 (0.2)**	**0**	**1 (0.2)**	**0**
Completed suicide	1 (0.2)	0	1 (0.2)	0
Renal and urinary disorders	**1 (0.2)**	**0**	**1 (0.2)**	**0**
Renal failure	1 (0.2)	0	1 (0.2)	0
Respiratory, thoracic and mediastinal disorders	**0**	**1 [a] (0.4)**	**0**	**0**
Pneumonitis	0	1 [a] (0.4)	0	0

[a] The reason of death reported was 'pneumonitis' in lieu of 'infectious pneumonitis' as reported in the AE CRF pages that was coded to pneumonia. The investigator confirmed that the event was infectious but the reason of death was not corrected on time for inclusion in the database for the interim analysis.

On-treatment deaths are deaths which occurred up to 28 days after the discontinuation of study treatment.

Other significant events

The most commonly occurring AEs necessitating dose interruption and/or reduction in the everolimus plus exemestane group were stomatitis (22.0% of patients), pneumonitis (6.0%), and thrombocytopenia (5.0%) with a total of 57.7% of such AEs compared to 12.2% in the placebo plus exemestane group). Dose adjustments as the result of AEs from the following SOCs were more common in the everolimus plus exemestane group: 'gastrointestinal disorders' (+24.6% relative to placebo), 'respiratory, thoracic and mediastinal disorders' (+12.0%), 'investigations' (+9.1%), 'blood and lymphatic system disorders (+7.5%), 'infections and infestations' (+7.3%), 'skin and subcutaneous tissue disorders' (+5.2%), and 'general disorders and administration site conditions' (+5.0%).

There were 6 AEs that required additional treatment in the everolimus plus exemestane group: stomatitis (+35.4% relative to placebo plus exemestane), rash (+14.3%), pneumonitis (+7.1%), anemia (+6.6%), hyperglycemia (+6.0%), and headache (+5.6%). On the other hand, in the placebo group bone pain and pain in extremities required about 3.5% more frequently additional therapy.

The incidence of bone-related AEs was low (less than 2.5% overall), and these events were reported in a similar proportion of patients across the two treatment arms. No grade 3-4 fractures were reported in the everolimus plus exemestane arm (0 out of 11 patients) compared with 3 grade-3 events in the exemestane plus placebo arm (1.3%; 3 out of 6 patients). One patient experienced spinal compression fracture (grade 2) in the everolimus plus exemestane arm which was considered related to study medication.

Laboratory findings

Higher rates of clinical and heamatological abnormalities were observed in treated patients with everolimus plus exemestane compared to placebo plus exemestane group (Table 43). Hyperglycemia and elevated lipids were managed with concomitant medication and/or dietary intervention. Anemia was commonly treated with blood transfusion. Patients with creatinine elevations required varied interventions, primarily volume repletion and/or change in potentially nephrotoxic medications.

Table 43: Grading of abnormal laboratory values for heamatology and clinical chemistry

Parameter	Everolimus plus exemestane N=482			Placebo plus exemestane N=238		
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Any abnormal value	**440 (91.3)**	**75 (15.6)**	**9 (1.9)**	**157 (66.0)**	**14 (5.9)**	**5 (2.1)**
Haemoglobin (hypo)	306 (63.5)	20 (4.1)	3 (0.6)	90 (37.8)	2 (0.8)	1 (0.4)
WBC (total) (hypo)	269 (55.8)	7 (1.5)	0	63 (26.5)	0	2 (0.8)
Platelet count (direct) (hypo)	259 (53.7)	14 (2.9)	1 (0.2)	11 (4.6)	0	1 (0.4)
Absolute lymphocytes (hypo)	250 (51.9)	47 (9.8)	4 (0.8)	83 (34.9)	12 (5.0)	2 (0.8)
Absolute neutrophils (seg. + bands) (hypo)	145 (30.1)	11 (2.3)	2 (0.4)	23 (9.7)	2 (0.8)	2 (0.8)
Any abnormal value	**478 (99.2)**	**111 (23.0)**	**15 (3.1)**	**220 (92.4)**	**42 (17.6)**	**8 (3.4)**
Glucose (hyper)	321 (66.6)	34 (7.1)	2 (0.4)	97 (40.8)	2 (0.8)	0
Cholesterol (total) (hyper)	320 (66.4)	2 (0.4)	1 (0.2)	86 (36.1)	2 (0.8)	0
SGOT (AST) (hyper)	316 (65.6)	18 (3.7)	1 (0.2)	101 (42.4)	8 (3.4)	1 (0.4)
Gamma glutamyltransferase (hyper)	268 (55.6)	42 (8.7)	8 (1.7)	122 (51.3)	28 (11.8)	7 (2.9)
SGPT (ALT) (hyper)	223 (46.3)	17 (3.5)	1 (0.2)	66 (27.7)	10 (4.2)	0
Triglycerides (hyper)	213 (44.2)	1 (0.2)	0	52 (21.8)	0	0
Alkaline phosphatase, serum (hyper)	158 (32.8)	3 (0.6)	0	97 (40.8)	8 (3.4)	0
Albumin (hypo)	138 (28.6)	3 (0.6)	0	35 (14.7)	1 (0.4)	0
Calcium (hypo)	132 (27.4)	1 (0.2)	2 (0.4)	27 (11.3)	2 (0.8)	0
Potassium (hypo)	127 (26.3)	19 (3.9)	1 (0.2)	16 (6.7)	3 (1.3)	0
Creatinine (hyper)	96 (19.9)	9 (1.9)	1 (0.2)	29 (12.2)	0	0
Sodium (hypo)	73 (15.1)	13 (2.7)	1 (0.2)	40 (16.8)	6 (2.5)	0
Sodium (hyper)	43 (8.9)	0	0	13 (5.5)	0	0
Calcium (hyper)	27 (5.6)	0	0	17 (7.1)	0	0
Potassium (hyper)	26 (5.4)	3 (0.6)	0	24 (10.1)	1 (0.4)	0
Bilirubin (total) (hyper)	18 (3.7)	4 (0.8)	0	23 (9.7)	1 (0.4)	0
Glucose (hypo)	10 (2.1)	0	1 (0.2)	8 (3.4)	0	0

SGOT (AST) Serum glutamic oxaloacetic transaminase; SGPT (ALT) Serum glutamic pyruvic transaminase

Abnormal glomerular filtration rates (defined as grades 2 to 4) were reported more frequently in the everolimus plus exemestane treated group (30.9%) compared to placebo plus exemestane (21.8%) group; most of these abnormalities were grade 2.

Differences in vital signs and body weight between treatment groups were not considered to be clinically noteworthy. No significant change in blood pressure, changes in pulse, respiratory rate, or temperature was recorded at any time during the study in either treatment arm.

Hypersensitivity Reactions

The rates of hypersensitivity for both treatment groups are shown in Table 44.

Table 44: Hypersensitivity reactions in patients treated with exemestane with and without everolimus – Study Y2301

Preferred term	Everolimus plus exemestane N=482			Placebo plus exemestane N=238		
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Any hypersensitivity reactions (anaphylactic reactions)	5 (1.0)	1 (0.2)	0	2 (0.8)	0	0

One patient (0.2%) in the everolimus plus exemestane arm required dose adjustment/interruption as a result of angio-oedema.

Safety in special populations

Age

38% (275/449) of the patients in the pivotal study were aged ≥ 65 years. The following AE categories were found to be higher in the age groups of ≥ 65 years versus < 65 years:

- AEs grade 3 (42.2% versus 32.8%) or grade 4 (9.9% versus 5.5%)
- AEs leading to study drug discontinuation: 29.2% versus 12.4% (e.g. dyspnea, fatigue, decreased appetite, rash)
- Deaths: 4.7% versus 1.0%
- SAEs: 29.2% versus 18.6%
- Clinically notable AEs:
  - renal events: 14.1% versus 6.2% (mainly blood creatinine increased)
  - haemorrhages: 24.0% versus 16.6% (mainly epistaxis)

Breakdown of the elderly population (≥ 75 years, ≥ 70 to < 75 years, and ≥ 65 to < 70 years) provided no further evidence of relevant differences across these subgroups as the numbers of patients were too low.

Safety related to drug-drug interactions and other interactions

Pharmacokinetic blood samples in 130 patients were collected for the assessment of everolimus, exemestane, and oestradiol levels (please refer to clinical pharmacokinectic section 2.4.2). Exposure to everolimus expressed as trough concentrations (Cmin) or 2 hours post administration (C2h) was (mean±SD) 16.04±9.356 ng/mL and 46.50±17.954 ng/m L, respectively.

Following co-administration of everolimus+exemestane, Cmin and C2h were 45% and 71% higher than placebo+exemestane values.

Discontinuation due to adverse events

Altogether, 13% of the patients in the everolimus+exemestane group withdrew due to AEs or 'patient wish' compared to 5% in the placebo+exemestane group. Discontinuations directly attributable to AEs were more frequent in the everolimus group (19.1% vs. 4.6% with placebo) and about half of the cases were grade 3 or 4 events. The most commonly reported AEs leading to discontinuation were

pneumonitis (3.9% of patients), stomatitis (2.3%), fatigue (1.9%), decreased appetite (1.7%), dyspnea (1.7%), anemia (1.2%), and nausea (1.0%), but except for dyspnea these events were predominantly of grades 1-2.

Discontinuations due to the following SOCs were more common in the everolimus plus exemestane arm: 'respiratory, thoracic and mediastinal disorders' (+7.3% relative to placebo plus exemestane), 'gastrointestinal disorders' (+4.4%), and 'general disorders and administration site conditions' (+3.7%).

Post marketing experience

The MAH did not submit new safety information on post-marketing usage in the claimed indication.

2.6.1. Discussion on clinical safety

The safety and tolerability of everolimus 10-mg daily in combination with exemestane 25-mg daily in the treatment of oestrogen-receptor positive postmenopausal women with advanced breast cancer after previous non-steroidal aromatase-inhibitors was assessed. The median duration of treatment for everolimus plus exemestane was 14.6 months, while the placebo plus exemestane group received treatment for a median of 12 months.

In general, the reported adverse events were similar to what has been reported for RCC and pNET treatments at the same dose. The most common adverse drug reactions, with an incidence ≥ 10%, reported in association with everolimus plus exemestane therapy were: stomatitis, rash, fatigue, decreased appetite, diarrhoea, dysgeusia, nausea, pneumonitis, weight decreased, epistaxis, and thrombocytopenia. Stomatitis was reported more than 5-fold compared to the placebo arm (64.5% vs. 10.9%). Haemorrhages were seen twice as often as in the placebo group (19.5% vs. 8.9%). The most common grade 3-4 adverse drug reactions, with an incidence ≥ 2% were: stomatitis, hyperglycaemia, pneumonitis, anaemia, fatigue, elevated alanine transaminase, thrombocytopenia, elevated aspartate transaminase, dyspnoea, and neutropenia.

The total percentage of on-treatment deaths were 2.5% in the combination group vs. 1.7% in the control group. In those patients with 'AE' as primary cause of death, the proportions were 1.5% vs. 0.4%, respectively. Infectious events might be the major cause of AE related deaths. Non-infectious pneumonitis, stomatitis/oral mucositis, and an increased susceptibility to infection represent the most important clinical issues.

Interestingly, the very common exemestane ADR 'hot-flushes' was reported less frequent in the everolimus plus exemestane group than in the placebo plus exemestane arm. The mechanism of action was unknown.

There were no unexpected results concerning abnormal laboratory values for everolimus plus exemestane treatment.

Concerning AEs in the elderly, AEs were reported more often in patients above 65 years. In a subgroup of Asian, i.e. Japanese patients, a higher rate of some ADRs, especially stomatitis was reported.

<u>Women of childbearing potential/Contraception in males and females</u>
Women of childbearing potential must use a highly effective method of contraception (e.g. oral, injected, or implanted non-oestrogen-containing hormonal method of birth control, progesterone-based contraceptives, hysterectomy, tubal ligation, complete abstinence, barrier methods, intrauterine device [IUD], and/or female/male sterilisation) while receiving everolimus, and for up to 8 weeks after ending treatment.

<u>Pregnancy</u>

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

Everolimus is not recommended during pregnancy and in women of childbearing potential not using contraception.

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

Fertility
The potential for everolimus to cause infertility in male and female patients is unknown, however secondary amenorrhoea and associated luteinising hormone (LH)/follicle stimulating hormone (FSH) imbalance has been observed in female patients. Based on non-clinical findings, male fertility may be compromised by treatment with everolimus (see section 5.3).

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

2.6.2. Conclusions on the clinical safety

The safety and tolerability of everolimus in study Y2301 showed no unexpected toxicities. No new safety concerns have emerged in the combination of everolimus plus exemestane. The SmPC already lists the ADRs observed in this phase III study and thus, no need to update the safety information in section 4.8.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

Risk Management Plan

The applicant submitted a risk management plan

Table 45: Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
Important identified risks		
Non-infectious pneumonitis	Routine pharmacovigilance. **Additional activities** Targeted follow-up of all serious spontaneous reports, post-marketing surveillance study reports, reports from other programs where data are being handled as solicited and all clinical trial SAE reports using a targeted product questionnaire/checklist.	Warning in SPC Section 4.4: "Non-infectious pneumonitis is a class effect of rapamycin derivatives, including Afinitor. Non-infectious pneumonitis (including interstitial lung disease) was described in 12% of patients taking Afinitor (see section 4.8). Some cases were severe and on rare occasions, a fatal outcome was

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
		observed. A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnoea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations. Patients should be advised to report promptly any new or worsening respiratory symptoms. Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue Afinitor therapy without dose adjustments. If symptoms are moderate, consideration should be given to interruption of therapy until symptoms improve. The use of corticosteroids may be indicated. Afinitor may be reinitiated at 5 mg daily. For cases where symptoms of non-infectious pneumonitis are severe, Afinitor therapy should be discontinued and the use of corticosteroids may be indicated until clinical symptoms resolve. Therapy with Afinitor may be reinitiated at 5 mg daily depending on the individual clinical circumstances." Pneumonitis is included as ADR in SPC Section 4.8.
Severe infections	Routine pharmacovigilance. **Additional activities** Targeted follow-up of all serious spontaneous reports, post-marketing surveillance study reports, reports from other programs where data are being handled as solicited and all clinical trial SAE reports using targeted product questionnaire/checklist.	Warning in SPC Section 4.4: "Afinitor has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoal infections, including infections with opportunistic pathogens (see section 4.8). Localised and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections such as aspergillosis or candidiasis, and viral infections including reactivation of hepatitis B virus, have been described in patients taking Afinitor. Some of these infections have been severe (e.g., leading to respiratory or hepatic failure) and occasionally fatal. Physicians and patients should be aware of the increased risk of infection with Afinitor. Pre-existing infections should be treated appropriately and should have

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
		resolved fully before starting treatment with Afinitor. While taking Afinitor, be vigilant for symptoms and signs of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of Afinitor. If a diagnosis of invasive systemic fungal infection is made, Afinitor treatment should be promptly and permanently discontinued and the patient treated with appropriate antifungal therapy." Infections are included as ADR in SPC Section 4.8.
Hypersensitivity (anaphylactic reactions)	Routine pharmacovigilance. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-serious marketing surveillance study reports, reports from other programs where data is being handled as solicited and all clinical trial SAE reports, using a targeted event questionnaire/checklist.	Contraindication in SPC Section 4.3: "Hypersensitivity to the active substance, to other rapamycin derivatives or to any of the excipients." Warning in SPC Section 4.4: "Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnoea, flushing, chest pain or angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus (see section 4.3)." Dyspnoea, flushing, angioedema, chest pain are included as ADRs in SPC Section 4.8.
Stomatitis	Routine pharmacovigilance.	Warning in SPC Section 4.4: "Mouth ulcers, stomatitis and oral mucositis have been observed in patients treated with Afinitor (see section 4.8). In such cases topical treatments are recommended, but alcohol- or peroxide-containing mouthwashes should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless fungal infection has been diagnosed (see section 4.5)." Stomatitis is included as ADR in SPC Section 4.8.
Wound healing complications	Routine pharmacovigilance.	Warning in SPC Section 4.4: "Impaired wound healing is a class effect of rapamycin derivates, including Afinitor. Caution should therefore be exercised with the use of Afinitor in the peri-surgical period." Impaired wound healing is included as an ADR in SPC Section 4.8.
Increased creatinine/proteinuria/ renal failure	Routine pharmacovigilance. **Additional activities**	Warning in SPC Section 4.4: Elevations of serum creatinine, usually mild, and proteinuria have

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
	Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, serious reports from other programs where data is being handled as solicited and all clinical trial SAE reports, using a targeted event questionnaire/checklist.	been reported in clinical trials (see section 4.8). Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein or serum creatinine, is recommended prior to the start of Afinitor therapy and periodically thereafter. Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with Afinitor (see section 4.8). Renal function of patients should be monitored particularly where patients have additional risk factors that may further impair renal function." Increased creatinine, proteinuria, and renal failure are included as ADRs in SPC Section 4.8.
Hyperglycaemia/new onset diabetes mellitus	Routine pharmacovigilance.	Warning in SPC Section 4.4: "Hyperglycaemia, hyperlipidaemia and hypertrigylceridaemia have been reported in clinical trials (see section 4.8). Monitoring of fasting serum glucose is recommended prior to the start of Afinitor therapy and periodically thereafter. When possible optimal glycaemic control should be achieved before starting a patient on Afinitor." Glucose increased, triglycerides increased, and new-onset diabetes mellitus are included as ADRs in SPC Section 4.8.
Dyslipidaemia	Routine pharmacovigilance.	Warning in SPC Section 4.4: "Hyperglycaemia, hyperlipidaemia and hypertrigylceridaemia have been reported in clinical trials (see section 4.8)." Cholesterol increased and triglycerides increased are included as ADRs in SPC Section 4.8.
Hypophosphataemia	Routine pharmacovigilance.	Phosphate decreased is included as ADR in SPC Section 4.8.
Cardiac failure	Routine pharmacovigilance including detailed cumulative review in the PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, serious reports from other programs where data is being handled as solicited and all clinical trial SAE reports, using a targeted event questionnaire/checklist.	Congestive cardiac failure is included as ADR in SPC Section 4.8.
Cytopenia	Routine pharmacovigilance including detailed cumulative	Warning in SPC Section 4.4: "Decreased haemoglobin,

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
	review in the PSUR.	lymphocytes, neutrophils and platelets have been reported in clinical trials (see section 4.8). Monitoring of complete blood count is recommended prior to the start of Afinitor therapy and periodically thereafter." Lymphocytes decreased, platelets decreased, and neutrophils decreased are included as ADRs in SPC Section 4.8.
Hemorrhages	Routine pharmacovigilance including detailed cumulative review in the PSUR.	Haemorrhage is included as ADR in SPC Section 4.8.
Thromboembolism	Routine pharmacovigilance including detailed cumulative review in the PSUR.	Pulmonary embolism is included as ADR in SPC Section 4.8.
Secondary amenorrhea in post-adolescent females	Routine pharmacovigilance including cumulative analysis in the PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, serious reports from other programs where data is being handled as solicited and all clinical trial SAE reports, using a targeted event questionnaire/checklist. Formal amenorrhea analysis across CRAD001C2485, CRAD001M2301, and CRAD001M2302 following study completions.	Relevant information in SPC Section 4.6: "The potential for everolimus to cause infertility in male and female patients is unknown, however secondary amenorrhoea and associated luteinising hormone (LH) /follicle stimulating hormone (FSH) imbalance has been observed in female patients." Secondary amenorrhea/LH/FSH imbalance included as ADRs in SPC Section 4.8.
Pre-existing infection (reactivation, aggravation, or exacerbation)	Routine pharmacovigilance including detailed cumulative review in the PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, serious reports from other programs where data is being handled as solicited and all clinical trial SAE reports, using a targeted product questionnaire/checklist.	Warning in SPC Section 4.4: "Afinitor has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoal infections, including infections with opportunistic pathogens (see section 4.8). Localised and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections such as aspergillosis or candidiasis, and viral infections including reactivation of hepatitis B virus, have been described in patients taking Afinitor. Some of these infections have been severe (e.g., leading to respiratory or hepatic failure) and occasionally fatal. Physicians and patients should be aware of the increased risk of infection with Afinitor. Pre-existing infections should be treated appropriately and should have resolved fully before starting treatment with Afinitor. While taking

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
		Afinitor, be vigilant for symptoms and signs of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of Afinitor. If a diagnosis of invasive systemic fungal infection is made, Afinitor treatment should be promptly and permanently discontinued and the patient treated with appropriate antifungal therapy." Infections are included as ADR in SPC Section 4.8. "In clinical studies, everolimus has been associated with serious cases of hepatitis B reactivation, including fatal outcome. Reactivation of infection is an expected event during periods of immunosuppression."
Safety in patients with hepatic impairment	Routine pharmacovigilance including detailed cumulative review in the PSUR.	Appropriate dosing information in SPC Section 4.2: "• Severe hepatic impairment (Child-Pugh C) – not recommended. Relevant information in SPC Section 4.4: "Votubia should not be used in patients with severe hepatic impairment (Child-Pugh class C) Further information in SPC Section 5.2: "Hepatic impairment The safety, tolerability and pharmacokinetics of Afinitor were evaluated in a single oral dose study of everolimus in 34 subjects with impaired hepatic function relative to subjects with normal hepatic function. Compared to normal subjects, there was a 1.6-fold, 3.3-fold, and 3.6-fold increase in exposure (i.e. AUC0-inf) for subjects with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment, respectively. Simulations of multiple dose pharmacokinetics support the dosing recommendations in hepatic impaired subjects based on their Child Pugh status. Dose adjustment is recommended for patients with hepatic impairment."
Important potential risks		
Postnatal developmental toxicity	Routine pharmacovigilance including detailed cumulative review in the PSUR.	Relevant information included in SPC Section 5.3: "In rats, everolimus caused embryo/

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
	Additional activities Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, and serious reports from other programs where data are being handled as solicited and all clinical trial SAE reports, using a targeted event questionnaire/checklist. Study CRAD001M2301: A randomized, double-blind, placebo-controlled study of RAD001 in the treatment of patients with subependymal giant cell astrocytomas (SEGA) associated with tuberous sclerosis complex (TSC). Study CRAD001C2485: Everolimus (RAD001) therapy of giant cell astrocytomas in patients with tuberous sclerosis complex (including children). Both studies: • Mandated evaluation of endocrine hormonal levels in all patients: LH, FSH, testosterone (males only), estradiol (females only) at screening and every 24 weeks thereafter through the end of the study; Tanner classification until stage V or until the age of 15 (females) or 16 (males) • Weight and height	foetotoxicity at systemic exposure below the therapeutic level. This was manifested as mortality and reduced foetal weight. The incidence of skeletal variations and malformations (e.g. sternal cleft) was increased at 0.3 and 0.9 mg/kg. In rabbits, embryotoxicity was evident in an increase in late resorptions."
Reproductive (teratogenicity) toxicity	Routine pharmacovigilance including detailed cumulative review in the PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, and serious reports from other programs where data are being handled as solicited and all clinical trial SAE reports, using a targeted event and pregnancy questionnaire/checklist.	Relevant information in SPC Section 4.6: "There are no or limited data from the use of everolimus in pregnant women. Studies in animals have shown reproductive toxicity effects (see section 5.3). Everolimus is not recommended during pregnancy and in women of childbearing potential not using contraception." Relevant information included in SPC Section 5.3: "In a male fertility study in rats, testicular morphology was affected at 0.5 mg/kg and above, and sperm motility, sperm head count, and plasma testosterone levels were diminished at 5 mg/kg, which is within the range of therapeutic exposure (52 ng•hr/mL and 414 ng•hr/mL, respectively, compared to 560 ng•hr/mL human exposure at 10 mg/day) and which caused a reduction in male fertility.

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
		There was evidence of reversibility. Female fertility was not affected, but everolimus crossed the placenta and was toxic to the foetus."
Intestinal obstruction/ileus	Routine pharmacovigilance including detailed cumulative review in the PSUR.	None.
Male infertility	Routine pharmacovigilance including detailed cumulative review in the PSUR.	Relevant information in SPC Section 4.6: "Studies in animals have shown reproductive toxicity effects (see Section 5.3). Based on non-clinical findings, male fertility may be compromised by treatment with everolimus (see section 5.3)." Relevant information included in SPC Section 5.3: "In a male fertility study in rats, testicular morphology was affected at 0.5 mg/kg and above, and sperm motility, sperm head count, and plasma testosterone levels were diminished at 5 mg/kg, which is within the range of therapeutic exposure and which caused a reduction in male fertility. There was evidence of reversibility. Female fertility was not affected, but everolimus crossed the placenta and was toxic to the foetus."
Pancreatitis	Routine pharmacovigilance including detailed cumulative review in the PSUR.	None
Cholelithiasis	Routine pharmacovigilance including detailed cumulative review in the PSUR.	None
Important identified interaction		
Strong CYP3A4 inhibitors and PgP inhibitors	Routine pharmacovigilance.	Relevant information in SPC Section 4.4: "Co-administration with inhibitors and inducers of CYP3A4 and/or the multidrug efflux pump P-glycoprotein (PgP) should be avoided. If co-administration of a moderate CYP3A4 and/or PgP inhibitor or inducer cannot be avoided, dose adjustments of Afinitor can be taken into consideration based on predicted AUC (see section 4.5). Concomitant treatment with potent CYP3A4 inhibitors result in dramatically increased plasma concentrations of everolimus (see section 4.5). There are currently not sufficient data to allow dosing recommendations in this situation. Hence, concomitant treatment of

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
		Afinitor and potent inhibitors is not recommended." Relevant information in SPC Section 4.5: "Substances that are inhibitors of CYP3A4 or PgP may increase everolimus blood concentrations by decreasing the metabolism or the efflux of everolimus from intestinal cells. Interaction by and recommendations regarding concomitant administration of specific CYP3A4 and PgP inhibitors is included in Table 1 in the same SPC section." Relevant information in SPC Section 5.2: "The results of a meta-analysis of pharmacokinetic data from blood samples collected from several clinical studies including 945 patients demonstrated that concomitant administration of CYP3A4 inducers and inhibitors did not appear to have a significant effect on the Cmin exposure of everolimus beyond the limits of variability. Moderate and strong inhibitors increased Cmin exposure by 5% and 10%, respectively, and potent inducers increased Cmin exposure by 7%."
Moderate CYP3A4 inhibitors and PgP inhibitor	Routine pharmacovigilance.	Relevant information in SPC Section 4.4: "Co-administration with inhibitors and inducers of CYP3A4 and/or the multidrug efflux pump P-glycoprotein (PgP) should be avoided. If co-administration of a moderate CYP3A4 and/or PgP inhibitor or inducer cannot be avoided, dose adjustments of Afinitor can be taken into consideration based on predicted AUC (see section 4.5). Concomitant treatment with potent CYP3A4 inhibitors result in dramatically increased plasma concentrations of everolimus (see section 4.5). There are currently not sufficient data to allow dosing recommendations in this situation. Hence, concomitant treatment of Afinitor and potent inhibitors is not recommended." Relevant information in SPC Section 4.5: "Substances that are inhibitors of CYP3A4 or PgP may increase everolimus blood concentrations by

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
		decreasing the metabolism or the efflux of everolimus from intestinal cells. Interaction by and recommendations regarding concomitant administration of specific CYP3A4 and PgP inhibitors is included in Table 1 in the same SPC section." Relevant information in SPC Section 5.2: "The results of a meta-analysis of pharmacokinetic data from blood samples collected from several clinical studies including 945 patients demonstrated that concomitant administration of CYP3A4 inducers and inhibitors did not appear to have a significant effect on the Cmin exposure of everolimus beyond the limits of variability. Moderate and strong inhibitors increased Cmin exposure by 5% and 10%, respectively, and potent inducers increased Cmin exposure by 7%."
Strong CYP3A4 inducers and PgP inducers	Routine pharmacovigilance.	Relevant information in SPC Section 4.4: "Co-administration with inhibitors and inducers of CYP3A4 and/or the multidrug efflux pump P-glycoprotein (PgP) should be avoided. If co-administration of a moderate CYP3A4 and/or PgP inhibitor or inducer cannot be avoided, dose adjustments of Afinitor can be taken into consideration based on predicted AUC (see section 4.5)." Relevant information in SPC Section 4.5: "Substances that are inducers of CYP3A4 or PgP may decrease everolimus blood concentrations by increasing metabolism or the efflux of everolimus from intestinal cells." Interaction by and recommendations regarding concomitant administration of specific CYP3A4 and PgP inducers is included in Table 1 in the same SPC section." Relevant information in SPC Section 5.2: "The results of a meta-analysis of pharmacokinetic data from blood samples collected from several clinical studies including 945 patients demonstrated that concomitant administration of CYP3A4 inducers and inhibitors did

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
		not appear to have a significant effect on the Cmin exposure of everolimus beyond the limits of variability. Moderate and strong inhibitors increased Cmin exposure by 5% and 10%, respectively, and potent inducers increased Cmin exposure by 7%."
CYP3A4 substrates and PgP substrates	Routine pharmacovigilance.	Relevant information in SPC Section 4.5: "Based on in vitro results, the systemic concentrations obtained after oral daily doses of 10 mg make inhibition of PgP, CYP3A4 and CYP2D6 unlikely. However, inhibition of CYP3A4 and PgP in the gut cannot be excluded; hence everolimus may affect the bioavailability of co-administered substances which are CYP3A4 and/or PgP substrates."
Important potential interaction		
Not applicable		None
Important missing information		
Pediatric patients less than 3 years old	Routine pharmacovigilance including cumulative analysis in PSUR.	Appropriate dosing information in SPC Section 4.2: "The safety and efficacy of Afinitor in children aged 0 to 18 years have not been established. No data are available." Relevant information in SPC Section 5.1: "The EMA has waived the obligation to submit the results of studies with Afinitor in all subsets of paediatric population in renal cell carcinoma (see section 4.2 for information on paediatric use)."
Off-label use in pediatric and adolescent patients	Routine pharmacovigilance including cumulative analysis in PSUR.	Appropriate dosing information in SPC Section 4.2: "The safety and efficacy of Afinitor in children aged 0 to 18 years have not been established. No data are available." Relevant information in SPC Section 5.1: "The EMA has waived the obligation to submit the results of studies with Afinitor in all subsets of paediatric population in renal cell carcinoma (see section 4.2 for information on paediatric use)."
Pregnant or breast-feeding women	Routine pharmacovigilance including cumulative analysis in PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-	Relevant information included in SPC Section 4.6: "There are no or limited amount of data from the use of everolimus in pregnant women. Everolimus is not recommended

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
	marketing surveillance study reports, and serious reports from other programs where data are being handled as solicited and all clinical trial SAE reports, using a targeted event and pregnancy questionnaire/checklist.	during pregnancy and in women of childbearing potential not using contraception. It is not known whether everolimus is excreted in breast milk. However, in rats, everolimus and/or its metabolites readily pass into the milk. Therefore, women taking everolimus should not breast-feed."
Hormonal contraceptive use	Routine pharmacovigilance.	Relevant information included in Afinitor SPC Section 4.6: "Women of childbearing potential must use effective method of contraception while receiving everolimus." Relevant information included in Votubia SPC Section 4.6: "Women of childbearing potential must use highly effective method of contraception (e.g. oral, injected, or implanted non-oestrogen-containing hormonal method of birth control, progesterone-based contraceptives, hysterectomy, tubal ligation, complete abstinence, barrier methods, intrauterine device [IUD], and/or female/male sterilisation) while receiving everolimus, and for up to 8 weeks after ending treatment."
Patients with renal impairment	Routine pharmacovigilance. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, and serious reports from other programs where data are being handled as solicited and all clinical trial SAE reports, using a targeted event questionnaire/ checklist.	Information in SPC Section 4.2: "No dose adjustment is required (see section 5.2)." Further information in SPC Section 5.2: "In a population pharmacokinetic analysis of 170 patients with advanced solid tumors, no significant influence of creatinine clearance (25-178 mL/min) was detected on CL/F of everolimus. Post-transplant renal impairment (creatinine clearance range, 11-107 mL/min) did not affect the pharmacokinetics of everolimus in transplant patients."
Long-term safety	Routine pharmacovigilance. **Additional activities** • TSC patients CRAD001M2301: A randomized, double-blind, placebo-controlled study of RAD001 in the treatment of patients with subependymal giant cell astrocytomas (SEGA) associated with tuberous sclerosis complex (TSC). CRAD001C2485: Everolimus (RAD001) therapy of giant cell astrocytomas in patients with	None

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
	tuberous sclerosis complex (including children). CRAD001M2302: A randomized double-blinded study of RAD001 10 mg/d versus placebo in the treatment of angiomyolipomata in patients with tuberous sclerosis complex and/or sporadic lymphangioleiomyomatosis All studies: Mandated evaluation of endocrine hormonal levels in all patients: LH, FSH, testosterone (males only), estradiol (females only) at screening and every 24 weeks thereafter through the end of the study; Tanner classification until stage V or until the age of 15 (females) or 16 (males) Weight and height Disease registry CRAD001MIC03: An international disease registry collecting data on manifestations, interventions, and outcomes in patients with tuberous sclerosis complex – TOSCA [draft protocol in progress] Safety assessments include dose/regimen changes, treatment discontinuation of mTOR inhibitors and other TSC therapies excluding symptomatic therapies (e.g. antiepileptics), frequency and type of follow-up visits (e.g. hospitalization, emergency room visit), frequency of surgical procedures, other safety outcomes (e.g. death), and safety monitoring and reporting (e.g. SAE, pregnancy). • Breast cancer patients CRAD001J2301: A randomized, phase III, double-blind, placebo-controlled multicenter trial of everolimus in combination with trastuzumab and paclitaxel as first-line therapy in women with HER2 positive locally advanced or metastatic breast cancer CRAD001W2301: A randomized, phase III, double-blind, placebo-controlled multicenter trial of daily everolimus in combination with trastuzumab and vinorelbine, in pretreated women with HER2/neu over-expressing locally advanced or metastatic breast cancer CRAD001Y2301: A randomized,	

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
	double-blind, placebo-controlled study of everolimus in combination with exemestane in the treatment of postmenopausal women with estrogen receptor positive locally advanced or metastatic breast cancer who are refractory to letrozole or anastrozole	
Patients with CNS metastases Patients with uncontrolled or cardiac disease Patients with impairment of GI function Patients undergoing chronic treatment with steroids or another immunosuppressive agent Carcinogenicity Product impurities	Routine pharmacovigilance.	None
Comparative safety of everolimus combination vs. monotherapy in BOLERO-6	Routine pharmacovigilance. **Additional activities** CRAD001Y2201: A three-arm randomized phase II study investigating the combination of everolimus with exemestane vs. everolimus alone vs. capecitabine in patients with estrogen-receptor positive metastatic breast cancer after recurrence or progression on letrozole or anastrozole	None
	Agreed pharmacovigilance activities (routine and non-routine)	**Agreed risk minimization activities (routine and non-routine)**
Important identified risks		
Non-infectious pneumonitis	Routine pharmacovigilance activities including cumulative analysis in PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, post-marketing surveillance study reports, reports from other programs where data are being handled as solicited and all clinical trial SAE reports using a targeted product questionnaire/checklist.	Warning in SPC Section 4.4: "Non-infectious pneumonitis is a class effect of rapamycin derivatives, including Afinitor. Non-infectious pneumonitis (including interstitial lung disease) was described in 12% of patients taking Afinitor (see section 4.8). Some cases were severe and on rare occasions, a fatal outcome was observed. A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnoea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations. Patients should be advised to report promptly any new or worsening respiratory symptoms. Patients who develop radiological

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
		changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue Afinitor therapy without dose adjustments. If symptoms are moderate, consideration should be given to interruption of therapy until symptoms improve. The use of corticosteroids may be indicated. Afinitor may be reinitiated at 5 mg daily. For cases where symptoms of non-infectious pneumonitis are severe, Afinitor therapy should be discontinued and the use of corticosteroids may be indicated until clinical symptoms resolve. Therapy with Afinitor may be reinitiated at 5 mg daily depending on the individual clinical circumstances." Pneumonitis is included as ADR in SPC Section 4.8.
Increased creatinine/Proteinuria/ Renal failure	Routine pharmacovigilance including detailed cumulative review in the PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, serious reports from other programs where data is being handled as solicited and all clinical trial SAE reports, using a targeted event questionnaire/checklist.	Warning in SPC Section 4.4: Elevations of serum creatinine, usually mild, and proteinuria have been reported in clinical trials (see section 4.8). Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein or serum creatinine, is recommended prior to the start of Afinitor therapy and periodically thereafter. Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with Afinitor (see section 4.8). Renal function of patients should be monitored particularly where patients have additional risk factors that may further impair renal function." Increased creatinine, proteinuria, and renal failure are included as ADRs in SPC Section 4.8.
Cardiac failure	Routine pharmacovigilance including detailed cumulative review in the PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, serious reports from other programs where data is being handled as solicited and all clinical trial SAE reports, using a targeted event questionnaire/checklist.	Congestive cardiac failure is included as ADR in SPC Section 4.8.
Hemorrhages	Routine pharmacovigilance including detailed cumulative	Haemorrhage is included as ADR in SPC Section 4.8.

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
	review in the PSUR.	
Thromboembolism	Routine pharmacovigilance including detailed cumulative review in the PSUR.	Pulmonary embolism is included as ADR in SPC Section 4.8.
Important potential risks		
Postnatal developmental toxicity	Routine pharmacovigilance including detailed cumulative review in the PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, and serious reports from other programs where data are being handled as solicited and all clinical trial SAE reports, using a targeted event questionnaire/checklist. Study CRAD001M2301: A randomized, double-blind, placebo-controlled study of RAD001 in the treatment of patients with subependymal giant cell astrocytomas (SEGA) associated with tuberous sclerosis complex (TSC). Study M2301 includes a trial extension phase to follow-up of all patients until they reach Tanner stage V, or until the age of 15 for females and 16 for males, regardless of end of trial therapy. Study CRAD001C2485: Everolimus (RAD001) therapy of giant cell astrocytomas in patients with tuberous sclerosis complex (including children). Assessments include the collection of weight and height (before and after enrollment into the study), changes in hormones (LH and FSH, all patients; estrogen, females; testosterone, males) as well as Tanner staging until sexual maturation. For study M2301, these potential developmental effects will continue to be assessed until patients reach Tanner stage V, or until the age of 15 for females and 16 for males, regardless of end of trial therapy.	Relevant information included in SPC Section 5.3: "In rats, everolimus caused embryo/ foetotoxicity at systemic exposure below the therapeutic level. This was manifested as mortality and reduced foetal weight. The incidence of skeletal variations and malformations (e.g. sternal cleft) was increased at 0.3 and 0.9 mg/kg. In rabbits, embryotoxicity was evident in an increase in late resorptions."
Reproductive (teratogenicity) toxicity	Routine pharmacovigilance including detailed cumulative review in the PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, and serious reports from other programs where data are	Relevant information in SPC Section 4.6: "There are no or limited data from the use of everolimus in pregnant women. Studies in animals have shown reproductive toxicity effects (see section 5.3). Everolimus is not recommended during pregnancy and in women of childbearing

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
	being handled as solicited and all clinical trial SAE reports, using a targeted event and pregnancy questionnaire/checklist.	potential not using contraception." Relevant information included in SPC Section 5.3: "In a male fertility study in rats, testicular morphology was affected at 0.5 mg/kg and above, and sperm motility, sperm head count, and plasma testosterone levels were diminished at 5 mg/kg, which is within the range of therapeutic exposure (52 ng.hr/mL and 414 ng.hr/mL, respectively, compared to 560 ng.hr/mL human exposure at 10 mg/day) and which caused a reduction in male fertility. There was evidence of reversibility. Female fertility was not affected, but everolimus crossed the placenta and was toxic to the foetus."
Intestinal obstruction/ileus	Routine pharmacovigilance including detailed cumulative review in the PSUR.	None.
Infertility	Routine pharmacovigilance including detailed cumulative review in the PSUR.	Relevant information in SPC Section 4.6: "There are no or limited amount of data from use of everolimus in pregnant women. Studies in animals have shown reproductive toxicity effects (see Section 5.3). Based on non-clinical findings, male fertility may be compromised by treatment with everolimus (see section 5.3)." Relevant information included in SPC Section 5.3: "In a male fertility study in rats, testicular morphology was affected at 0.5 mg/kg and above, and sperm motility, sperm head count, and plasma testosterone levels were diminished at 5 mg/kg, which is within the range of therapeutic exposure and which caused a reduction in male fertility. There was evidence of reversibility. Female fertility was not affected, but everolimus crossed the placenta and was toxic to the foetus."
Secondary amenorrhea in post-adolescent females	Routine pharmacovigilance including detailed cumulative review in the PSUR.	Relevant information in SPC Section 4.6: "The potential for everolimus to cause infertility in male and female patients is unknown, however secondary amenorrhoea and associated luteinising hormone (LH)/follicle stimulating hormone (FSH) imbalance has been observed in female patients." Secondary amenorrhea and LH/FSH imbalance included as

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
		ADRs in SPC Section 4.8.
Important identified interaction		
Strong CYP3A4 inhibitors and PgP inhibitors	Routine pharmacovigilance including cumulative analysis in PSUR.	Relevant information in SPC Section 4.4: "Co-administration with inhibitors and inducers of CYP3A4 and/or the multidrug efflux pump P-glycoprotein (PgP) should be avoided. If co-administration of a moderate CYP3A4 and/or PgP inhibitor or inducer cannot be avoided, dose adjustments of Afinitor can be taken into consideration based on predicted AUC (see section 4.5). Concomitant treatment with potent CYP3A4 inhibitors result in dramatically increased plasma concentrations of everolimus (see section 4.5). There are currently not sufficient data to allow dosing recommendations in this situation. Hence, concomitant treatment of Afinitor and potent inhibitors is not recommended." Relevant information in SPC Section 4.5: "Substances that are inhibitors of CYP3A4 or PgP may increase everolimus blood concentrations by decreasing the metabolism or the efflux of everolimus from intestinal cells. Interaction by and recommendations regarding concomitant administration of specific CYP3A4 and PgP inhibitors is included in Table 1 in the same SPC section." Relevant information in SPC Section 5.2: "The results of a meta-analysis of pharmacokinetic data from blood samples collected from several clinical studies including 945 patients demonstrated that concomitant administration of CYP3A4 inducers and inhibitors did not appear to have a significant effect on the C_{min} exposure of everolimus beyond the limits of variability. Moderate and strong inhibitors increased C_{min} exposure by 5% and 10%, respectively, and potent inducers increased C_{min} exposure by 7%."
Moderate CYP3A4 inhibitors and PgP inhibitor	Routine pharmacovigilance including cumulative analysis in PSUR.	Relevant information in SPC Section 4.4: "Co-administration with inhibitors and inducers of CYP3A4 and/or the

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
		multidrug efflux pump P-glycoprotein (PgP) should be avoided. If co-administration of a moderate CYP3A4 and/or PgP inhibitor or inducer cannot be avoided, dose adjustments of Afinitor can be taken into consideration based on predicted AUC (see section 4.5). Concomitant treatment with potent CYP3A4 inhibitors result in dramatically increased plasma concentrations of everolimus (see section 4.5). There are currently not sufficient data to allow dosing recommendations in this situation. Hence, concomitant treatment of Afinitor and potent inhibitors is not recommended." Relevant information in SPC Section 4.5: "Substances that are inhibitors of CYP3A4 or PgP may increase everolimus blood concentrations by decreasing the metabolism or the efflux of everolimus from intestinal cells. Interaction by and recommendations regarding concomitant administration of specific CYP3A4 and PgP inhibitors is included in Table 1 in the same SPC section." Relevant information in SPC Section 5.2: "The results of a meta-analysis of pharmacokinetic data from blood samples collected from several clinical studies including 945 patients demonstrated that concomitant administration of CYP3A4 inducers and inhibitors did not appear to have a significant effect on the C_{min} exposure of everolimus beyond the limits of variability. Moderate and strong inhibitors increased C_{min} exposure by 5% and 10%, respectively, and potent inducers increased C_{min} exposure by 7%."
Strong CYP3A4 inducers and PgP inducers	Routine pharmacovigilance including cumulative analysis in PSUR.	Relevant information in SPC Section 4.4: "Co-administration with inhibitors and inducers of CYP3A4 and/or the multidrug efflux pump P-glycoprotein (PgP) should be avoided. If co-administration of a moderate CYP3A4 and/or PgP inhibitor or inducer cannot be avoided, dose adjustments of Afinitor can be taken into

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
		consideration based on predicted AUC (see section 4.5)." Relevant information in SPC Section 4.5: "Substances that are inducers of CYP3A4 or PgP may decrease everolimus blood concentrations by increasing metabolism or the efflux of everolimus from intestinal cells." Interaction by and recommendations regarding concomitant administration of specific CYP3A4 and PgP inducers is included in Table 1 in the same SPC section." Relevant information in SPC Section 5.2: "The results of a meta-analysis of pharmacokinetic data from blood samples collected from several clinical studies including 945 patients demonstrated that concomitant administration of CYP3A4 inducers and inhibitors did not appear to have a significant effect on the C_{min} exposure of everolimus beyond the limits of variability. Moderate and strong inhibitors increased C_{min} exposure by 5% and 10%, respectively, and potent inducers increased C_{min} exposure by 7%."
CYP3A4 substrates and PgP substrates	Routine pharmacovigilance including cumulative analysis in PSUR.	Relevant information in SPC Section 4.5: "Based on in vitro results, the systemic concentrations obtained after oral daily doses of 10 mg make inhibition of PgP, CYP3A4 and CYP2D6 unlikely. However, inhibition of CYP3A4 and PgP in the gut cannot be excluded; hence everolimus may affect the bioavailability of co-administered substances which are CYP3A4 and/or PgP substrates."
Important potential interaction		
Not applicable		None
Important missing information		
Pediatric patients less than 3 years old	Routine pharmacovigilance including cumulative analysis in PSUR.	Appropriate dosing information in SPC Section 4.2: "The safety and efficacy of Afinitor in children aged 0 to 18 years have not been established. No data are available." Relevant information in SPC Section 5.1: "The EMA has waived the obligation to submit the results of studies with Afinitor in all subsets of paediatric

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
		population in renal cell carcinoma (see section 4.2 for information on paediatric use)."
Off-label use in pediatric and adolescent patients	Routine pharmacovigilance including cumulative analysis in PSUR.	Appropriate dosing information in SPC Section 4.2: "The safety and efficacy of Afinitor in children aged 0 to 18 years have not been established. No data are available." Relevant information in SPC Section 5.1: "The EMA has waived the obligation to submit the results of studies with Afinitor in all subsets of paediatric population in renal cell carcinoma (see section 4.2 for information on paediatric use)."
Pregnant or breast-feeding women	Routine pharmacovigilance including cumulative analysis in PSUR. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, and serious reports from other programs where data are being handled as solicited and all clinical trial SAE reports, using a targeted event and pregnancy questionnaire/checklist.	Relevant information included in SPC Section 4.6: "There are no or limited amount of data from the use of everolimus in pregnant women. Everolimus is not recommended during pregnancy and in women of childbearing potential not using contraception. It is not known whether everolimus is excreted in breast milk. However, in rats, everolimus and/or its metabolites readily pass into the milk. Therefore, women taking everolimus should not breast-feed."
Hormonal contraceptive use	Routine pharmacovigilance.	Relevant information included in SPC Section 4.6: "Women of childbearing potential must use a highly effective method of contraception while receiving everolimus."
Patients with renal impairment	Routine pharmacovigilance. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, and serious reports from other programs where data are being handled as solicited and all clinical trial SAE reports, using a targeted event questionnaire/ checklist.	Information in SPC Section 4.2: "No dose adjustment is required (see section 5.2)." Further information in SPC Section 5.2: "In a population pharmacokinetic analysis of 170 patients with advanced solid tumors, no significant influence of creatinine clearance (25-178 mL/min) was detected on CL/F of everolimus. Post-transplant renal impairment (creatinine clearance range, 11-107 mL/min) did not affect the pharmacokinetics of everolimus in transplant patients."
Patients with CNS metastases Patients with uncontrolled or significant cardiac disease Patients with impairment of GI	Routine pharmacovigilance.	None

Safety concern	Proposed pharmacovigilance activities (routine and non-routine)	Proposed risk minimization activities (routine and non-routine)
function Patients undergoing chronic treatment with steroids or another immunosuppressive agent Race other than Caucasian		
Long-term safety	Routine pharmacovigilance. **Additional activities** Study CRAD001M2301: Follow-up of all patients until they reach Tanner stage V, or until the age of 15 for females and 16 for males, regardless of end of trial therapy. Study CRAD001C2485: Follow-up of all patients for 5 years after last patient randomized. • Breast cancer patients CRAD001J2301: A randomized, phase III, double-blind, placebo-controlled multicenter trial of everolimus in combination with trastuzumab and paclitaxel as first-line therapy in women with HER2 positive locally advanced or metastatic breast cancer CRAD001W2301: A randomized, phase III, double-blind, placebo-controlled multicenter trial of daily everolimus in combination with trastuzumab and vinorelbine, in pretreated women with HER2/neu over-expressing locally advanced or metastatic breast cancer CRAD001Y2301: A randomized, double-blind, placebo-controlled study of everolimus in combination with exemestane in the treatment of postmenopausal women with estrogen receptor positive locally advanced or metastatic breast cancer who are refractory to letrozole or anastrozole	None
Patients with pre-existing infections (other than systemic invasive fungal infections) Patients with HIV or hepatitis B or C seropositivity	Routine pharmacovigilance. **Additional activities** Targeted follow-up of all serious spontaneous reports, serious post-marketing surveillance study reports, serious reports from other programs where data is being handled as solicited and all clinical trial SAE reports, using a targeted product questionnaire/checklist.	Relevant information in SPC section 4.8: "In clinical studies, everolimus has been associated with serious cases of hepatitis B reactivation, including fatal outcome. Reactivation of infection is an expected event during periods of immunosuppression."

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns related to long term safety of everolimus as well as to comparative safety of everolimus and exemestane combination therapy versus everolimus monotherapy:

Description	CSR due date
CRAD001J2301	4Q2013
CRAD001W2301	1Q2013
CRAD001Y2301	Dec-2014
BOLERO-6 (Y2201): A three-arm randomized phase II study investigating the combination of everolimus with exemestane versus everolimus alone versus capecitabine in patients with estrogen-receptor positive metastatic breast cancer after recurrence or progression on letrozole or anastrozole. The trial aims to estimate the value of exemestane when added to everolimus versus everolimus monotherapy in this group of patients in terms of progression-free survival, response rate, clinical benefit rate, pharmacokinetics, and safety. The trial will also evaluate capecitabine monotherapy relative to the combination of everolimus and exemestane, with respect to the same endpoints. Patients will be followed for survival for up to two years after randomization of last patient. A total of 300 patients (100 per treatment arm) are planned to be recruited uniformly over a 18 month period.	3Q 2017

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

- Addition of comparator data for all approved indications in section 1.5.2.
- Addition of information on observed outcomes for the important identified and potential risks, e.g. number and percentage of fatal, recovered/with/without treatment/sequelae, not recovered or hospitalised in section 1.5.2.
- Update of the summary table to include information on developmental toxicity and not on teratogenicity (the corresponding studies were summarised in the part on non-clinical safety: In an oral neonatal and juvenile development study with rats, the administration of everolimus at 0.15, 0.5, and 1.5 mg/kg, or rapamycin at 1.5 mg/kg on postpartum days 7 to 70 with 13- and 26-week recovery periods resulted in systemic toxicity at all doses, including reduced absolute body weight gain and food consumption, and delayed attainment of some developmental landmarks, with full or partial recovery after cessation of dosing [.]).

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

2.8. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

- The changes to the Package Leaflet were considered minor with no consequential impact on the readability of the package leaflet.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The pivotal trial met its primary endpoint and the efficacy of everolimus in combination with exemestane "for the treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor" is considered

established. The median PFS was prolonged by 4.63 months, from 3.19 months for patients receiving placebo plus exemestane to 7.82 months for patients treated with everolimus plus exemestane.

The secondary endpoints, tumour related endpoints (ORR) and OS, and subgroup analyses were supportive of the primary analysis.

Uncertainty in the knowledge about the beneficial effects

There is uncertainty concerning the magnitude of the additional benefit of exemestane in the combination treatment effect over everolimus treatment alone. The design of the study precludes any information on the potential benefit of everolimus treatment as a single agent in the patient population studied in the clinical trial. The MAH was requested to submit the results of the study BOLERO-6, a study comparing everolimus alone with everolimus plus exemestane after prior therapy with NSAI in order to confirm the synergistic/additive effect of exemestane.

The interim results for OS, which were immature at the time of assessment, appeared to suggest a trend favouring the combination treatment. However, as the number of events and criteria for unblinding had not been met, there was uncertainty over the final results of OS. The MAH was asked to submit the final OS results as part of an RMP measure.

Risks

Unfavourable effects

The safety and tolerability of everolimus in combination with exemestane was in general consistent with the approved SmPC for Afinitor. However, everolimus plus exemestane treatment was accompanied by substantially more toxicity than exemestane treatment alone with 10% more SAEs, 35% more drug-related AEs and a threefold increase in the number of on-treatment deaths. The risk of non-infectious pneumonitis, infections, stomatitis and hemorrhages was also increased in the combination treatment.

Uncertainty in the knowledge about the unfavourable effects

There were no uncertainties in the knowledge about the unfavourable effects that could affect the benefit-risk balance of the final proposed indication.

Benefit-risk balance

Importance of favourable and unfavourable effects

Overall, the pivotal study provided satisfactory results with respect to efficacy (prolongation of PFS) and safety (no emergence of a major safety signal) in the proposed indication. Thus, the beneficial effect of everolimus plus exemestane treatment in patients with metastatic breast cancer was regarded as clinically relevant.

Benefit-risk balance

Based on the results of the pivotal trial Y2301, the benefits of everolimus in combination with exemestane treatment for patients with metastatic breast cancer (PFS prolongation of 4.63 months) outweighed the adverse events (stomatitis, rash, fatigue, decreased appetite, diarrhoea, dysgeusia, nausea, pneumonitis, weight decreased, epistaxis, and thrombocytopenia). Therefore, the CHMP

considered that the benefit-risk balance for everolimus in the indication "for the treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor" is positive.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change(s):

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

Extension of indication to include Afinitor for the treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor. Consequently sections 4.1, 4.5, 4.8 and 5.1 of the SmPC were updated. Section 4.6 was updated to align with wording in the SmPC for Votubia and minor editorial changes were made to section 5.3 to revise the wording to correlate exposure in rats in a male fertility study and clinical exposure. The Risk Management Plan and the Package Leaflet were updated accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Conditions and requirements of the marketing authorisation

Risk management system

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

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 7.1 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

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

In addition, an updated RMP should be submitted:

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

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

None.

Obligation to complete post-authorisation measures

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

Description	Due date
A three-arm randomized study investigating the combination of everolimus with exemestane versus everolimus alone versus capecitabine in patients with estrogen-receptor positive metastatic breast cancer after recurrence or progression on letrozole or anastrozole based on a CHMP approved protocol.	Final CSR: 3Q 2017

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

None.

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