CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 22-334/S-016

Trade Name: Afinitor

Generic Name: everolimus

Sponsor: Novartis Pharmaceuticals

Approval Date: July 20, 2012

Indication: treatment of postmenopausal women with advanced hormone receptor-positive, HER-2 negative breast cancer in combination with exemestane, after failure of treatment with letrozole or anastrozole.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-334/S-016

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022334/S-016

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Attention: Lincy Thomas, Pharm.D.
Senior Associate Director, Drug Regulatory Affairs

Dear Dr. Thomas:

Please refer to your Supplemental New Drug Application (sNDA) dated November 2, 2011, received November 3, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Afinitor® (everolimus) Tablets, 2.5 mg, 5 mg, 7.5 mg, and 10 mg.

We also refer to our approval letter dated July 20, 2012, which contained an error of two electronic signatures. The letter should only contain the signature of the Division Director, Robert L. Justice.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain July 20, 2012, the date of the original approval letter.

We acknowledge receipt of your amendments dated December 2, 21, and 22, 2011; January 19 and 20, February 2 (2) and 8, March 21, April 17, May 9 and 18, June 15, and July 10, July 12, July 17, and July 19, 2012.

This "Prior Approval" supplemental new drug application provides for a new indication for the treatment of postmenopausal women with advanced hormone receptor-positive, HER-2 negative breast cancer in combination with exemestane, after failure of treatment with letrozole or anastrozole.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA

automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.
The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable since this indication does not occur in children.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

1899-1: Submit a final report, including datasets, for the final overall survival results from trial CRAD001Y2301 (BOLERO-2).

The timetable you submitted on July 10, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	December 2011
Trial Completion:	June 2014
Final Report Submission:	June 2015

1899-2: Conduct a 3-arm randomized trial 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 anastrazole.

The timetable you submitted on July 10, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	November 2012
Trial Completion:	August 2016
Final Report Submission:	August 2017

Submit clinical protocols to your IND 066279 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Christy Cottrell, Regulatory Project Manager, at (301) 796-4256.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L JUSTICE
07/20/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-334/S-016

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AFINITOR safely and effectively. See full prescribing information for AFINITOR.

AFINITOR (everolimus) tablets for oral administration
Initial U.S. Approval: 2009

----------RECENT MAJOR CHANGES----------

Indications and Usage, Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer (1.1), Dosage and Administration (2.1, 2.2), Warnings and Precautions (5.1, 5.3, 5.5, 5.10) 07/2012
Indications and Usage (1.4, 1.5), Dosage and Administration (2.1, 2.2), Warnings and Precautions (5.1, 5.3, 5.8) 04/2012
Dosage and Administration (2.2, 2.4), Warnings and Precautions (5.7, 5.8) 03/2012

----------INDICATIONS AND USAGE----------

AFINITOR is a kinase inhibitor indicated for the treatment of:

- postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+ BC) in combination with exemestane after failure of treatment with letrozole or anastrozole. (1.1)
- adults with progressive neuroendocrine tumors of pancreatic origin (PNET) that is unresectable, locally advanced or metastatic. The safety and effectiveness of AFINITOR in the treatment of patients with carcinoid tumors have not been established. (1.2)
- adults with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib. (1.3)
- adults with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery. The effectiveness of AFINITOR in treatment of renal angiomyolipoma is based on an analysis of durable objective responses in patients treated for a median of 8.3 months. Further follow-up of patients is required to determine long-term outcomes. (1.4)
- adults and children ≥ 3 years of age with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TSC) who require therapeutic intervention but are not candidates for curative surgical resection. The effectiveness of AFINITOR is based on an analysis of change in SEGA volume. Clinical benefit such as improvement in disease-related symptoms or increase in overall survival has not been demonstrated. (1.5)

----------DOSAGE AND ADMINISTRATION----------

Advanced HR+ BC, advanced PNET, advanced RCC, or renal angiomyolipoma with TSC:

- 10 mg once daily with or without food. (2.1)
- For patients with hepatic impairment, reduce the AFINITOR dose. (2.2)
- If moderate inhibitors of CYP3A4 and/or P-glycoprotein (PgP) are required, reduce the AFINITOR dose to 2.5 mg once daily; if tolerated, consider increasing to 5 mg once daily. (2.2)
- If strong inducers of CYP3A4 are required, increase AFINITOR dose in 5 mg increments to a maximum of 20 mg once daily. (2.2)

SEGA:

- Initial dose based on body surface area with subsequent titration to attain trough concentrations of 5-10 ng/mL. (2.3)
- If moderate inhibitors of CYP3A4 and/or PgP are required, reduce the AFINITOR dose by approximately 50%. Subsequent dosing should be based on therapeutic drug monitoring (TDM). (2.4)
- If strong inducers of CYP3A4 are required, double the AFINITOR dose. Subsequent dosing should be based on TDM. (2.4)

Dose reduction or treatment interruption may be needed to manage adverse drug reactions. (2.2, 2.4)

----------DOSAGE FORMS AND STRENGTHS----------

2.5 mg, 5 mg, 7 5 mg, and 10 mg tablets with no score (3)

----------CONTRAINDICATIONS----------

Hypersensitivity to everolimus, to other rapamycin derivatives, or to any of the excipients (4)

----------WARNINGS AND PRECAUTIONS----------

- Non-infectious pneumonitis: Monitor for clinical symptoms or radiological changes; fatal cases have occurred. Manage by dose reduction or discontinuation until symptoms resolve, and consider use of corticosteroids. (5.1)
- Infections: Increased risk of infections, some fatal. Monitor for signs and symptoms, and treat promptly. (5.2)
- Oral ulceration: Mouth ulcers, stomatitis, and oral mucositis are common. Management includes mouthwashes (without alcohol or peroxide) and topical treatments. (5.3)
- Renal failure: Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with AFINITOR. (5.4)
- Laboratory test alterations: Elevations of serum creatinine, blood glucose, and lipids may occur. Decreases in hemoglobin, neutrophils, and platelets may also occur. Monitor renal function, blood glucose, lipids, and hematologic parameters prior to treatment and periodically thereafter. (5.6)
- Vaccinations: Avoid live vaccines and close contact with those who have received live vaccines. (5.9)
- Embryo-fetal toxicity: Fetal harm can occur when administered to a pregnant woman. Apprise women of potential harm to the fetus. (5.10, 8.1)

----------ADVERSE REACTIONS----------

Advanced HR+ BC, Advanced PNET, Advanced RCC: Most common adverse reactions (incidence ≥30%) include stomatitis, infections, rash, fatigue, diarrhea, edema, abdominal pain, nausea, fever, asthenia, cough, headache and decreased appetite. (6.1, 6.2, 6.3)
Renal angiomyolipoma with TSC: Most common adverse reaction (incidence ≥ 30%) is stomatitis. (6.4)
SEGA: Most common adverse reactions (incidence ≥ 30%) are stomatitis, upper respiratory tract infection, sinusitis, otitis media, and pyrexia. (6.5)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Strong CYP3A4 inhibitors: Avoid concomitant use. (2.2, 2.4, 5.7, 7.1)
- Moderate CYP3A4 and/or PgP inhibitors: If combination is required, use caution and reduce dose of AFINITOR. (2.2, 2.4, 5.7, 7.1)
- Strong CYP3A4 inducers: Avoid concomitant use. If combination cannot be avoided, increase dose of AFINITOR. (2,2, 2.4, 5.7, 7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Nursing mothers: Discontinue drug or nursing, taking into consideration the importance of drug to the mother. (8.3)
- Hepatic impairment: For advanced HR+ BC, advanced PNET, advanced RCC, and renal angiomyolipoma with TSC patients with hepatic impairment, reduce AFINITOR dose. For SEGA patients with Child-Pugh class A or Child-Pugh class B hepatic impairment, adjustment to the starting dose may not be needed; however, subsequent dosing should be based on TDM. AFINITOR should not be used in SEGA patients with Child-Pugh class C hepatic impairment. (2.2, 2.4, 5.8, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 07/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer (Advanced HR+ BC)

AFINITOR® is indicated for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole.

1.2 Advanced Neuroendocrine Tumors of Pancreatic Origin (PNET)

AFINITOR® is indicated for the treatment of adult patients with progressive neuroendocrine tumors of pancreatic origin (PNET) with unresectable, locally advanced or metastatic disease.

The safety and effectiveness of AFINITOR® in the treatment of patients with carcinoid tumors have not been established.

1.3 Advanced Renal Cell Carcinoma (RCC)

AFINITOR® is indicated for the treatment of adult patients with advanced RCC after failure of treatment with sunitinib or sorafenib.

1.4 Renal Angiomyolipoma with Tuberous Sclerosis Complex (TSC)

AFINITOR® is indicated for the treatment of adult patients with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery.

The effectiveness of AFINITOR in treatment of renal angiomyolipoma is based on an analysis of durable objective responses in patients treated for a median of 8.3 months. Further follow-up of patients is required to determine long-term outcomes.

1.5 Subependymal Giant Cell Astrocytoma (SEGA)

AFINITOR® is indicated for the treatment of adult and pediatric patients, 3 years of age or older, with SEGA associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not candidates for curative surgical resection.

The effectiveness of AFINITOR is based on an analysis of change in SEGA volume *[see Clinical Studies (14.5)]*. Clinical benefit such as improvement in disease-related symptoms or increase in overall survival has not been demonstrated.

2 DOSAGE AND ADMINISTRATION

AFINITOR should be administered orally once daily at the same time every day, either consistently with food or consistently without food *[see Clinical Pharmacology (12.3)]*.

AFINITOR tablets should be swallowed whole with a glass of water. AFINITOR tablets should not be crushed. Do not take tablets which are crushed or broken. For patients unable to swallow tablets, AFINITOR tablet(s) should be dispersed completely in a glass of water (containing approximately 30 mL) by gently stirring, immediately prior to drinking. The glass should be rinsed with the same volume of water and the rinse should be completely swallowed to ensure that the entire dose is administered.

Continue treatment as long as clinical benefit is observed or until unacceptable toxicity occurs.

2.1 Recommended Dose in Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer, Advanced PNET, Advanced RCC and Renal Angiomyolipoma with TSC

The recommended dose of AFINITOR is 10 mg, to be taken once daily.

2.2 Dose Modifications in Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer, Advanced PNET, Advanced RCC, and Renal Angiomyolipoma with TSC

Management of Adverse Reactions

Management of severe or intolerable adverse reactions may require temporary dose reduction and/or interruption of AFINITOR therapy. If dose reduction is required, the suggested dose is approximately 50% lower than the daily dose previously administered *[see Warnings and Precautions (5)]*.

Table 1 summarizes recommendations for dose reduction, interruption or discontinuation of AFINITOR in the management of adverse reactions. General management recommendations are also provided as applicable. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Table 1: AFINITOR Dose Adjustment and Management Recommendation for Adverse Reactions

Adverse Drug Reaction	Severity[a]	AFINITOR Dose Adjustment[b] and Management Recommendations
Non-infectious pneumonitis	Grade 1 Asymptomatic, radiographic findings only	No dose adjustment required. Initiate appropriate monitoring.
	Grade 2 Symptomatic, not interfering with ADL[c]	Consider interruption of therapy, rule out infection and consider treatment with corticosteroids until symptoms improve to ≤ grade 1. Re-initiate AFINITOR at a lower dose. Discontinue treatment if failure to recover within 4 wks.
	Grade 3 Symptomatic, interfering with ADL[c]; O_2 indicated	Interrupt AFINITOR until symptoms resolve to ≤ grade 1. Rule out infection, and consider treatment with corticosteroids. Consider re-initiating AFINITOR at a lower dose. If toxicity recurs at grade 3, consider discontinuation.
	Grade 4 Life-threatening, ventilatory support indicated	Discontinue AFINITOR, rule out infection, and consider treatment with corticosteroids.
Stomatitis	Grade 1 Minimal symptoms, normal diet	No dose adjustment required. Manage with non-alcoholic or salt water (0.9%) mouth wash several times a day.
	Grade 2 Symptomatic but can eat and swallow modified diet	Temporary dose interruption until recovery to grade ≤1. Re-initiate AFINITOR at the same dose. If stomatitis recurs at grade 2, interrupt dose until recovery to grade ≤1. Re-initiate AFINITOR at a lower dose. Manage with topical analgesic mouth treatments (e.g. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[d]
	Grade 3 Symptomatic and unable to adequately aliment or hydrate orally	Temporary dose interruption until recovery to grade ≤1. Re-initiate AFINITOR at a lower dose. Manage with topical analgesic mouth treatments (i.e. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[d]
	Grade 4 Symptoms associated with life-threatening consequences	Discontinue AFINITOR and treat with appropriate medical therapy.
Other non-hematologic toxicities (excluding metabolic events)	Grade 1	If toxicity is tolerable, no dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	If toxicity is tolerable, no dose adjustment required. Initiate appropriate medical therapy and monitor. If toxicity becomes intolerable, temporary dose interruption until recovery to grade ≤1. Re-initiate AFINITOR at the same dose. If toxicity recurs at grade 2, interrupt AFINITOR until recovery to grade ≤1. Re-initiate AFINITOR at a lower dose.
	Grade 3	Temporary dose interruption until recovery to grade ≤1. Initiate appropriate medical therapy and monitor. Consider re-initiating AFINITOR at a lower dose. If toxicity recurs at grade 3, consider discontinuation.
	Grade 4	Discontinue AFINITOR and treat with appropriate medical therapy.
Metabolic events (e.g. hyperglycemia, dyslipidemia)	Grade 1	No dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	No dose adjustment required. Manage with appropriate medical therapy and monitor.

Adverse Drug Reaction	Severity[a]	AFINITOR Dose Adjustment[b] and Management Recommendations
	Grade 3	Temporary dose interruption. Re-initiate Afinitor at a lower dose. Manage with appropriate medical therapy and monitor.
	Grade 4	Discontinue AFINITOR and treat with appropriate medical therapy.

[a] Severity grade description: 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms; 4 = life-threatening symptoms.

[b] If dose reduction is required, the suggested dose is approximately 50% lower than the dose previously administered.

[c] Activities of daily living (ADL)

[d] Avoid using agents containing hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis as they may worsen mouth ulcers.

Hepatic Impairment

Hepatic impairment will increase the exposure to everolimus *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.7)]*. Dose adjustments are recommended:

- Mild hepatic impairment (Child-Pugh class A) – The recommended dose is 7.5 mg daily; the dose may be decreased to 5 mg if not well tolerated.

- Moderate hepatic impairment (Child-Pugh class B) – The recommended dose is 5 mg daily; the dose may be decreased to 2.5 mg if not well tolerated.

- Severe hepatic impairment (Child-Pugh class C) – If the desired benefit outweighs the risk, a dose of 2.5 mg daily may be used but must not be exceeded.

Dose adjustments should be made if a patient's hepatic (Child-Pugh) status changes during treatment.

CYP3A4 and/or P-glycoprotein (PgP) Inhibitors

Avoid the use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) *[see Warnings and Precautions (5.7) and Drug Interactions (7.1)]*.

Use caution when co-administered with moderate CYP3A4 and/or PgP inhibitors (e.g., amprenavir, fosamprenavir, aprepitant, erythromycin, fluconazole, verapamil, diltiazem). If patients require co-administration of a moderate CYP3A4 and/or PgP inhibitor, reduce the AFINITOR dose to 2.5 mg daily. The reduced dose of AFINITOR is predicted to adjust the area under the curve (AUC) to the range observed without inhibitors. An AFINITOR dose increase from 2.5 mg to 5 mg may be considered based on patient tolerance. If the moderate inhibitor is discontinued, a washout period of approximately 2 to 3 days should be allowed before the AFINITOR dose is increased. If the moderate inhibitor is discontinued, the AFINITOR dose should be returned to the dose used prior to initiation of the moderate CYP3A4 and/or PgP inhibitor.

Strong CYP3A4 Inducers

Avoid the use of concomitant strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital). If patients require co-administration of a strong CYP3A4 inducer, consider increasing the AFINITOR dose from 10 mg daily up to 20 mg daily, using 5 mg increments. This dose of AFINITOR is predicted, based on pharmacokinetic data, to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued, the AFINITOR dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer *[see Warnings and Precautions (5.7) and Drug Interactions (7.2)]*.

Grapefruit, grapefruit juice, and other foods that are known to inhibit cytochrome P450 and PgP activity may increase everolimus exposures and should be avoided during treatment. St. John's Wort (*Hypericum perforatum*) may decrease everolimus exposure unpredictably and should be avoided.

2.3 Recommended Dose in Subependymal Giant Cell Astrocytoma

The recommended starting dose of AFINITOR for treatment of patients with SEGA is according to Table 2:

Table 2: Recommended Starting Dose of AFINITOR for Treatment of Patients with SEGA

Body Surface Area (BSA)	Starting Dose
0.5 m^2 to 1.2 m^2	2.5 mg once daily
1.3 m^2 to 2.1 m^2	5 mg once daily
Greater than or equal to 2.2 m^2	7.5 mg once daily

Patients receiving AFINITOR may require dose adjustments based on everolimus whole blood trough concentrations achieved, tolerability, individual response, and change in concomitant medications including CYP3A4-inducing antiepileptic drugs *[see Warnings and Precautions (5.7) and Drug Interactions (7.1, 7.2)]*. Dose adjustments can be made at two week intervals *[see Dosage and Administration (2.4, 2.5)]*.

Evaluate SEGA volume approximately 3 months after commencing AFINITOR therapy and periodically thereafter, with subsequent dose adjustments taking into consideration changes in SEGA volume, corresponding trough concentration, and tolerability. Responses have been observed at trough concentrations as low as 3 ng/mL; as such, once acceptable efficacy has been achieved, additional dose increases may not be necessary.

AFINITOR has not been studied in patients with SEGA < 3 years of age or with BSA < 0.58 m^2.

The optimal duration of therapy for patients with SEGA is unknown.

2.4 Dose Modifications in Subependymal Giant Cell Astrocytoma

Management of Adverse Reactions

Management of severe or intolerable adverse reactions may require temporary dose reduction and/or interruption of AFINITOR therapy. If a dose reduction is required, the suggested dose is approximately 50% lower than the dose previously administered *[see Table 1 in Dosage and Administration (2.2) and Warnings and Precautions (5]*. For dose reductions below the lowest available strength, consider alternate day dosing.

Hepatic Impairment

Adjustment to the recommended starting dose for patients with SEGA who have mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment may not be needed; however, subsequent dosing should be based on therapeutic drug monitoring (TDM).

AFINITOR is not recommended for use in patients with SEGA who have severe hepatic impairment (Child-Pugh class C).

Everolimus whole blood trough concentration should be assessed approximately 2 weeks after commencing treatment or after any change in hepatic status (Child-Pugh). Dosing should be titrated to attain trough concentrations of 5 to 10 ng/mL *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*.

CYP3A4 and/or P-glycoprotein (PgP) Inhibitors

Avoid the use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole*) [see Warnings and Precautions (5.7) and Drug Interactions (7.1)]*.

Use caution when co-administered with moderate CYP3A4 and/or PgP inhibitors (e.g., amprenavir, fosamprenavir, aprepitant, erythromycin, fluconazole, verapamil, diltiazem). If patients require co-administration of a moderate CYP3A4 and/or PgP inhibitor, reduce the AFINITOR dose by approximately 50% to maintain trough concentrations of 5 to 10 ng/mL. If dose reduction is required for patients receiving 2.5 mg daily, consider alternate day dosing. Subsequent dosing should be individualized based on therapeutic drug monitoring. Everolimus trough concentrations should be assessed approximately 2 weeks after the addition of a moderate CYP3A4 and/or PgP inhibitor. If the moderate inhibitor is discontinued, the AFINITOR dose should be returned to the dose used prior to initiation of the moderate CYP3A4 and/or PgP inhibitor and the everolimus trough concentration should be re-assessed approximately 2 weeks later *[see Dosage and Administration (2.5), Warnings and Precautions (5.7) and Drug Interactions (7.1)]*.

Strong CYP3A4 Inducers

Avoid the use of concomitant strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital). For patients requiring a concomitant strong CYP3A4 inducer, double the AFINITOR dose. Subsequent

dosing should be individualized based on therapeutic drug monitoring. If the strong inducer is discontinued, the AFINITOR dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer and the everolimus trough concentrations should be assessed approximately 2 weeks later *[see Dosage and Administration (2.5), Warnings and Precautions (5.7) and Drug Interactions (7.2)]*.

Grapefruit, grapefruit juice, and other foods that are known to inhibit cytochrome P450 and PgP activity may increase everolimus exposures and should be avoided during treatment. St. John's Wort (*Hypericum perforatum*) may decrease everolimus exposure unpredictably and should be avoided.

2.5 Therapeutic Drug Monitoring in Subependymal Giant Cell Astrocytoma

Routine everolimus whole blood therapeutic drug concentration monitoring is recommended for all patients using a validated assay. Trough concentrations should be assessed approximately 2 weeks after commencing treatment. Dosing should be titrated to attain trough concentrations of 5 to 10 ng/mL.

There is limited safety experience with patients having trough concentrations > 10 ng/mL. If concentrations are between 10 and 15 ng/mL, and the patient has demonstrated adequate tolerability and tumor response, no dose reductions are needed. The dose of AFINITOR should be reduced if trough concentrations > 15 ng/mL are observed.

If concentrations are < 5 ng/mL, the daily dose may be increased by 2.5 mg every 2 weeks, subject to tolerability. Daily dose may be reduced by 2.5 mg every 2 weeks to attain a target of 5 to 10 ng/mL. If dose reduction is required for patients receiving 2.5 mg daily, alternate day dosing should be used.

Trough concentrations should be assessed approximately 2 weeks after any change in dose, after an initiation or change in co-administration of CYP3A4 and/or PgP inducers or inhibitors, or after any change in hepatic status (Child-Pugh Classification) *[see Dosage and Administration (2.4), Warnings and Precautions (5.7, 5.8), Drug Interactions (7.1, 7.2)]*.

3 DOSAGE FORMS AND STRENGTHS

2.5 mg tablet
White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with "LCL" on one side and "NVR" on the other.

5 mg tablet
White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with "5" on one side and "NVR" on the other.

7.5 mg tablet
White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with "7P5" on one side and "NVR" on the other.

10 mg tablet
White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with "UHE" on one side and "NVR" on the other.

4 CONTRAINDICATIONS

Hypersensitivity to the active substance, to other rapamycin derivatives, or to any of the excipients. Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, flushing, chest pain, or angioedema (e.g., swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus and other rapamycin derivatives.

5 WARNINGS AND PRECAUTIONS

5.1 Non-infectious Pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives, including AFINITOR. Non-infectious pneumonitis was reported in up to 19% of patients treated with AFINITOR in clinical trials. The incidence of Common Terminology Criteria (CTC) grade 3 and 4 non-infectious pneumonitis was up to 4.0% and up to 0.2%, respectively *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5)]*. Fatal outcomes have been observed.

Consider a diagnosis of non-infectious pneumonitis in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough, or dyspnea, and in whom infectious, neoplastic, and other causes have been excluded by means of appropriate investigations. Advise patients 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 alteration. Imaging appears to overestimate the incidence of clinical pneumonitis.

If symptoms are moderate, consider interrupting therapy until symptoms improve. The use of corticosteroids may be indicated. AFINITOR may be reintroduced at a daily dose approximately 50% lower than the dose previously administered *[see Table 1 in Dosage and Administration (2.2)]*.

For cases of grade 4 non-infectious pneumonitis, discontinue AFINITOR. Corticosteroids may be indicated until clinical symptoms resolve. For cases of grade 3 non-infectious pneumonitis interrupt AFINITOR until resolution to less than or equal to grade 1. AFINITOR may be re-introduced at a daily dose approximately 50% lower than the dose previously administered depending on the individual clinical circumstances *[see Table 1 in Dosage and Administration (2.2)]*. If toxicity recurs at grade 3, consider discontinuation of AFINITOR. The development of pneumonitis has been reported even at a reduced dose.

5.2 Infections

AFINITOR has immunosuppressive properties and may predispose patients to bacterial, fungal, viral, or protozoal infections, including infections with opportunistic pathogens *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5)]*. Localized and systemic infections, including pneumonia, mycobacterial infections, other bacterial infections, invasive fungal infections, such as aspergillosis or candidiasis, and viral infections including reactivation of hepatitis B virus have occurred in patients taking AFINITOR. Some of these infections have been severe (e.g., leading to respiratory or hepatic failure) or fatal. Physicians and patients should be aware of the increased risk of infection with AFINITOR. Complete treatment of pre-existing invasive fungal infections prior to starting treatment with AFINITOR. While taking AFINITOR, be vigilant for signs and symptoms of infection; if a diagnosis of an infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of AFINITOR. If a diagnosis of invasive systemic fungal infection is made, discontinue AFINITOR and treat with appropriate antifungal therapy.

5.3 Oral Ulceration

Mouth ulcers, stomatitis, and oral mucositis have occurred in patients treated with AFINITOR at an incidence ranging from 44-86% across the clinical trial experience. Grade 3 or 4 stomatitis was reported in 4-8% of patients *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5)]*. 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 Drug Interactions (7.1)]*.

5.4 Renal Failure

Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with AFINITOR *[see Laboratory Tests and Monitoring (5.6)]*.

5.5 Geriatric Patients

In the randomized advanced hormone receptor positive, HER2-negative breast cancer study, the incidence of deaths due to any cause within 28 days of the last AFINITOR dose was 6% in patients ≥ 65 years of age compared to 2% in patients < 65 years of age. Adverse reactions leading to permanent treatment discontinuation occurred in 33% of patients ≥ 65 years of age compared to 17% in patients < 65 years of age. Careful monitoring and appropriate dose adjustments for adverse reactions are recommended *[see Dosage and Administration (2.2), Use in Specific Populations (8.5)]*.

5.6 Laboratory Tests and Monitoring

Renal Function

Elevations of serum creatinine and proteinuria have been reported in clinical trials *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5)]*. 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.

Blood Glucose and Lipids

Hyperglycemia, hyperlipidemia, and hypertriglyceridemia have been reported in clinical trials *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5)]*. Monitoring of fasting serum glucose and lipid profile is recommended prior to the start of AFINITOR therapy and periodically thereafter. When possible, optimal glucose and lipid control should be achieved before starting a patient on AFINITOR.

Hematologic Parameters

Decreased hemoglobin, lymphocytes, neutrophils, and platelets have been reported in clinical trials *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5)]*. Monitoring of complete blood count is recommended prior to the start of AFINITOR therapy and periodically thereafter.

5.7 Drug-drug Interactions

Due to significant increases in exposure of everolimus, co-administration with strong CYP3A4 inhibitors should be avoided *[see Dosage and Administration (2.2, 2.4) and Drug Interactions (7.1)]*.

A reduction of the AFINITOR dose is recommended when co-administered with a moderate CYP3A4 and/or PgP inhibitor *[see Dosage and Administration (2.2, 2.4) and Drug Interactions (7.1)]*.

An increase in the AFINITOR dose is recommended when co-administered with a strong CYP3A4 inducer *[see Dosage and Administration (2.2, 2.4) and Drug Interactions (7.2)]*.

5.8 Hepatic Impairment

Exposure to everolimus was increased in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

For advanced HR+ BC, advanced PNET, advanced RCC, and renal angiomyolipoma with TSC patients with severe hepatic impairment (Child-Pugh class C), AFINITOR may be used at a reduced dose if the desired benefit outweighs the risk. For patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, a dose reduction is recommended *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

For SEGA patients with severe hepatic impairment, AFINITOR is not recommended. For SEGA patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, adjustment to the starting dose may not be needed; however subsequent dosing should be individualized based on therapeutic drug monitoring *[see Dosage and Administration (2.4, 2.5)]*.

5.9 Vaccinations

The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with AFINITOR. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

The timing of routine vaccinations in pediatric patients with SEGA should be considered prior to the start of everolimus therapy.

5.10 Embryo-fetal Toxicity

There are no adequate and well-controlled studies of AFINITOR in pregnant women; however, based on the mechanism of action, AFINITOR can cause fetal harm. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to use an effective method of contraception while using AFINITOR and for up to 8 weeks after ending treatment *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in another section of the label *[see Warnings and Precautions (5)]*:

- Non-infectious pneumonitis *[see Warnings and Precautions (5.1)]*.
- Infections *[see Warnings and Precautions (5.2)]*.
- Oral ulcers *[see Warnings and Precautions (5.3)]*.
- Renal failure *[see Warnings and Precautions (5.4)]*.

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

6.1 Clinical Study Experience in Advanced Hormone-Receptor-Positive, HER2-Negative Breast Cancer

The efficacy and safety of AFINITOR (10 mg/day) plus exemestane (25 mg/day) (n=485) versus placebo plus exemestane (25 mg/day) (n=239) was evaluated in a randomized, controlled trial in patients with advanced or metastatic hormone-

receptor-positive, HER2-negative breast cancer. The median age of patients was 61 years (range 28-93), and 75% were Caucasian. Safety results are based on a median follow-up of approximately 13 months.

The most common adverse reactions (incidence ≥ 30%) were stomatitis, infections, rash, fatigue, diarrhea, and decreased appetite. The most common grade 3/4 adverse reactions (incidence ≥ 2%) were stomatitis, infections, hyperglycemia, fatigue, dyspnea, pneumonitis, and diarrhea. The most common laboratory abnormalities (incidence ≥ 50%) were hypercholesterolemia, hyperglycemia, increased AST, anemia, leukopenia, thrombocytopenia, lymphopenia, increased ALT, and hypertriglyceridemia. The most common grade 3/4 laboratory abnormalities (incidence ≥ 3%) were lymphopenia, hyperglycemia, anemia, decreased potassium, increased AST, increased ALT, and thrombocytopenia.

Fatal adverse reactions occurred more frequently in patients who received AFINITOR plus exemestane (2%) compared to patients on the placebo plus exemestane arm (0.4%). The rates of treatment-emergent adverse events resulting in permanent discontinuation were 24% and 5% for the AFINITOR plus exemestane and placebo plus exemestane treatment groups, respectively. Dose adjustments (interruptions or reductions) were more frequent among patients in the AFINITOR plus exemestane arm than in the placebo plus exemestane arm (63% versus 14%).

Table 3 compares the incidence of treatment-emergent adverse reactions reported with an incidence of ≥10% for patients receiving AFINITOR 10 mg daily versus placebo.

Table 3: Adverse Reactions Reported ≥ 10% of Patients with Advanced HR+ BC*

	AFINITOR (10 mg/day) + exemestane[a] N=482			Placebo + exemestane[a] N=238		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Any adverse reaction	**100**	**41**	**9**	**90**	**22**	**5**
Gastrointestinal disorders						
Stomatitis[b]	67	8	0	11	0.8	0
Diarrhea	33	2	0.2	18	0.8	0
Nausea	29	0.2	0.2	28	1	0
Vomiting	17	0.8	0.2	12	0.8	0
Constipation	14	0.4	0	13	0.4	0
Dry mouth	11	0	0	7	0	0
General disorders and administration site conditions						
Fatigue	36	4	0.4	27	1	0
Edema peripheral	19	1	0	6	0.4	0
Pyrexia	15	0.2	0	7	0.4	0
Asthenia	13	2	0.2	4	0	0
Infections and infestations						
Infections[c]	50	4	1	25	2	0
Investigations						
Weight decreased	25	1	0	6	0	0
Metabolism and nutrition disorders						
Decreased appetite	30	1	0	12	0.4	0
Hyperglycemia	14	5	0.4	2	0.4	0
Musculoskeletal and connective tissue disorders						
Arthralgia	20	0.8	0	17	0	0
Back pain	14	0.2	0	10	0.8	0
Pain in extremity	9	0.4	0	11	2	0
Nervous system disorders						
Dysgeusia	22	0.2	0	6	0	0
Headache	21	0.4	0	14	0	0
Psychiatric disorders						

	AFINITOR (10 mg/day) + exemestane[a] N=482			Placebo + exemestane[a] N=238		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Insomnia	13	0.2	0	8	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	24	0.6	0	12	0	0
Dyspnea	21	4	0.2	11	0.8	0.4
Epistaxis	17	0	0	1	0	0
Pneumonitis[d]	19	4	0.2	0.4	0	0
Skin and subcutaneous tissue disorders						
Rash	39	1	0	6	0	0
Pruritus	13	0.2	0	5	0	0
Alopecia	10	0	0	5	0	0
Vascular disorders						
Hot flush	6	0	0	14	0	0
Median Duration of Treatment[e]	**23.9 weeks**			**13.4 weeks**		

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*160 patients (33.2%) were exposed to AFINITOR therapy for a period of ≥ 32 weeks)

[a] Exemestane (25 mg/day)

[b] Includes stomatitis, mouth ulceration, aphthous stomatitis, glossodynia, gingival pain, glossitis and lip ulceration

[c] Includes all preferred terms within the 'infections and infestations' system organ class, the most common being nasopharyngitis (10%), urinary tract infection (10%), upper respiratory tract infection (5%), pneumonia (4%), bronchitis (4%), cystitis (3%), sinusitis (3%), and also including candidiasis (<1%), and sepsis (<1%), and hepatitis C (<1%).

[d] Includes pneumonitis, interstitial lung disease, lung infiltration, and pulmonary fibrosis

[e] Exposure to AFINITOR or placebo

Key observed laboratory abnormalities are presented in Table 4.

Table 4: Key Laboratory Abnormalities Reported in ≥ 10% of Patients with Advanced HR+ BC

Laboratory parameter	AFINITOR (10 mg/day) + exemestane[a] N=482			Placebo + exemestane[a] N=238		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Hematology[b]						
Hemoglobin decreased	68	6	0.6	40	0.8	0.4
WBC decreased	58	1	0	28	5	0.8
Platelets decreased	54	3	0.2	5	0	0.4
Lymphocytes decreased	54	11	0.6	37	5	0.8
Neutrophils decreased	31	2	0	11	0.8	0.8
Clinical Chemistry						
Glucose increased	69	9	0.4	44	0.8	0.4
Cholesterol increased	70	0.6	0.2	38	0.8	0.8
Aspartate transaminase (AST) increased	69	4	0.2	45	3	0.4
Alanine transaminase (ALT) increased	51	4	0.2	29	5	0
Triglycerides increased	50	0.8	0	26	0	0
Albumin decreased	33	0.8	0	16	0.8	0
Potassium decreased	29	4	0.2	7	1	0
Creatinine increased	24	2	0.2	13	0	0

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[a] Exemestane (25 mg/day)

[b] Reflects corresponding adverse drug reaction reports of anemia, leukopenia, lymphopenia, neutropenia, and thrombocytopenia (collectively as pancytopenia), which occurred at lower frequency.

6.2 Clinical Study Experience in Advanced Pancreatic Neuroendocrine Tumors

In a randomized, controlled trial of AFINITOR (n=204) versus placebo (n=203) in patients with advanced PNET the median age of patients was 58 years (range 20-87), 79% were Caucasian, and 55% were male. Patients on the placebo arm could cross over to open-label AFINITOR upon disease progression.

The most common adverse reactions (incidence ≥ 30%) were stomatitis, rash, diarrhea, fatigue, edema, abdominal pain, nausea, fever, and headache. The most common grade 3-4 adverse reactions (incidence ≥ 5%) were stomatitis and diarrhea. The most common laboratory abnormalities (incidence ≥ 50%) were decreased hemoglobin, hyperglycemia, alkaline phosphatase increased, hypercholesterolemia, bicarbonate decreased, and increased aspartate transaminase (AST). The most common grade 3-4 laboratory abnormalities (incidence ≥ 3%) were hyperglycemia, lymphopenia, decreased hemoglobin, hypophosphatemia, increased alkaline phosphatase, neutropenia, increased aspartate transaminase (AST), potassium decreased, and thrombocytopenia. Deaths during double-blind treatment where an adverse event was the primary cause occurred in 7 patients on AFINITOR and 1 patient on placebo. Causes of death on the AFINITOR arm included one case of each of the following: acute renal failure, acute respiratory distress, cardiac arrest, death (cause unknown), hepatic failure, pneumonia, and sepsis. There was 1 death due to pulmonary embolism on the placebo arm. After cross-over to open-label AFINITOR, there were 3 additional deaths, one due to hypoglycemia and cardiac arrest in a patient with insulinoma, one due to MI with CHF, and the other due to sudden death. The rates of treatment-emergent adverse events resulting in permanent discontinuation were 20% and 6% for the AFINITOR and placebo treatment groups, respectively. Dose delay or reduction was necessary in 61% of everolimus patients and 29% of placebo patients. grade 3-4 renal failure occurred in 6 patients in the everolimus arm and 3 patients in the placebo arm. Thrombotic events included 5 patients with pulmonary embolus in the everolimus arm and 1 in the placebo arm as well as 3 patients with thrombosis in the everolimus arm and 2 in the placebo arm.

Table 5 compares the incidence of treatment-emergent adverse reactions reported with an incidence of ≥ 10% for patients receiving AFINITOR 10 mg daily versus placebo.

Table 5: Adverse Reactions Reported ≥ 10% of Patients with Advanced PNET

	AFINITOR N=204			Placebo N=203		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Any adverse reaction	**100**	**49**	**13**	**98**	**32**	**8**
Gastrointestinal disorders						
Stomatitis[a]	70	7	0	20	0	0
Diarrhea[b]	50	5	0.5	25	3	0
Abdominal pain	36	4	0	32	6	1
Nausea	32	2	0	33	2	0
Vomiting	29	1	0	21	2	0
Constipation	14	0	0	13	0.5	0
Dry mouth	11	0	0	4	0	0
General disorders and administration site conditions						
Fatigue/malaise	45	3	0.5	27	2	0.5
Edema (general and peripheral)	39	1	0.5	12	1	0
Fever	31	0.5	0.5	13	0.5	0
Asthenia	19	3	0	20	3	0
Infections and infestations						
Nasopharyngitis/rhinitis/URI	25	0	0	13	0	0
Urinary tract infection	16	0	0	6	0.5	0
Investigations						
Weight decreased	28	0.5	0	11	0	0
Metabolism and nutrition disorders						
Decreased appetite	30	1	0	18	1	0
Diabetes mellitus	10	2	0	0.5	0	0
Musculoskeletal and connective tissue disorders						
Arthralgia	15	1	0.5	7	0.5	0
Back pain	15	1	0	11	1	0
Pain in extremity	14	0.5	0	6	1	0
Muscle spasms	10	0	0	4	0	0

	AFINITOR N=204			Placebo N=203		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Nervous system disorders						
Headache/migraine	30	0.5	0	15	1	0
Dysgeusia	19	0	0	5	0	0
Dizziness	12	0.5	0	7	0	0
Psychiatric disorders						
Insomnia	14	0	0	8	0	0
Respiratory, thoracic and mediastinal disorders						
Cough/productive cough	25	0.5	0	13	0	0
Epistaxis	22	0	0	1	0	0
Dyspnea/dyspnea exertional	20	2	0.5	7	0.5	0
Pneumonitis[c]	17	3	0.5	0	0	0
Oropharyngeal pain	11	0	0	6	0	0
Skin and subcutaneous disorders						
Rash	59	0.5	0	19	0	0
Nail disorders	22	0.5	0	2	0	0
Pruritus/pruritus generalized	21	0	0	13	0	0
Dry skin/xeroderma	13	0	0	6	0	0
Vascular disorders						
Hypertension	13	1	0	6	1	0
Median duration of treatment (wks)		**37**			**16**	

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[a] Includes stomatitis, aphthous stomatitis, gingival pain/swelling/ulceration, glossitis, glossodynia, lip ulceration, mouth ulceration, tongue ulceration, and mucosal inflammation.

[b] Includes diarrhea, enteritis, enterocolitis, colitis, defecation urgency, and steatorrhea.

[c] Includes pneumonitis, interstitial lung disease, pulmonary fibrosis and restrictive pulmonary disease.

Key observed laboratory abnormalities are presented in Table 6.

Table 6: Key Laboratory Abnormalities Reported in ≥ 10% of Patients with Advanced PNET

Laboratory parameter	AFINITOR N=204		Placebo N=203	
	All grades %	Grade 3-4 %	All grades %	Grade 3-4 %
Hematology				
Hemoglobin decreased	86	15	63	1
Lymphocytes decreased	45	16	22	4
Platelets decreased	45	3	11	0
WBC decreased	43	2	13	0
Neutrophils decreased	30	4	17	2
Clinical chemistry				
Alkaline phosphatase increased	74	8	66	8
Glucose (fasting) increased	75	17	53	6
Cholesterol increased	66	0.5	22	0
Bicarbonate decreased	56	0	40	0
Aspartate transaminase (AST) increased	56	4	41	4
Alanine transaminase (ALT) increased	48	2	35	2
Phosphate decreased	40	10	14	3
Triglycerides increased	39	0	10	0
Calcium decreased	37	0.5	12	0
Potassium decreased	23	4	5	0
Creatinine increased	19	2	14	0
Sodium decreased	16	1	16	1
Albumin decreased	13	1	8	0

Bilirubin increased	10	1	14	2
Potassium increased	7	0	10	0.5

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6.3 Clinical Study Experience in Advanced Renal Cell Carcinoma

The data described below reflect exposure to AFINITOR (n=274) and placebo (n=137) in a randomized, controlled trial in patients with metastatic renal cell carcinoma who received prior treatment with sunitinib and/or sorafenib. The median age of patients was 61 years (range 27-85), 88% were Caucasian, and 78% were male. The median duration of blinded study treatment was 141 days (range 19-451) for patients receiving AFINITOR and 60 days (range 21-295) for those receiving placebo.

The most common adverse reactions (incidence ≥ 30%) were stomatitis, infections, asthenia, fatigue, cough, and diarrhea. The most common grade 3-4 adverse reactions (incidence ≥ 3%) were infections, dyspnea, fatigue, stomatitis, dehydration, pneumonitis, abdominal pain, and asthenia. The most common laboratory abnormalities (incidence ≥ 50%) were anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine. The most common grade 3-4 laboratory abnormalities (incidence ≥ 3%) were lymphopenia, hyperglycemia, anemia, hypophosphatemia, and hypercholesterolemia. Deaths due to acute respiratory failure (0.7%), infection (0.7%), and acute renal failure (0.4%) were observed on the AFINITOR arm but none on the placebo arm. The rates of treatment-emergent adverse events (irrespective of causality) resulting in permanent discontinuation were 14% and 3% for the AFINITOR and placebo treatment groups, respectively. The most common adverse reactions (irrespective of causality) leading to treatment discontinuation were pneumonitis and dyspnea. Infections, stomatitis, and pneumonitis were the most common reasons for treatment delay or dose reduction. The most common medical interventions required during AFINITOR treatment were for infections, anemia, and stomatitis.

Table 7 compares the incidence of treatment-emergent adverse reactions reported with an incidence of ≥ 10% for patients receiving AFINITOR 10 mg daily versus placebo. Within each MedDRA system organ class, the adverse reactions are presented in order of decreasing frequency.

Table 7: Adverse Reactions Reported in at least 10% of Patients with RCC and at a Higher Rate in the AFINITOR Arm than in the Placebo Arm

	AFINITOR 10 mg/day N=274			Placebo N=137		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Any adverse reaction	97	52	13	93	23	5
Gastrointestinal disorders						
Stomatitis[a]	44	4	<1	8	0	0
Diarrhea	30	1	0	7	0	0
Nausea	26	1	0	19	0	0
Vomiting	20	2	0	12	0	0
Infections and infestations[b]	37	7	3	18	1	0
General disorders and administration site conditions						
Asthenia	33	3	<1	23	4	0
Fatigue	31	5	0	27	3	<1
Edema peripheral	25	<1	0	8	<1	0
Pyrexia	20	<1	0	9	0	0
Mucosal inflammation	19	1	0	1	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	30	<1	0	16	0	0
Dyspnea	24	6	1	15	3	0
Epistaxis	18	0	0	0	0	0
Pneumonitis[c]	14	4	0	0	0	0
Skin and subcutaneous tissue disorders						
Rash	29	1	0	7	0	0
Pruritus	14	<1	0	7	0	0
Dry skin	13	<1	0	5	0	0
Metabolism and nutrition disorders						
Anorexia	25	1	0	14	<1	0
Nervous system disorders						
Headache	19	<1	<1	9	<1	0

	AFINITOR 10 mg/day N=274			Placebo N=137		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Dysgeusia	10	0	0	2	0	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	10	1	0	7	0	0
Median duration of treatment (d)		**141**			**60**	

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[a] Stomatitis (including aphthous stomatitis), and mouth and tongue ulceration.

[b] Includes all preferred terms within the 'infections and infestations' system organ class, the most common being nasopharyngitis (6%), pneumonia (6%), urinary tract infection (5%), bronchitis (4%), and sinusitis (3%), and also including aspergillosis (<1%), candidiasis (<1%), and sepsis (<1%).

[c] Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, and alveolitis.

Other notable adverse reactions occurring more frequently with AFINITOR than with placebo, but with an incidence of < 10% include:

Gastrointestinal disorders: Abdominal pain (9%), dry mouth (8%), hemorrhoids (5%), dysphagia (4%)

General disorders and administration site conditions: Weight decreased (9%), chest pain (5%), chills (4%), impaired wound healing (< 1%)

Respiratory, thoracic and mediastinal disorders: Pleural effusion (7%), pharyngolaryngeal pain (4%), rhinorrhea (3%)

Skin and subcutaneous tissue disorders: Hand-foot syndrome (reported as palmar-plantar erythrodysesthesia syndrome) (5%), nail disorder (5%), erythema (4%), onychoclasis (4%), skin lesion (4%), acneiform dermatitis (3%)

Metabolism and nutrition disorders: Exacerbation of pre-existing diabetes mellitus (2%), new onset of diabetes mellitus (< 1%)

Psychiatric disorders: Insomnia (9%)

Nervous system disorders: Dizziness (7%), paresthesia (5%)

Eye disorders: Eyelid edema (4%), conjunctivitis (2%)

Vascular disorders: Hypertension (4%), deep vein thrombosis (< 1%)

Renal and urinary disorders: Renal failure (3%)

Cardiac disorders: Tachycardia (3%), congestive cardiac failure (1%)

Musculoskeletal and connective tissue disorders: Jaw pain (3%)

Hematologic disorders: Hemorrhage (3%)

Key laboratory abnormalities are presented in Table 8.

Table 8: Key Laboratory Abnormalities Reported in Patients with RCC at a Higher Rate in the AFINITOR Arm than the Placebo Arm

Laboratory parameter	AFINITOR 10 mg/day N=274			Placebo N=137		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Hematology[a]						
Hemoglobin decreased	92	12	1	79	5	<1
Lymphocytes decreased	51	16	2	28	5	0
Platelets decreased	23	1	0	2	0	<1
Neutrophils decreased	14	0	<1	4	0	0
Clinical chemistry						
Cholesterol increased	77	4	0	35	0	0
Triglycerides increased	73	<1	0	34	0	0
Glucose increased	57	15	<1	25	1	0
Creatinine increased	50	1	0	34	0	0
Phosphate decreased	37	6	0	8	0	0
Aspartate transaminase (AST) increased	25	<1	<1	7	0	0
Alanine transaminase (ALT) increased	21	1	0	4	0	0
Bilirubin increased	3	<1	<1	2	0	0

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[a] Reflects corresponding adverse drug reaction reports of anemia, leukopenia, lymphopenia, neutropenia, and thrombocytopenia (collectively pancytopenia), which occurred at lower frequency.

6.4 Clinical Study Experience in Renal Angiomyolipoma with Tuberous Sclerosis Complex

The data described below are based on a randomized (2:1), double-blind, placebo-controlled trial of AFINITOR in 118 patients with renal angiomyolipoma as a feature of TSC (n=113) or sporadic lymphangioleiomyomatosis (n=5). The median age of patients was 31 years (range 18 to 61 years), 89% were Caucasian, and 34% were male. The median duration of blinded study treatment was 48 weeks (range 2 to 115 weeks) for patients receiving AFINITOR and 45 weeks (range 9 to 115 weeks) for those receiving placebo.

The most common adverse reaction reported for AFINITOR (incidence ≥ 30%) was stomatitis. The most common grade 3-4 adverse reactions (incidence ≥ 2%) were stomatitis, amenorrhea, and convulsion. The most common laboratory abnormalities (incidence ≥ 50%) were hypercholesterolemia, hypertriglyceridemia, and anemia. The most common grade 3-4 laboratory abnormality (incidence ≥ 3%) was hypophosphatemia.

The rate of treatment-emergent adverse events resulting in permanent discontinuation was 3.8% in the AFINITOR-treated patients. Adverse reactions leading to permanent discontinuation in the AFINITOR arm were hypersensitivity/angioedema/bronchospasm, convulsion, and hypophosphatemia. Dose adjustments (interruptions or reductions) due to adverse reactions occurred in 52% of AFINITOR-treated patients. The most common adverse reaction leading to AFINITOR dose adjustment was stomatitis.

Table 9 compares the incidence of treatment-emergent adverse reactions reported with an incidence of ≥ 10% for patients receiving AFINITOR and occurring more frequently with AFINITOR than with placebo. Laboratory abnormalities are described separately in Table 10.

Table 9: Treatment-emergent Adverse Reactions Reported in ≥ 10% of AFINITOR-treated Patients with Renal Angiomyolipoma

	AFINITOR N=79			Placebo N=39		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Any adverse reaction	**100**	**25**	**5**	**97**	**8**	**5**
Gastrointestinal disorders						
Stomatitis[a]	78	6	0	23	0	0
Nausea	16	0	0	13	0	0
Vomiting	15	0	0	5	0	0
Diarrhea	14	0	0	5	0	0
Abdominal pain	11	0	0	8	3	0
General disorders and administration site conditions						
Peripheral edema	13	0	0	8	0	0
Infections and infestations						
Upper respiratory tract infection	11	0	0	5	0	0
Musculoskeletal and connective tissue disorders						
Arthralgia	13	0	0	5	0	0
Nervous system disorders						
Headache	22	0	0	21	3	0
Respiratory, thoracic and mediastinal disorders						
Cough	20	0	0	13	0	0
Skin and subcutaneous tissue disorders			0			
Acne	22	0	0	5	0	0
Eczema	10	0	0	8	0	0

Grading according to CTCAE Version 3.0

[a] Includes stomatitis, aphthous stomatitis, mouth ulceration, gingival pain, glossitis, and glossodynia.

Amenorrhea occurred in 15% of AFINITOR-treated females (8 of 52) and 4% (1 of 26) of females in the placebo group. Other adverse reactions involving the female reproductive system were menorrhagia (10%), menstrual irregularities (10%), and vaginal hemorrhage (8%).

Other notable adverse reactions occurring more frequently with AFINITOR than with placebo, but with an incidence of < 10% include:

Immune system disorders: Hypersensitivity (3%)

Infections and infestations: Otitis media (6%), sinusitis (6%), pustular rash (5%)

Metabolism and nutrition disorders: Decreased appetite (6%)

Nervous system disorders: Convulsions (5%), migraine (5%), dysgeusia (4%), ageusia (1%)

Psychiatric disorders: Depression (5%)

Respiratory, thoracic and mediastinal disorders: Epistaxis (9%), pneumonitis (1%)

Skin and subcutaneous tissue disorders: Dry skin (9%), dermatitis acneiform (8%), papule (5%)

Vascular disorders: Hypertensive crisis (1%)

Table 10: Key Laboratory Abnormalities Reported in AFINITOR-treated Patients with Renal Angiomyolipoma

	AFINITOR N=79			Placebo N=39		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Hematology						
Anemia	61	0	0	49	0	0
Leucopenia	37	0	0	21	0	0
Neutropenia	25	0	1	26	0	0
Lymphopenia	20	1	0	8	0	0
Thrombocytopenia	19	0	0	3	0	0
Clinical chemistry						
Hypercholesterolemia	85	1	0	46	0	0
Hypertriglyceridemia	52	0	0	10	0	0
Hypophosphatemia	49	5	0	15	0	0
Alkaline phosphatase increased	32	1	0	10	0	0
Elevated aspartate transaminase (AST)	23	1	0	8	0	0
Elevated alanine transaminase (ALT)	20	1	0	15	0	0
Fasting hyperglycemia	14	0	0	8	0	0

Grading according to CTCAE Version 3.0

6.5 Clinical Study Experience in Subependymal Giant Cell Astrocytoma

The data described below reflect exposure to AFINITOR (n=28) in an open-label, single-arm trial for the treatment of patients with SEGA. The reliability of the frequency of adverse reactions and laboratory abnormalities reported in this trial is limited because of the small number of patients. The median age of patients was 11 years (range 3-34), 86% were Caucasian, and 61% were male. In total, 17 of the 28 patients were exposed to AFINITOR for ≥ 21 months.

The most common adverse reactions (incidence ≥ 30%) were stomatitis, upper respiratory tract infection, sinusitis, otitis media, and pyrexia. The grade 3 adverse reactions were convulsion, infections (single cases of sinusitis, pneumonia, tooth infection, and bronchitis viral), and single cases of stomatitis, aspiration, cyclic neutropenia, sleep apnea syndrome, vomiting, dizziness, white blood cell count decreased, and neutrophil count decreased. A grade 4 convulsion was also reported.

Table 11 summarizes the incidence of treatment-emergent adverse reactions reported with an incidence of ≥ 10%. Within each MedDRA system organ class, the adverse reactions are presented in order of decreasing frequency.

Table 11: Adverse Reactions Reported in at least 10% of Patients with SEGA

	AFINITOR N=28		
	All grades %	Grade 3 %	Grade 4 %
Any adverse reaction	100	36	4
Gastrointestinal disorders			
Stomatitis	86	4	0
Diarrhea	25	0	0
Vomiting	21	4	0
Abdominal pain	11	0	0
Constipation	11	0	0

Infections and infestations			
Upper respiratory tract infection	82	0	0
Sinusitis	39	4	0
Otitis media	36	0	0
Cellulitis	21	0	0
Body tinea	18	0	0
Gastroenteritis	18	0	0
Skin infection	18	0	0
Gastric infection	14	0	0
Otitis externa	14	0	0
Pharyngitis	11	0	0
General disorders and administration site conditions			
Pyrexia	32	0	0
Nervous system disorders			
Convulsion	29	7	4
Headache	18	0	0
Dizziness	14	4	0
Skin and subcutaneous tissue disorders			
Dermatitis acneiform	25	0	0
Dry skin	18	0	0
Rash	18	0	0
Dermatitis contact	14	0	0
Acne	11	0	0
Respiratory, thoracic and mediastinal disorders			
Cough	21	0	0
Nasal congestion	14	0	0
Rhinitis allergic	14	0	0
Psychiatric disorders			
Personality change	18	0	0
Injury, poisoning and procedural complications			
Excoriation	14	0	0

CTCAE Version 3.0

Other notable adverse reactions occurring with an incidence of < 10% include:

Gastrointestinal disorders: Gastritis (7%)

Skin and subcutaneous tissue disorders: Pityriasis rosea (4%)

Investigations: Chest x-ray abnormal (4%)

General disorders and administration site conditions: Fatigue (7%), edema peripheral (4%)

Respiratory, thoracic and mediastinal disorders: Pharyngeal inflammation (7%)

Nervous system disorders: Somnolence (7%)

Psychiatric disorders: Anxiety (7%)

Renal and urinary disorders: Proteinuria (7%)

Eye disorders: Ocular hyperemia (4%)

Vascular disorders: Hypertension (4%)

Key Laboratory Abnormalities

Single cases of grade 3 elevated aspartate transaminase (AST) concentrations and low absolute neutrophil count (ANC) were reported. No grade 4 laboratory abnormalities were noted. Laboratory abnormalities observed in > 1 patient (and listed in decreasing order of frequency) included elevations in AST concentrations (89%), total cholesterol (68%), alanine transaminase (ALT) (46%), triglycerides (43%) (hypertriglyceridemia reported as adverse reaction in 11% of patients, blood triglycerides increased reported as adverse reaction in 7% of patients), glucose (25%), and creatinine (11%), and reductions in white blood cell counts (54%) (reported as adverse reaction in 11% of patients), hemoglobin (39%), glucose (32%), and platelet counts (21%). Most of these laboratory abnormalities were mild (grade 1).

Two cases of neutrophil count decreased and blood immunoglobulin G decreased were reported as adverse reactions.

7 DRUG INTERACTIONS

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of the multidrug efflux pump PgP. *In vitro*, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

7.1 Agents that may Increase Everolimus Blood Concentrations

CYP3A4 Inhibitors and PgP Inhibitors

In healthy subjects, compared to AFINITOR treatment alone there were significant increases in everolimus exposure when AFINITOR was coadministered with:

- ketoconazole (a strong CYP3A4 inhibitor and a PgP inhibitor) - C_{max} and AUC increased by 3.9- and 15.0-fold, respectively.
- erythromycin (a moderate CYP3A4 inhibitor and a PgP inhibitor) - C_{max} and AUC increased by 2.0- and 4.4-fold, respectively.
- verapamil (a moderate CYP3A4 inhibitor and a PgP inhibitor) - C_{max} and AUC increased by 2.3- and 3.5-fold, respectively.

Concomitant strong inhibitors of CYP3A4 should not be used *[see Dosage and Administration (2.2, 2.4) and Warnings and Precautions (5.7)]*.

Use caution when AFINITOR is used in combination with moderate CYP3A4 and/or PgP inhibitors. If alternative treatment cannot be administered reduce the AFINITOR dose *[see Dosage and Administration (2.2, 2.4) and Warnings and Precautions (5.7)]*.

7.2 Agents that may Decrease Everolimus Blood Concentrations

CYP3A4 Inducers

In healthy subjects, co-administration of AFINITOR with rifampin, a strong inducer of CYP3A4, decreased everolimus AUC and C_{max} by 63% and 58% respectively, compared to everolimus treatment alone. Consider a dose increase of AFINITOR when co-administered with strong CYP3A4 inducers if alternative treatment cannot be administered. St. John's Wort may decrease everolimus exposure unpredictably and should be avoided *[see Dosage and Administration (2.2, 2.4)]*.

7.3 Agents whose Plasma Concentrations may be Altered by Everolimus

Studies in healthy subjects indicate that there are no clinically significant pharmacokinetic interactions between AFINITOR and the HMG-CoA reductase inhibitors atorvastatin (a CYP3A4 substrate) and pravastatin (a non-CYP3A4 substrate) and population pharmacokinetic analyses also detected no influence of simvastatin (a CYP3A4 substrate) on the clearance of AFINITOR.

A study in healthy subjects demonstrated that co-administration of an oral dose of midazolam (sensitive CYP3A4 substrate) with everolimus resulted in a 25% increase in midazolam C_{max} and a 30% increase in midazolam $AUC_{(0\text{-}inf)}$.

Coadministration of everolimus and exemestane increased exemestane C_{min} by 45% and C_{2h} by 64%. However, the corresponding estradiol 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, HER2-negative advanced breast cancer receiving the combination.

Coadministration of everolimus and depot octreotide increased octreotide Cmin by approximately 50%.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.10)]*.

There are no adequate and well-controlled studies of AFINITOR in pregnant women; however, based on the mechanism of action, AFINITOR can cause fetal harm when administered to a pregnant woman. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to use an effective method of contraception while receiving AFINITOR and for up to 8 weeks after ending treatment.

In animal reproductive studies, oral administration of everolimus to female rats before mating and through organogenesis induced embryo-fetal toxicities, including increased resorption, pre-implantation and post-implantation loss, decreased numbers of live fetuses, malformation (e.g., sternal cleft), and retarded skeletal development. These effects occurred in the absence of maternal toxicities. Embryo-fetal toxicities in rats occurred at doses ≥ 0.1 mg/kg (0.6 mg/m^2) with resulting exposures of approximately 4% of the exposure (AUC_{0-24h}) achieved in patients receiving the 10 mg daily dose of everolimus. In rabbits, embryotoxicity evident as an increase in resorptions occurred at an oral dose of 0.8 mg/kg (9.6 mg/m^2), approximately 1.6 times either the 10 mg daily dose or the median dose administered to SEGA patients on a body surface area basis. The effect in rabbits occurred in the presence of maternal toxicities.

In a pre- and post-natal development study in rats, animals were dosed from implantation through lactation. At the dose of 0.1 mg/kg (0.6 mg/m^2), there were no adverse effects on delivery and lactation or signs of maternal toxicity; however, there were reductions in body weight (up to 9% reduction from the control) and in survival of offspring (~5% died or missing). There were no drug-related effects on the developmental parameters (morphological development, motor activity, learning, or fertility assessment) in the offspring.

8.3 Nursing Mothers

It is not known whether everolimus is excreted in human milk. Everolimus and/or its metabolites passed into the milk of lactating rats at a concentration 3.5 times higher than in maternal serum. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from everolimus, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

AFINITOR is recommended for use only in patients with SEGA who are aged ≥ 3 years.

A prospective, open-label, single-arm trial was conducted to evaluate the safety and efficacy of AFINITOR in patients with SEGA associated with TSC. In total, 28 patients received treatment with AFINITOR; median age was 11 years (range 3-34). AFINITOR has not been studied in patients with SEGA < 3 years of age.

8.5 Geriatric Use

In the randomized advanced hormone receptor positive, HER2-negative breast cancer study, 40% of AFINITOR-treated patients were ≥ 65 years of age, while 15% were 75 and over. No overall differences in effectiveness were observed between elderly and younger subjects. The incidence of deaths due to any cause within 28 days of the last AFINITOR dose was 6% in patients ≥ 65 years of age compared to 2% in patients < 65 years of age. Adverse reactions leading to permanent treatment discontinuation occurred in 33% of patients ≥ 65 years of age compared to 17% in patients < 65 years of age *[see Warnings and Precautions (5.5)]*.

In two other randomized trials (advanced renal cell carcinoma and advanced neuroendocrine tumors of pancreatic origin), no overall differences in safety or effectiveness were observed between elderly and younger subjects. In the randomized advanced RCC study, 41% of AFINITOR treated patients were ≥ 65 years of age, while 7% were 75 and over. In the randomized advanced PNET study, 30% of AFINITOR-treated patients were ≥ 65 years of age, while 7% were 75 and over.

Other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out *[see Clinical Pharmacology (12.3)]*.

No dosage adjustment in initial dosing is required in elderly patients, but close monitoring and appropriate dose adjustments for adverse reactions is recommended. *[see Dosage and Administration (2.2), Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

No clinical studies were conducted with AFINITOR in patients with decreased renal function. Renal impairment is not expected to influence drug exposure and no dosage adjustment of everolimus is recommended in patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

The safety, tolerability and pharmacokinetics of AFINITOR were evaluated in a 34 subject single oral dose study of everolimus in subjects with impaired hepatic function relative to subjects with normal hepatic function. Exposure was increased in patients with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment *[see Clinical Pharmacology (12.3)]*.

For advanced HR+ BC, advanced PNET, advanced RCC, and renal angiomyolipoma with TSC patients with severe hepatic impairment, AFINITOR may be used at a reduced dose if the desired benefit outweighs the risk. For patients with

mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, a dose reduction is recommended *[see Dosage and Administration (2.2)*].

For SEGA patients with severe hepatic impairment (Child-Pugh class C), AFINITOR is not recommended. For SEGA patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, adjustment to the starting dose may not be needed; however, subsequent dosing should be individualized based on therapeutic drug monitoring *[see Dosage and Administration (2.4, 2.5)]*.

10 OVERDOSAGE

In animal studies, everolimus showed a low acute toxic potential. No lethality or severe toxicity were observed in either mice or rats given single oral doses of 2000 mg/kg (limit test).

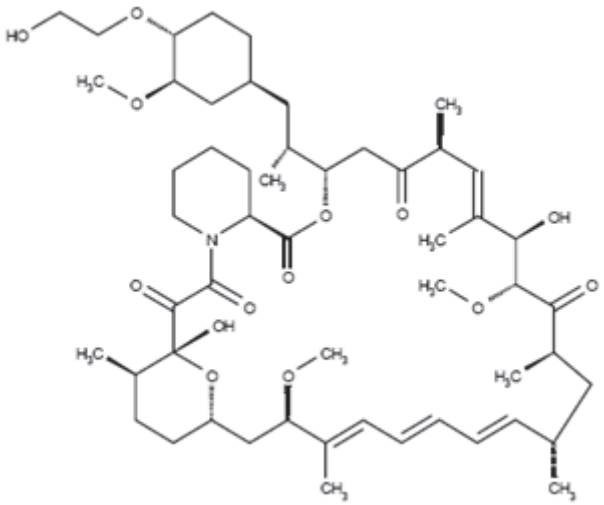
Reported experience with overdose in humans is very limited. Single doses of up to 70 mg have been administered. The acute toxicity profile observed with the 70 mg dose was consistent with that for the 10 mg dose.

11 DESCRIPTION

AFINITOR (everolimus), an inhibitor of mTOR, is an antineoplastic agent.

The chemical name of everolimus is (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-{(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.$0^{4,9}$]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone.

The molecular formula is $C_{53}H_{83}NO_{14}$ and the molecular weight is 958.2. The structural formula is:



AFINITOR is supplied as tablets for oral administration containing 2.5 mg, 5 mg, 7.5 mg, or 10 mg of everolimus together with butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, crospovidone, and lactose anhydrous as inactive ingredients.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Everolimus is an inhibitor of mammalian target of rapamycin (mTOR), a serine-threonine kinase, downstream of the PI3K/AKT pathway. The mTOR pathway is dysregulated in several human cancers. Everolimus binds to an intracellular protein, FKBP-12, resulting in an inhibitory complex formation with mTOR complex 1 (mTORC1) and thus inhibition of mTOR kinase activity. Everolimus reduced the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4E-BP1), downstream effectors of mTOR, involved in protein synthesis. S6K1 is a substrate of mTORC1 and phosphorylates the activation domain 1 of the estrogen receptor which results in ligand-independent activation of the receptor. In addition, everolimus inhibited the expression of hypoxia-inducible factor (e.g., HIF-1) and reduced the expression of vascular endothelial growth factor (VEGF). Inhibition of mTOR by everolimus has been shown to reduce cell proliferation, angiogenesis, and glucose uptake in *in vitro* and/or *in vivo* studies.

Constitutive activation of the PI3K/Akt/mTOR pathway can contribute to endocrine resistance in breast cancer. *In vitro* studies show that estrogen-dependent and HER2+ breast cancer cells are sensitive to the inhibitory effects of everolimus,

and that combination treatment with everolimus and Akt, HER2, or aromatase inhibitors enhances the anti-tumor activity of everolimus in a synergistic manner.

Two regulators of mTORC1 signaling are the oncogene suppressors tuberin-sclerosis complexes 1 and 2 (*TSC1*, *TSC2*). Loss or inactivation of either *TSC1* or *TSC2* leads to activation of downstream signaling. In TSC, a genetic disorder, inactivating mutations in either the *TSC1* or the *TSC2* gene lead to hamartoma formation throughout the body.

12.2 Pharmacodynamics

QT/QTc Prolongation Potential

In a randomized, placebo-controlled, crossover study, 59 healthy subjects were administered a single oral dose of AFINITOR (20 mg and 50 mg) and placebo. There is no indication of a QT/QTc prolonging effect of AFINITOR in single doses up to 50 mg.

Exposure Response Relationships

Markers of protein synthesis show that inhibition of mTOR is complete after a 10 mg daily dose.

In patients with SEGA, higher everolimus trough concentrations appear to be associated with larger reductions in SEGA volume. However, as responses have been observed at trough concentrations as low as 3 ng/mL, once acceptable efficacy has been achieved, additional dose increase may not be necessary.

12.3 Pharmacokinetics

Absorption

In patients with advanced solid tumors, peak everolimus concentrations are reached 1 to 2 hours after administration of oral doses ranging from 5 mg to 70 mg. Following single doses, C_{max} is dose-proportional between 5 mg and 10 mg. At doses of 20 mg and higher, the increase in C_{max} is less than dose-proportional, however AUC shows dose-proportionality over the 5 mg to 70 mg dose range. Steady-state was achieved within 2 weeks following once-daily dosing.

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

Distribution

The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 to 5000 ng/mL, is 17% to 73%. The amount of everolimus confined to the plasma is approximately 20% at blood concentrations observed in cancer patients given AFINITOR 10 mg/day. Plasma protein binding is approximately 74% both in healthy subjects and in patients with moderate hepatic impairment.

Metabolism

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

In vitro, everolimus competitively inhibited the metabolism of CYP3A4 and was a mixed inhibitor of the CYP2D6 substrate dextromethorphan.

Excretion

No specific excretion studies have been undertaken in cancer patients. Following the administration of a 3 mg single dose of radiolabeled everolimus in patients who were receiving cyclosporine, 80% of the radioactivity was recovered from the feces, while 5% was excreted in the urine. The parent substance was not detected in urine or feces. The mean elimination half-life of everolimus is approximately 30 hours.

Patients with Renal Impairment

Approximately 5% of total radioactivity was excreted in the urine following a 3 mg dose of [^{14}C]-labeled everolimus. In a population pharmacokinetic analysis which included 170 patients with advanced cancer, no significant influence of creatinine clearance (25–178 mL/min) was detected on oral clearance (CL/F) of everolimus *[see Use in Specific Populations (8.6)]*.

Patients with Hepatic Impairment

The safety, tolerability and pharmacokinetics of AFINITOR were evaluated in a single oral dose study of everolimus in subjects with impaired hepatic function relative to subjects with normal hepatic function. Compared to normal subjects (N=13), there was a 1.8-fold, 3.2-fold, and 3.6-fold increase in exposure (i.e. AUC) for subjects with mild (Child-Pugh class A, N=6), moderate (Child-Pugh class B, N=9), and severe (Child-Pugh class C, N=6) hepatic impairment, respectively. In another study, the average AUC of everolimus in eight subjects with moderate hepatic impairment (Child-Pugh class B) was twice that found in eight subjects with normal hepatic function.

For advanced HR+ BC, advanced PNET, advanced RCC, and renal angiomyolipoma with TSC patients with severe hepatic impairment, AFINITOR may be used at a reduced dose if the desired benefit outweighs the risk. For patients with moderate or mild hepatic impairment, a dose reduction is recommended *[see Dosage and Administration (2.2)]*.

For SEGA patients with mild (Child-Pugh class A) or moderate hepatic impairment (Child-Pugh class B), adjustment to the starting dose may not be needed; however, subsequent dosing should be individualized based on therapeutic drug monitoring *[see Dosage and Administration (2.4, 2.5)]*. For SEGA patients with severe hepatic impairment (Child-Pugh class C), AFINITOR should not be used.

Effects of Age and Gender

In a population pharmacokinetic evaluation in cancer patients, no relationship was apparent between oral clearance and patient age or gender.

Ethnicity

Based on a cross-study comparison, Japanese patients (n=6) had on average exposures that were higher than non-Japanese patients receiving the same dose.

Based on analysis of population pharmacokinetics, oral clearance (CL/F) is on average 20% higher in Black patients than in Caucasians.

The significance of these differences on the safety and efficacy of everolimus in Japanese or Black patients has not been established.

Dose Proportionality in Patients with SEGA

In patients with SEGA, intra-patient steady-state trough concentrations were dose-proportional at daily doses of 1.5 to 14.6 mg/m^2 *[see Dosage and Administration (2.3, 2.4)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Administration of everolimus for up to 2 years did not indicate oncogenic potential in mice and rats up to the highest doses tested (0.9 mg/kg) corresponding respectively to 3.9 and 0.2 times the estimated clinical exposure (AUC_{0-24h}) at the 10 mg daily human dose.

Everolimus was not genotoxic in a battery of *in vitro* assays (Ames mutation test in *Salmonella*, mutation test in L5178Y mouse lymphoma cells, and chromosome aberration assay in V79 Chinese hamster cells). Everolimus was not genotoxic in an *in vivo* mouse bone marrow micronucleus test at doses up to 500 mg/kg/day (1500 mg/m^2/day, approximately 255-fold the 10 mg daily human dose, and 103-fold the maximum dose administered to patients with SEGA, based on the body surface area), administered as two doses, 24 hours apart.

Based on non-clinical findings, male fertility may be compromised by treatment with AFINITOR. In a 13-week male fertility study in rats, testicular morphology was affected at 0.5 mg/kg and above. Sperm motility, sperm count, and plasma testosterone levels were diminished in rats treated with at 5 mg/kg. These doses result in exposures which are 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 resulted in infertility in the rats at 5 mg/kg. Effects on male fertility occurred at the AUC_{0-24h} values below that of therapeutic exposure (approximately 10%-81% of the AUC_{0-24h} in patients receiving the 10 mg daily dose). After a 10-13 week non-treatment period, the fertility index increased from zero (infertility) to 60% (12/20 mated females were pregnant).

Oral doses of everolimus in female rats at ≥0.1 mg/kg (approximately 4% the AUC_{0-24h} in patients receiving the 10 mg daily dose) resulted in increases in pre-implantation loss, suggesting that the drug may reduce female fertility. Everolimus crossed the placenta and was toxic to the conceptus *[see Use in Specific Populations (8.1)]*.

13.2 Animal Toxicology and/or Pharmacology

In juvenile rat toxicity studies, dose-related delayed attainment of developmental landmarks including delayed eye-opening, delayed reproductive development in males and females and increased latency time during the learning and memory phases were observed at doses as low as 0.15 mg/kg/day.

14 CLINICAL STUDIES

14.1 Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer

A randomized, double-blind, multicenter study of AFINITOR plus exemestane versus placebo plus exemestane was conducted in 724 postmenopausal women with estrogen receptor-positive, HER 2/neu-negative advanced breast cancer with recurrence or progression following prior therapy with letrozole or anastrozole. Randomization was stratified by documented sensitivity to prior hormonal therapy (yes vs. no) and by the presence of visceral metastasis (yes vs. no). Sensitivity to prior hormonal therapy was defined as either (1) documented clinical benefit (complete response [CR], partial response [PR], stable disease ≥ 24 weeks) to at least one prior hormonal therapy in the advanced setting or (2) at least 24 months of adjuvant hormonal therapy prior to recurrence. Patients were permitted to have received 0-1 prior lines of chemotherapy for advanced disease.

The primary endpoint for the trial was progression-free survival (PFS) evaluated by RECIST (Response Evaluation Criteria in Solid Tumors), based on investigator (local radiology) assessment. Other endpoints included overall survival (OS), objective response rate (ORR), and safety.

Patients were randomly allocated in a 2:1 ratio to AFINITOR 10 mg/day plus exemestane 25 mg/day (n = 485) or to placebo plus exemestane 25 mg/day (n = 239). The two treatment groups were generally balanced with respect to baseline demographics and disease characteristics. Patients were not permitted to cross over to AFINITOR at the time of disease progression.

The median progression-free survival by investigator assessment at the time of the final PFS analysis was 7.8 and 3.2 months in the AFINITOR and placebo arms, respectively [HR = 0.45 (95% CI: 0.38, 0.54), one-sided log-rank p < 0.0001] (see Table 12 and Figure 1). The results of the PFS analysis based on independent central radiological assessment were consistent with the investigator assessment. PFS results were also consistent across the subgroups of age, race, presence and extent of visceral metastases, and sensitivity to prior hormonal therapy.

Objective response rate was 12.6% (95% CI: 9.8, 15.9) in the AFINITOR plus exemestane arm vs. 1.7% (95% CI: 0.5, 4.2) in the placebo plus exemestane arm. There were 3 complete responses (0.6%) and 58 partial responses (12.0%) in the AFINITOR plus exemestane arm. There were no complete responses and 4 partial responses (1.7%) in the placebo plus exemestane arm.

The overall survival results were not mature at the time of the interim analysis, and no statistically significant treatment-related difference in OS was noted [HR=0.77 (95% CI: 0.57, 1.04)].

Table 12: Progression-free Survival Results

Analysis	AFINITOR + exemestane[a] N = 485	Placebo + exemestane[a] N = 239	Hazard ratio	P-value
Median progression-free survival (months, 95% CI)				
Investigator radiological review	7.8 (6.9 to 8.5)	3.2 (2.8 to 4.1)	0.45[b] (0.38 to 0 54)	<0.0001[c]
Independent radiological review	11.0 (9.7 to 15.0)	4.1 (2.9 to 5.6)	0.38[b] (0.3 to 0.5)	<0.0001[c]
Best overall response (%, 95% CI)				
Objective response rate (ORR)[d]	12.6% (9.8 to 15.9)	1.7% (0.5 to 4.2)	n/a[e]	

[a] Exemestane (25 mg/day)

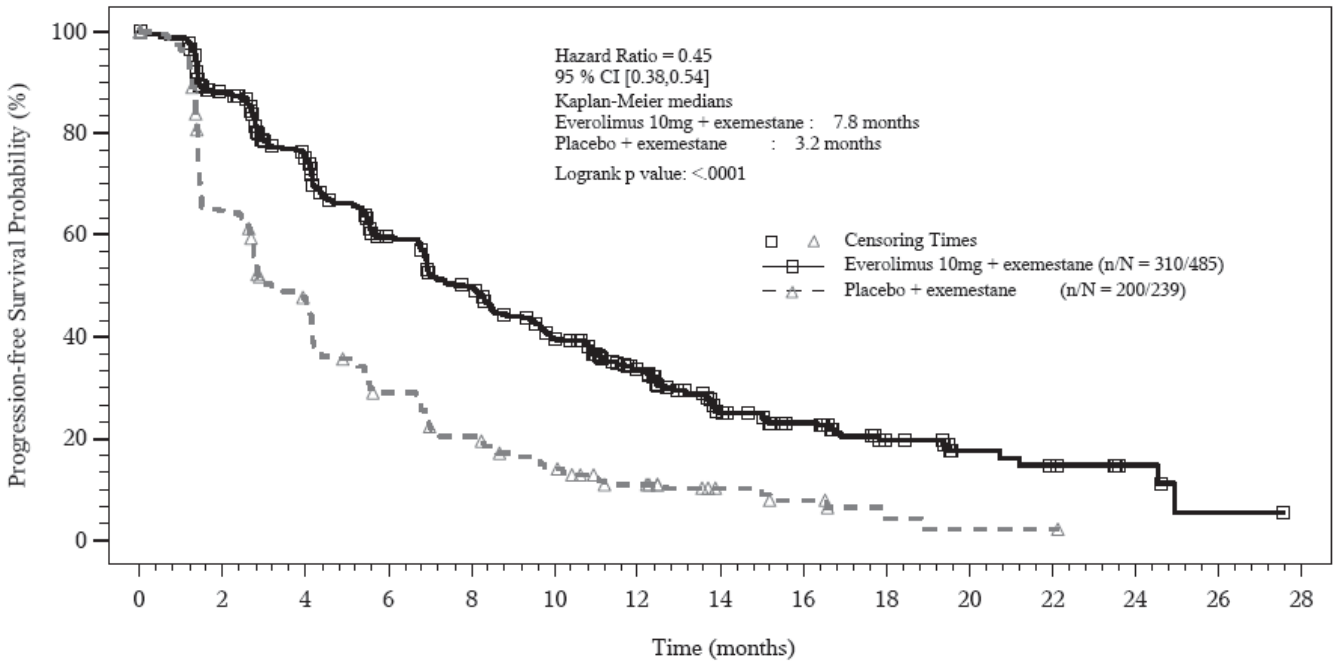
[b] Hazard ratio is obtained from the stratified Cox proportional-hazards model by sensitivity to prior hormonal therapy and presence of visceral metastasis

[c] p-value is obtained from the one-sided log-rank test stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis

[d] Objective response rate = proportion of patients with CR or PR

[e] not applicable

Figure 1: Kaplan-Meier Progression-free Survival Curves (Investigator Radiological Review)



14.2 Advanced Neuroendocrine Tumors

Locally Advanced or Metastatic Advanced Pancreatic Neuroendocrine Tumors (PNET):

A randomized, double-blind, multi-center trial of AFINITOR plus best supportive care (BSC) versus placebo plus BSC was conducted in patients with locally advanced or metastatic advanced pancreatic neuroendocrine tumors (PNET) and disease progression within the prior 12 months. Patients were stratified by prior cytotoxic chemotherapy (yes/no) and by WHO performance status (0 vs. 1 and 2). Treatment with somatostatin analogs was allowed as part of BSC. The primary endpoint for the trial was progression-free survival (PFS) evaluated by RECIST (Response Evaluation Criteria in Solid Tumors). After documented radiological progression, patients could be unblinded by the investigator; those randomized to placebo were then able to receive open-label AFINITOR. Other endpoints included safety, objective response rate [ORR (complete response (CR) or partial response (PR)], response duration, and overall survival.

Patients were randomized 1:1 to receive either AFINITOR 10mg/day (n=207) or placebo (n=203). Demographics were well balanced (median age 58 years, 55% male, 79% Caucasian). Crossover from placebo to open-label AFINITOR occurred in 73% (148/203) of patients.

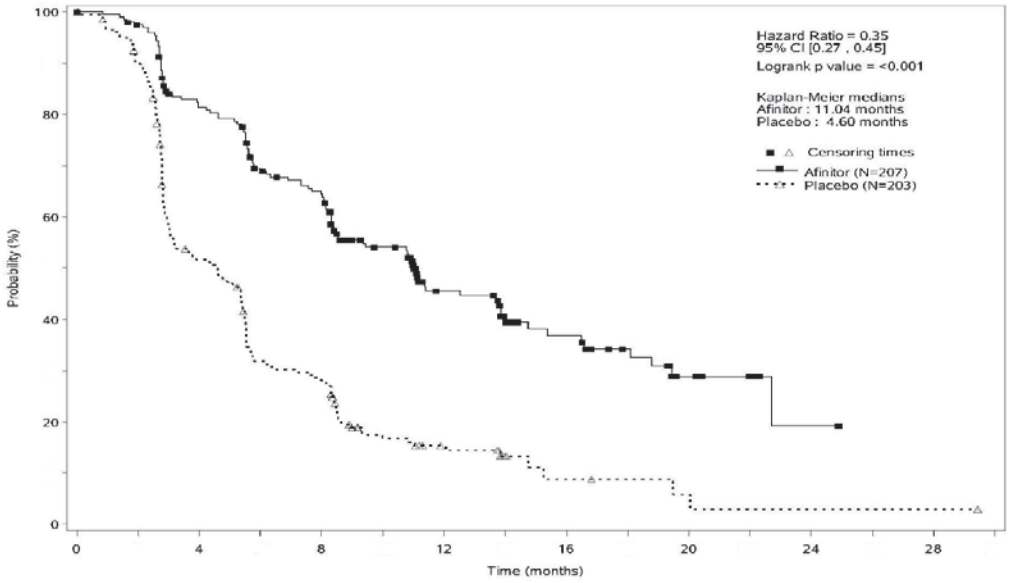
The trial demonstrated a statistically significant improvement in PFS (median 11.0 months versus 4.6 months), resulting in a 65% risk reduction in investigator-determined PFS (HR 0.35; 95%CI: 0.27 to 0.45; p<0.001) (see Table 13 and Figure 2). PFS improvement was observed across all patient subgroups, irrespective of prior somatostatin analog use. The PFS results by investigator radiological review, central radiological review and adjudicated radiological review are shown below in Table 13.

Table 13: Progression-free Survival Results

Analysis	N	AFINITOR N=207	Placebo N=203	Hazard Ratio (95%CI)	p-value
	410	Median progression-free survival (months) (95% CI)			
Investigator radiological review		11.0 (8.4 to 13.9)	4.6 (3.1 to 5.4)	0.35 (0.27 to 0.45)	<0.001
Central radiological review		13.7 (11.2 to 18.8)	5.7 (5.4 to 8.3)	0.38 (0.28 to 0.51)	<0.001
Adjudicated radiological review[a]		11.4 (10.8 to 14.8)	5.4 (4.3 to 5.6)	0.34 (0.26 to 0.44)	<0.001

[a] includes adjudication for discrepant assessments between investigator radiological review and central radiological review

Figure 2: Kaplan-Meier Investigator-Determined Progression-free Survival Curves



Investigator-determined response rate was low (4.8%) in the AFINITOR arm and there were no complete responses. The overall survival results are not yet mature and no statistically significant treatment-related difference in OS was noted [HR=1.05 (95% CI: 0.71 to 1.55)].

Locally Advanced or Metastatic Carcinoid Tumors

In a randomized, double-blind, multi-center trial in 429 patients with carcinoid tumors, AFINITOR plus depot octreotide (Sandostatin LAR®) was compared to placebo plus depot octreotide. After documented radiological progression, patients could be unblinded by the investigator: those randomized to placebo were then able to receive open-label AFINITOR plus depot octreotide. The study did not meet the primary efficacy endpoint (PFS) and the OS interim analysis numerically favored the placebo plus depot octreotide arm. Therefore, the use of AFINITOR in patients with carcinoid tumors remains investigational.

14.3 Advanced Renal Cell Carcinoma

An international, multi-center, randomized, double-blind trial comparing AFINITOR 10 mg daily and placebo, both in conjunction with best supportive care, was conducted in patients with metastatic RCC whose disease had progressed despite prior treatment with sunitinib, sorafenib, or both sequentially. Prior therapy with bevacizumab, interleukin 2, or interferon-α was also permitted. Randomization was stratified according to prognostic score and prior anticancer therapy *[see References (15)]*.

Progression-free survival (PFS), documented using Response Evaluation Criteria in Solid Tumors (RECIST) was assessed via a blinded, independent, central radiologic review. After documented radiological progression, patients could be unblinded by the investigator: those randomized to placebo were then able to receive open-label AFINITOR 10 mg daily.

In total, 416 patients were randomized 2:1 to receive AFINITOR (n=277) or placebo (n=139). Demographics were well balanced between the two arms (median age 61 years; 77% male, 88% Caucasian, 74% received prior sunitinib or sorafenib, and 26% received both sequentially).

AFINITOR was superior to placebo for PFS (see Table 14 and Figure 3). The treatment effect was similar across prognostic scores and prior sorafenib and/or sunitinib. Final overall survival (OS) results yield a hazard ratio of 0.90 (95% CI: 0.71 to 1.14), with no statistically significant difference between the two treatment groups. Planned crossover from placebo due to disease progression to open label AFINITOR occurred in 111 of the 139 patients (79.9%) and may have confounded the OS benefit.

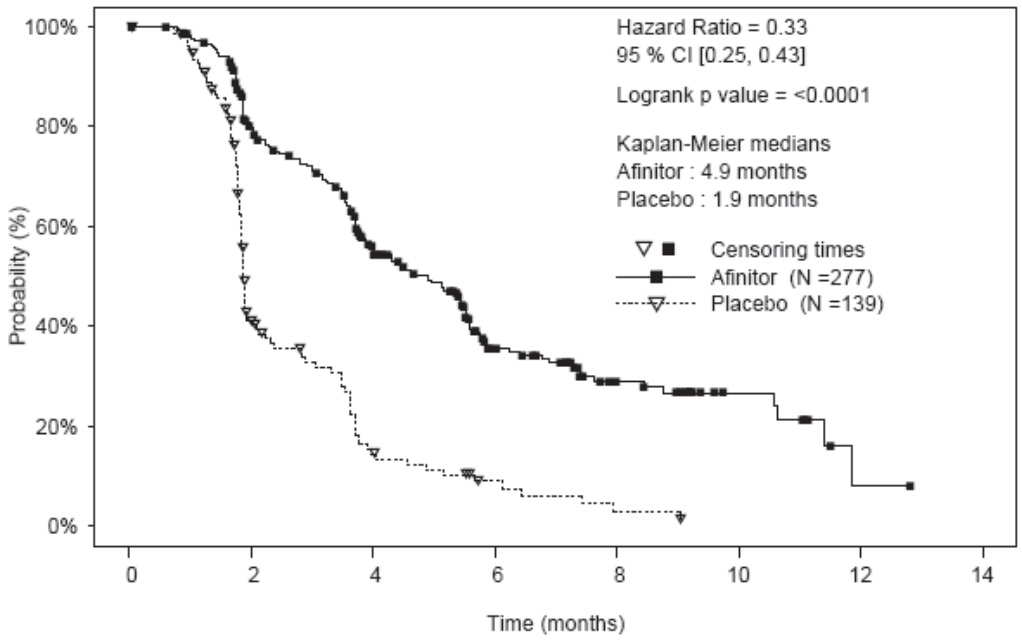
Table 14: Efficacy Results by Central Radiologic Review

	AFINITOR N=277	Placebo N=139	Hazard Ratio (95% CI)	p-value [a]
Median Progression-free Survival (95% CI)	4.9 months (4.0 to 5 5)	1.9 months (1.8 to 1.9)	0.33 (0.25 to 0.43)	<0.0001
Objective Response Rate	2%	0%	n/a [b]	n/a [b]

[a] Log-rank test stratified by prognostic score.

[b] Not applicable.

Figure 3: Kaplan-Meier Progression-free Survival Curves



14.4 Renal Angiomyolipoma with Tuberous Sclerosis Complex

A randomized (2:1), double-blind, placebo-controlled trial of AFINITOR was conducted in 118 patients with renal angiomyolipoma as a feature of TSC (n=113) or sporadic lymphangioleiomyomatosis (n=5).

The key eligibility requirements for this trial were at least one angiomyolipoma of ≥ 3 cm in longest diameter on CT/MRI based on local radiology assessment, no immediate indication for surgery, and age ≥ 18 years. Patients received daily oral AFINITOR 10 mg or matching placebo until disease progression or unacceptable toxicity. CT or MRI scans for disease assessment were obtained at baseline, 12, 24, and 48 weeks and annually thereafter. Clinical and photographic assessment of skin lesions were conducted at baseline and every 12 weeks thereafter until treatment discontinuation. The major efficacy outcome measure was angiomyolipoma response rate based on independent central radiology review, which was defined as a ≥ 50% reduction in angiomyolipoma volume, absence of new angiomyolipoma lesion ≥ 1 cm, absence of kidney volume increase ≥ 20%, and no angiomyolipoma related bleeding of ≥ grade 2. Key supportive efficacy outcome measures were time to angiomyolipoma progression and skin lesion response rate. Analyses of efficacy outcome measures were limited to the blinded treatment period which ended 6 months after the last patient was randomized. The comparative angiomyolipoma response rate analysis was stratified by use of enzyme-inducing antiepileptic drugs (EIAEDs) at randomization (yes/no).

Of the 118 patients enrolled, 79 were randomized to AFINITOR and 39 to placebo. The median age was 31 years (range 18 to 61 years), 34% were male, and 89% were Caucasian. At baseline, 17% of patients were receiving EIAEDs. On central radiology review at baseline, 92% of patients had at least one angiomyolipoma of ≥ 3 cm in longest diameter, 29% had angiomyolipomas ≥ 8 cm, 78% had bilateral angiomyolipomas, and 97% had skin lesions. The median values for the sum of all target renal angiomyolipoma lesions at baseline were 85 cm^3 (range 9 to 1612 cm^3) and 120 cm^3 (range 3 to 4520 cm^3) in the AFINITOR and placebo arms respectively. Forty-six (39%) patients had prior renal embolization or nephrectomy. The median duration of follow-up was 8.3 months (range 0.7 to 24.8 months).

The renal angiomyolipoma response rate was statistically significantly higher in AFINITOR-treated patients; there were 33 (41.8%) patients with angiomyolipoma responses in the AFINITOR arm as compared to none in the placebo arm. Results are displayed in Table 15. The median response duration is 5.3+ months (range 2.3+ to 19.6+ months).

Table 15: Angiomyolipoma Response

	AFINITOR N=79	**Placebo N=39**	**p-value**
Primary analysis			
Angiomyolipoma response rate[a] - %	**41.8**	**0**	**<0.0001**
95% CI	(30.8, 53.4)	(0.0, 9.0)	

[a] Per independent central radiology review

There were 3 patients in the AFINITOR arm and 8 patients in the placebo arm with documented angiomyolipoma progression by central radiologic review. The time to angiomyolipoma progression was statistically significantly longer in the AFINITOR arm (HR 0.08 [95% CI: 0.02, 0.37]; p <0.0001).

Skin lesion response rates were assessed by local investigators in 77 patients in the AFINITOR arm and 37 patients in the placebo arm with skin lesions at study entry. The skin lesion response rate was statistically significantly higher in the AFINITOR arm (26% vs. 0, p=0.0011); all skin lesion responses were partial responses, defined as visual improvement in 50%-99% skin lesions, considering all skin lesions, durable for at least eight weeks (Physician's Global Assessment of Clinical Condition).

14.5 Subependymal Giant Cell Astrocytoma

An open-label, single-arm trial was conducted to evaluate the safety and efficacy of AFINITOR in patients with SEGA associated with TSC. Serial radiological evidence of SEGA growth was required for entry. Change in SEGA volume at the end of the core 6-month treatment phase was assessed via an independent central radiology review. In total, 28 patients received treatment with AFINITOR; median age was 11 years (range 3-34), 61% male, 86% Caucasian. Four patients had surgical resection of their SEGA lesions with subsequent re-growth prior to receiving AFINITOR treatment. After the core treatment phase, patients could continue to receive AFINITOR treatment as part of an extension treatment phase where SEGA volume was assessed every 6 months. The median duration of treatment was 24.4 months (range 4.7-37.3 months).

At 6 months, 9 out of 28 patients (32%, 95% CI: 16% to 52%) had a ≥ 50% reduction in the tumor volume of their largest SEGA lesion. Duration of response for these 9 patients ranged from 97 to 946 days with a median of 266 days. Seven of these 9 patients had an ongoing volumetric reduction of ≥ 50% at the data cutoff.

Three of 4 patients who had prior surgery experienced a ≥ 50% reduction in the tumor volume of their largest SEGA lesion. One of these three patients responded by month 6. No patient developed new lesions.

15 REFERENCES

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- OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html
- American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. Am J Health-Syst Pharm. (2006) 63:1172-93.
- Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

16 HOW SUPPLIED/STORAGE AND HANDLING

2.5 mg tablets
White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with “LCL” on one side and “NVR” on the other; available in:
Blisters of 28 tablets……NDC 0078-0594-51
Each carton contains 4 blister cards of 7 tablets each

5 mg tablets
White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with “5” on one side and “NVR” on the other; available in:
Blisters of 28 tablets……NDC 0078-0566-51
Each carton contains 4 blister cards of 7 tablets each

7.5 mg tablets
White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with “7P5” on one side and “NVR” on the other; available in:
Blisters of 28 tablets.....NDC 0078-0620-51

Each carton contains 4 blister cards of 7 tablets each

10 mg tablets
White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with “UHE” on one side and “NVR” on the other; available in:
Blisters of 28 tablets……NDC 0078-0567-51
Each carton contains 4 blister cards of 7 tablets each

Store AFINITOR (everolimus) tablets at 25°C (77°F); excursions permitted between 15°–30°C (59°–86°F). See USP Controlled Room Temperature. Store in the original container, protect from light and moisture. Keep this and all drugs out of the reach of children.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published *[see References (15)]*.

AFINITOR tablets should not be crushed. Do not take tablets which are crushed or broken.

17 PATIENT COUNSELING INFORMATION

17.1 Non-infectious Pneumonitis

Warn patients of the possibility of developing non-infectious pneumonitis. In clinical studies, some non-infectious pneumonitis cases have been severe and occasionally fatal. Advise patients to report promptly any new or worsening respiratory symptoms *[see Warnings and Precautions (5.1)]*.

17.2 Infections

Inform patients that they are more susceptible to infections while being treated with AFINITOR and that cases of hepatitis B reactivation have been associated with AFINITOR treatment. In clinical studies, some of these infections have been severe (e.g., leading to respiratory or hepatic failure) and occasionally fatal. Patients should be aware of the signs and symptoms of infection and should report any such signs or symptoms promptly to their physician *[see Warnings and Precautions (5.2)]*.

17.3 Oral Ulceration

Inform patients of the possibility of developing mouth ulcers, stomatitis, and oral mucositis. In such cases, mouthwashes and/or topical treatments are recommended, but these should not contain alcohol or peroxide *[see Warnings and Precautions (5.3)]*.

17.4 Renal Failure

Inform patients of the possibility of developing kidney failure. In some cases kidney failure has been severe and occasionally fatal. Inform patients of the need for the healthcare provider to monitor kidney function, especially in patients with risk factors that may impair kidney function *[see Warnings and Precautions (5.4)]*.

17.5 Laboratory Tests and Monitoring

Inform patients of the need to monitor blood chemistry and hematology prior to the start of AFINITOR therapy and periodically thereafter *[see Warnings and Precautions (5.6)]*.

17.6 Drug-drug Interactions

Advise patients to inform their healthcare providers of all concomitant medications, including over-the-counter medications and dietary supplements. Inform the patients to avoid concomitant administration of strong CYP3A4 inhibitors or inducers while on AFINITOR treatment *[see Dosage and Administration (2.2, 2.4), Warnings and Precautions (5.7), Drug Interactions (7.1, 7.2)]*.

17.7 Vaccinations

Advise patients to avoid the use of live vaccines and close contact with those who have received live vaccines *[see Warnings and Precautions (5.9)]*.

17.8 Pregnancy

Advise female patients of childbearing potential that AFINITOR may cause fetal harm and that an effective method of contraception should be used during therapy with AFINITOR and for 8 weeks after ending treatment.

17.9 Dosing Instructions

Inform patients to take AFINITOR orally once daily at the same time every day, either consistently with food or consistently without food. AFINITOR should be swallowed whole with a glass of water. For patients unable to swallow

tablets, AFINITOR tablet(s) should be dispersed completely in a glass of water (containing approximately 30 mL) by gently stirring, immediately prior to drinking. The glass should be rinsed with the same volume of water and the rinse should be completely swallowed to ensure that the entire dose is administered.

Instruct patients that if they miss a dose of AFINITOR, they may still take it up to 6 hours after the time they would normally take it. If more than 6 hours have elapsed, they should be instructed to skip the dose for that day. The next day, they should take AFINITOR at the usual time. Warn patients to not take 2 doses to make up for the one that they missed.

PATIENT INFORMATION
AFINITOR® (a-fin-it-or)
(everolimus)
tablets

Read this Patient Information leaflet that comes with AFINITOR before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about AFINITOR?

AFINITOR can cause serious side effects. These serious side effects include:

1. **You may develop lung or breathing problems.** In some people lung or breathing problems may be severe, and can even lead to death. Tell your healthcare provider right away if you have any of these symptoms:
   - New or worsening cough
   - Shortness of breath
   - Chest pain
   - Difficulty breathing or wheezing
2. **You may be more likely to develop an infection,** such as pneumonia, or a bacterial, fungal or viral infection. Viral infections may include active hepatitis B in people who have had hepatitis B in the past (reactivation). In some people these infections may be severe, and can even lead to death. You may need to be treated as soon as possible.

   Tell your healthcare provider right away if you have a temperature of 100.5°F or above, chills, or do not feel well.

   Symptoms of hepatitis B or infection may include the following:

   - Fever
   - Skin rash
   - Joint pain and inflammation
   - Tiredness
   - Loss of appetite
   - Nausea
   - Pale stool or dark urine
   - Yellowing of the skin
   - Pain in your upper right side

3. **You may develop kidney failure.** In some people this may be severe and can even lead to death. Your healthcare provider should do tests to check your kidney function before and during your treatment with AFINITOR.

If you have any of the serious side effects listed above, you may need to stop taking AFINITOR for a while or use a lower dose. Follow your healthcare provider's instructions.

What is AFINITOR?

AFINITOR is a prescription medicine used to treat:

- o advanced hormone receptor-positive, HER2-negative breast cancer, along with the medicine exemestane, in postmenopausal women who have already received certain other medicines for their cancer.

- adults with a type of pancreatic cancer known as pancreatic neuroendocrine tumor (PNET), that has progressed and cannot be treated with surgery.
  It is not known if AFINITOR is safe and effective in people with carcinoid tumors.
- adults with advanced kidney cancer (renal cell carcinoma or RCC) when certain other medicines have not worked.
- people with the following types of tumors that are seen with a genetic condition called tuberous sclerosis complex (TSC):
  - a kidney tumor called angiomyolipoma, when their kidney tumor does not require surgery right away.
  - a brain tumor called subependymal giant cell astrocytoma (SEGA) in adults and children 3 years and older who cannot have surgery for their tumor.

    It is not known if AFINITOR is safe and effective in children under 3 years of age with SEGA.

Who should not take AFINITOR?

Do not take AFINITOR if you are allergic to AFINITOR or to any of its ingredients. See the end of this leaflet for a complete list of ingredients in AFINITOR. Talk to your healthcare provider before taking this medicine if you are allergic to:

- sirolimus (Rapamune®)
- temsirolimus (Torisel®)

Ask your healthcare provider if you do not know.

What should I tell my healthcare provider before taking AFINITOR?

Before taking AFINITOR, tell your healthcare provider about all of your medical conditions, including if you:

- Have or have had kidney problems
- Have or have had liver problems
- Have diabetes or high blood sugar
- Have high blood cholesterol levels
- Have any infections
- Previously had hepatitis B
- Are scheduled to receive any vaccinations. You should not receive a live vaccine or be around people who have recently received a live vaccine during your treatment with AFINITOR. If you are not sure about the type of immunization or vaccine, ask your healthcare provider.
- Have other medical conditions.
- Are pregnant, or could become pregnant. It is not known if AFINITOR will harm your unborn baby. You should use effective birth control while using AFINITOR and for 8 weeks after stopping treatment.
- Are breast-feeding or plan to breast-feed. It is not known if AFINITOR passes into your breast milk. You and your healthcare provider should decide if you will take AFINITOR or breast-feed. You should not do both.

Tell your healthcare provider about all of the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

AFINITOR may affect the way other medicines work, and other medicines can affect how AFINITOR works. Using AFINITOR with other medicines can cause serious side effects.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine. Especially tell your healthcare provider if you take:

- St. John's Wort (Hypericum perforatum)

- Medicine for:
    - Fungal infections
    - Bacterial infections
    - Tuberculosis
    - Seizures
    - HIV-AIDS
    - Heart conditions or high blood pressure
- Medicines that suppress your immune system

Ask your healthcare provider or pharmacist if you are not sure if your medicine is one of those taken for the conditions listed above. If you are taking any medicines for the conditions listed above, your healthcare provider might need to prescribe a different medicine or your dose of AFINITOR may need to be changed. You should also tell your healthcare provider before you start taking any new medicine.

How should I take AFINITOR?

- Your healthcare provider will prescribe the dose of AFINITOR that is right for you.
- Take AFINITOR exactly as your healthcare provider tells you. Your healthcare provider may change your dose of AFINITOR if needed.
- Swallow AFINITOR tablets whole with a glass of water. Do not crush AFINITOR tablets. Do not take AFINITOR tablets which are crushed or broken.
- If you cannot swallow AFINITOR tablets whole, you can stir them into a glass of water:
    - Put the prescribed number of tablets into a glass that contains about 2 Tablespoons (30 mL) of water
    - Gently stir the contents until the tablets break apart and then drink the mixture right away
    - Add about 2 Tablespoons (30 mL) of water to the glass and drink all of the water. This will help to make sure that you get the full dose of AFINITOR.
- Take AFINITOR one time every day, at about the same time every day.
- Take AFINITOR the same way each time, either with food or without food.
- You may use scissors to open the blister to avoid spillage.
- If you take too much AFINITOR contact your healthcare provider or go to the nearest hospital emergency department right away. Take the pack of AFINITOR with you.
- If you miss a dose of AFINITOR, you may still take it up to 6 hours after the time you normally take it. If it is more than 6 hours after you normally take your AFINITOR, skip the dose for that day. The next day, take AFINITOR at your usual time. Do not take 2 doses to make up for the one that you missed. If you are not sure about what to do, call your healthcare provider.
- You should have regular blood tests before you start AFINITOR and as needed during your treatment. These will include tests to check your blood cell count, kidney and liver function, cholesterol, and blood sugar levels.
- If you take AFINITOR to treat SEGA, you will need to have blood tests regularly to measure how much AFINITOR is in your blood. This will help your healthcare provider decide how much AFINITOR you need to take.

What should I avoid while taking AFINITOR?

You should not drink grapefruit juice or eat grapefruit during your treatment with AFINITOR. It may make the amount of AFINITOR in your blood increase to a harmful level.

What are the possible side effects of AFINITOR?

AFINITOR can cause serious side effects.

- **See "What is the most important information I should know about AFINITOR?"**

Common side effects of AFINITOR in patients with advanced hormone receptor-positive, HER2-negative breast cancer, advanced pancreatic neuroendocrine tumors, and advanced kidney cancer include:

- Mouth ulcers. AFINITOR can cause mouth ulcers and sores. Tell your healthcare provider if you have pain, discomfort, or open sores in your mouth. Your healthcare provider may tell you to use a special mouthwash or mouth gel that does not contain alcohol or peroxide.
- Infections
- Feeling weak or tired
- Cough, shortness of breath
- Diarrhea and constipation
- Rash, dry skin, and itching
- Nausea and vomiting
- Fever
- Loss of appetite,weight loss
- Swelling of arms, hands, feet, ankles, face or other parts of the body
- Abnormal taste
- Dry mouth
- Inflammation of lining of the digestive system
- Headache
- Nose bleeds
- Pain in arms and legs, mouth and throat, back or joints
- High blood glucose
- High blood pressure
- Difficulty sleeping
- Hair loss
- Muscle spasms
- Feeling dizzy
- Nail disorders

Common side effects of AFINITOR in patients who have angiomyolipoma with TSC include:

- Mouth ulcers. AFINITOR can cause mouth ulcers and sores. Tell your healthcare provider if you have pain, discomfort, or open sores in your mouth. Your healthcare provider may tell you to use a special mouthwash or mouth gel that does not contain alcohol or peroxide.
- Acne or eczema
- Nausea and vomiting
- Headache
- Cough
- Diarrhea
- Joint pain
- Swelling of your hands, arms, legs, and feet
- Stomach-area (abdomen) pain
- Respiratory tract infection
- Increased blood cholesterol level and certain other blood tests
- Decreased blood phosphate level
- Low red blood cells and white blood cells
- Increased blood sugar levels

- Absence of menstrual periods (menstruation). You may miss one or more menstrual periods. Tell your healthcare provider if this happens.

Common side effects of AFINITOR in patients with SEGA include:
- Infections of the respiratory tract, sinuses and ears
- Mouth ulcers. AFINITOR can cause mouth ulcers and sores. Tell your healthcare provider if you have pain, discomfort, or open sores in your mouth. Your healthcare provider may tell you to use a special mouthwash or mouth gel that does not contain alcohol or peroxide.
- Diarrhea and constipation
- Vomiting
- Stomach pain
- Fever
- Seizure
- Headache
- Dizziness
- Skin problems (such as rash, acne, dry skin, or scratching of the skin)
- Cough
- Stuffy or runny nose
- Change in personality
- Low white blood cells (a type of blood cell that fights infection; your healthcare provider will periodically check you for this problem)
- High levels of fats in the blood (raised triglycerides)

Tell your healthcare provider if you have any side effect that bothers you or does not go away.

These are not all the possible side effects of AFINITOR. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store AFINITOR?
- Store AFINITOR at room temperature, between 68°F to 77°F (20°C to 25°C)
- Keep AFINITOR in the package it comes in.
- Open the blister package just before taking AFINITOR.
- Keep the blister package and tablets dry prior to taking.
- Keep AFINITOR out of light.
- Throw away AFINITOR that is out of date or no longer needed.

Keep AFINITOR and all medicines out of the reach of children.

General information about AFINITOR
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use AFINITOR for a condition for which it was not prescribed. Do not give AFINITOR to other people, even if they have the same problem you have. It may harm them.

This leaflet summarizes the most important information about AFINITOR. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information written for healthcare professionals.

For more information call 1-888-423-4648 or go to www.AFINITOR.com.

What are the ingredients in AFINITOR?

Active ingredient: everolimus.
Inactive ingredients: butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, crospovidone, and lactose anhydrous.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Novartis Pharma Stein AG
Stein, Switzerland

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

July 2012/July 2012

T2012-XX/T2012-XX

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-334/S-016

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	July 20, 2012
From	Robert L. Justice, M.D., M.S.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	NDA 022334 SE1-016
Applicant Name	Novartis Pharmaceuticals Corporation
Date of Submission	November 2, 2011
PDUFA Goal Date	September 3, 2012
Proprietary Name / **Established (USAN) Name**	Afinitor everolimus
Dosage Forms / Strength	Tablets, 2.5 mg, 5 mg, 7.5 mg, 10 mg
Proposed Indication	AFINITOR® is indicated for the treatment of postmenopausal women (b) (4) [redacted]
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Tatiana Prowell (efficacy), Geoffrey Kim (safety)
Statistical Review	Lijun Zhang, Shenghui Tang
Pharmacology Toxicology Review	Mary-Jane Masson-Hinrichs, Anne Pilaro
CMC/Biopharmaceutics Reviews	Z. Jean Tang/Elsbeth Chikhale
Microbiology Review	N/A
Clinical Pharmacology Review	Elimika Pfuma, Jingyu Yu
DPDP	Marybeth Toscano, Michelle Safarik
OSI	Robert Young
CDTL Review	Patricia Cortazar
OSE/DMEPA	N/A
OSE/DDRE	N/A
DMPP	Sharon R. Mills
Other	

OND = Office of New Drugs
DDMAC = Division of Drug Marketing, Advertising and Communication
OSE = Office of Surveillance and Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
OSI = Office of Scientific Investigations
DDRE = Division of Drug Risk Evaluation
DRISK = Division of Risk Management
DPDP = Division of Professional Drug Promotion
DMPP = Division of Medical Policy Programs
CDTL = Cross-Discipline Team Leader
N/A = not applicable

Signatory Authority Review

1. Introduction

This efficacy supplement was submitted on 11/2/11 and was received on 11/3/11. The proposed new indication is "AFINITOR® is indicated for the treatment of postmenopausal women with (b) (4) This review will summarize the efficacy and safety data that support the new indication and the recommendations of each review discipline.

2. Background

Afinitor (everolimus) is an inhibitor of the mammalian target of rapamycin (mTOR), a serine-threonine kinase, downstream of the PI3K/AKT pathway. Everolimus was first approved in 2009 for the treatment of advanced renal cell carcinoma in patients who received prior treatment with sunitinib or sorafenib. In 2010, it received accelerated approval for the treatment of subependymal giant cell astrocytoma (tumors in the brain) associated with tuberous sclerosis complex (TSC) in patients requiring therapeutic intervention, but who are not candidates for curative surgical therapy. In 2011, Afinitor was approved for the treatment of progressive pancreatic neuroendocrine tumors in patients with unresectable, locally advanced, or metastatic disease. In 2012, accelerated approval was granted for treating renal angiomyolipoma (kidney tumors) that does not require immediate surgery in patients with TSC.

The rationale for studying everolimus in patients with hormone receptor-positive breast cancer is based on data suggesting that constitutive activation of the PI3K/Akt/mTOR pathway can contribute to endocrine resistance in breast cancer. *In vitro* studies show that estrogen-dependent breast cancer cells are sensitive to the inhibitory effects of everolimus and that combination treatment with everolimus and aromatase inhibitors enhances the anti-tumor activity of everolimus in a synergistic manner.

3. CMC/Biopharmaceutics

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the categorical exclusion from the requirement to prepare an environmental assessment. I also concur with the ONDQA biopharmaceutics reviewer's recommendation for approval. There are no outstanding CMC issues.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewers that based on the nonclinical data submitted with this supplemental NDA, the supplement can be approved. Labeling recommendations have been incorporated into the package insert and there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology

The following information in the package insert on the effects of everolimus on the plasma concentrations of exemestane were reviewed by the clinical pharmacology reviewers and were found to be acceptable.

> Coadministration of everolimus and exemestane increased exemestane C_{min} by 45% and C_{2h} by 64%. However, the corresponding estradiol 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.

I concur with the conclusions reached by the clinical pharmacology reviewers and their recommendations regarding labeling. There are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

The trial design and efficacy results are provided in the following excerpt from section 14.1 of the agreed-upon physician labeling.

> A randomized, double-blind, multicenter study of AFINITOR plus exemestane versus placebo plus exemestane was conducted in 724 postmenopausal women with estrogen receptor-positive, HER 2/neu-negative advanced breast cancer with recurrence or progression following prior therapy with letrozole or anastrozole. Randomization was stratified by documented sensitivity to prior hormonal therapy (yes vs. no) and by the presence of visceral metastasis (yes vs. no). Sensitivity to prior hormonal therapy was defined as either (1) documented clinical benefit (complete response [CR], partial response [PR], stable disease $\geq$ 24 weeks) to at least one prior hormonal therapy in the advanced setting or (2) at least 24 months of adjuvant hormonal therapy prior to recurrence. Patients were permitted to have received 0-1 prior lines of chemotherapy for advanced disease.

The primary endpoint for the trial was progression-free survival (PFS) evaluated by RECIST (Response Evaluation Criteria in Solid Tumors), based on investigator (local radiology) assessment. Other endpoints included overall survival (OS), objective response rate (ORR), and safety.

Patients were randomly allocated in a 2:1 ratio to AFINITOR 10 mg/day plus exemestane 25 mg/day (n = 485) or to placebo plus exemestane 25 mg/day (n = 239). The two treatment groups were generally balanced with respect to baseline demographics and disease characteristics. Patients were not permitted to cross over to AFINITOR at the time of disease progression.

The median progression-free survival by investigator assessment at the time of the final PFS analysis was 7.8 and 3.2 months in the AFINITOR and placebo arms, respectively [HR = 0.45 (95% CI: 0.38, 0.54), one-sided log-rank p < 0.0001] (see Table 12 and Figure 1). The results of the PFS analysis based on independent central radiological assessment were consistent with the investigator assessment. PFS results were also consistent across the subgroups of age, race, presence and extent of visceral metastases, and sensitivity to prior hormonal therapy.

Objective response rate was 12.6% (95% CI: 9.8, 15.9) in the AFINITOR plus exemestane arm vs. 1.7% (95% CI: 0.5, 4.2) in the placebo plus exemestane arm. There were 3 complete responses (0.6%) and 58 partial responses (12.0%) in the AFINITOR plus exemestane arm. There were no complete responses and 4 partial responses (1.7%) in the placebo plus exemestane arm.

The overall survival results were not mature at the time of the interim analysis, and no statistically significant treatment-related difference in OS was noted [HR=0.77 (95% CI: 0.57, 1.04)].

Table 12: Progression-free Survival Results

Analysis	AFINITOR + exemestane[a] N = 485	Placebo + exemestane[a] N = 239	Hazard ratio	P-value
Median progression-free survival (months, 95% CI)				
Investigator radiological review	7.8 (6.9 to 8.5)	3.2 (2.8 to 4.1)	0.45[b] (0.38 to 0.54)	<0.0001[c]
Independent radiological review	11.0 (9.7 to 15.0)	4.1 (2.9 to 5.6)	0.38[b] (0.3 to 0.5)	<0.0001[c]
Best overall response (%, 95% CI)				
Objective response rate (ORR)[d]	12.6% (9.8 to 15.9)	1.7% (0.5 to 4.2)	n/a[e]	

[a] Exemestane (25 mg/day)

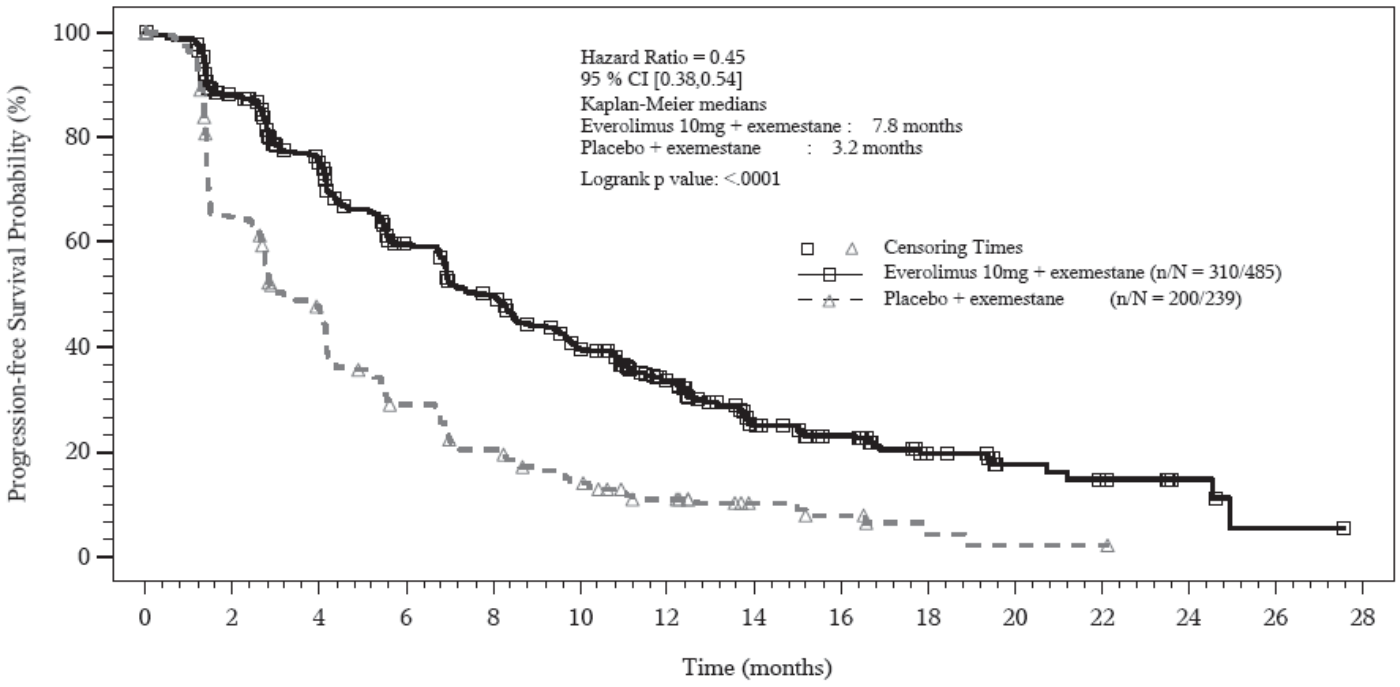
[b] Hazard ratio is obtained from the stratified Cox proportional-hazards model by sensitivity to prior hormonal therapy and presence of visceral metastasis

[c] p-value is obtained from the one-sided log-rank test stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis

[d] Objective response rate = proportion of patients with CR or PR

[e] not applicable

Figure 1: Kaplan-Meier Progression-free Survival Curves (Investigator Radiological Review)



8. Safety

The safety results from this trial are summarized below in the following excerpt from section 6.1 of the agreed-upon package insert.

> The efficacy and safety of AFINITOR (10 mg/day) plus exemestane (25 mg/day) (n=485) versus placebo plus exemestane (25 mg/day) (n=239) was evaluated in a randomized, controlled trial in patients with advanced or metastatic hormone-receptor-positive, HER2-negative breast cancer. The median age of patients was 61 years (range 28-93), and 75% were Caucasian. Safety results are based on a median follow-up of approximately 13 months.
>
> The most common adverse reactions (incidence ≥ 30%) were stomatitis, infections, rash, fatigue, diarrhea, and decreased appetite. The most common grade 3/4 adverse reactions (incidence ≥ 2%) were stomatitis, infections, hyperglycemia, fatigue, dyspnea, pneumonitis, and diarrhea. The most common laboratory abnormalities (incidence ≥ 50%) were hypercholesterolemia, hyperglycemia, increased AST, anemia, leukopenia, thrombocytopenia, lymphopenia, increased ALT, and hypertriglyceridemia. The most common grade 3/4 laboratory abnormalities (incidence ≥ 3%) were lymphopenia, hyperglycemia, anemia, decreased potassium, increased AST, increased ALT, and thrombocytopenia.
>
> Fatal adverse reactions occurred more frequently in patients who received AFINITOR plus exemestane (2%) compared to patients on the placebo plus exemestane arm

(0.4%). The rates of treatment-emergent adverse events resulting in permanent discontinuation were 24% and 5% for the AFINITOR plus exemestane and placebo plus exemestane treatment groups, respectively. Dose adjustments (interruptions or reductions) were more frequent among patients in the AFINITOR plus exemestane arm than in the placebo plus exemestane arm (63% versus 14%).

Table 3 compares the incidence of treatment-emergent adverse reactions reported with an incidence of ≥10% for patients receiving AFINITOR 10 mg daily versus placebo.

Table 3: Adverse Reactions Reported ≥ 10% of Patients with Advanced HR+ BC*

	AFINITOR (10 mg/day) + exemestane[a] N=482			Placebo + exemestane[a] N=238		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Any adverse reaction	**100**	**41**	**9**	**90**	**22**	**5**
Gastrointestinal disorders						
Stomatitis[b]	67	8	0	11	0.8	0
Diarrhea	33	2	0.2	18	0.8	0
Nausea	29	0.2	0.2	28	1	0
Vomiting	17	0.8	0.2	12	0.8	0
Constipation	14	0.4	0	13	0.4	0
Dry mouth	11	0	0	7	0	0
General disorders and administration site conditions						
Fatigue	36	4	0.4	27	1	0
Edema peripheral	19	1	0	6	0.4	0
Pyrexia	15	0.2	0	7	0.4	0
Asthenia	13	2	0.2	4	0	0
Infections and infestations						
Infections[c]	50	4	1	25	2	0
Investigations						
Weight decreased	25	1	0	6	0	0
Metabolism and nutrition disorders						
Decreased appetite	30	1	0	12	0.4	0
Hyperglycemia	14	5	0.4	2	0.4	0
Musculoskeletal and connective tissue disorders						
Arthralgia	20	0.8	0	17	0	0
Back pain	14	0.2	0	10	0.8	0
Pain in extremity	9	0.4	0	11	2	0
Nervous system disorders						
Dysgeusia	22	0.2	0	6	0	0
Headache	21	0.4	0	14	0	0
Psychiatric disorders						

Insomnia	13	0.2	0	8	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	24	0.6	0	12	0	0
Dyspnea	21	4	0.2	11	0.8	0.4
Epistaxis	17	0	0	1	0	0
Pneumonitis[d]	19	4	0.2	0.4	0	0
Skin and subcutaneous tissue disorders						
Rash	39	1	0	6	0	0
Pruritus	13	0.2	0	5	0	0
Alopecia	10	0	0	5	0	0
Vascular disorders						
Hot flush	6	0	0	14	0	0
Median Duration of Treatment[e]	**23.9 weeks**			**13.4 weeks**		

CTCAE Version 3.0

*160 patients (33.2%) were exposed to AFINITOR therapy for a period of ≥ 32 weeks)

[a] Exemestane (25 mg/day)

[b] Includes stomatitis, mouth ulceration, aphthous stomatitis, glossodynia, gingival pain, glossitis and lip ulceration

[c] Includes all preferred terms within the 'infections and infestations' system organ class, the most common being nasopharyngitis (10%), urinary tract infection (10%), upper respiratory tract infection (5%), pneumonia (4%), bronchitis (4%), cystitis (3%), sinusitis (3%), and also including candidiasis (<1%), and sepsis (<1%), and hepatitis C (<1%).

[d] Includes pneumonitis, interstitial lung disease, lung infiltration, and pulmonary fibrosis

[e] Exposure to AFINITOR or placebo

Key observed laboratory abnormalities are presented in Table 4.

Table 4: Key Laboratory Abnormalities Reported in ≥ 10% of Patients with Advanced HR+ BC

Laboratory parameter	AFINITOR (10 mg/day) + exemestane[a] N=482			Placebo + exemestane[a] N=238		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Hematology[b]						
Hemoglobin decreased	68	6	0.6	40	0.8	0.4
WBC decreased	58	1	0	28	5	0.8
Platelets decreased	54	3	0.2	5	0	0.4
Lymphocytes decreased	54	11	0.6	37	5	0.8
Neutrophils decreased	31	2	0	11	0.8	0.8
Clinical Chemistry						
Glucose increased	69	9	0.4	44	0.8	0.4
Cholesterol increased	70	0.6	0.2	38	0.8	0.8
Aspartate transaminase (AST) increased	69	4	0.2	45	3	0.4
Alanine transaminase (ALT) increased	51	4	0.2	29	5	0
Triglycerides increased	50	0.8	0	26	0	0
Albumin decreased	33	0.8	0	16	0.8	0
Potassium decreased	29	4	0.2	7	1	0
Creatinine increased	24	2	0.2	13	0	0

CTCAE Version 3.0

[a] Exemestane (25 mg/day)

[b] Reflects corresponding adverse drug reaction reports of anemia, leukopenia, lymphopenia, neutropenia, and thrombocytopenia (collectively as pancytopenia), which occurred at lower frequency.

The safety review identified new safety signals that were incorporated into the Warnings and Precautions section and the Geriatric Use subsection of the Use in Specific Populations section of the physician labeling:

5.5 Geriatric Patients

In the randomized advanced hormone receptor positive, HER2-negative breast cancer study, the incidence of deaths due to any cause within 28 days of the last AFINITOR dose was 6% in patients ≥ 65 years of age compared to 2% in patients < 65 years of age. Adverse reactions leading to permanent treatment discontinuation occurred in 33% of patients ≥ 65 years of age compared to 17% in patients < 65 years of age. Careful monitoring and appropriate dose adjustments for adverse reactions are recommended *[see Dosage and Administration (2.2), Use in Specific Populations (8.5)]*.

8.5 Geriatric Use

In the randomized advanced hormone receptor positive, HER2-negative breast cancer study, 40% of AFINITOR-treated patients were ≥ 65 years of age, while 15% were 75 and over. No overall differences in effectiveness were observed between elderly and

younger subjects. The incidence of deaths due to any cause within 28 days of the last AFINITOR dose was 6% in patients ≥ 65 years of age compared to 2% in patients < 65 years of age. Adverse reactions leading to permanent treatment discontinuation occurred in 33% of patients ≥ 65 years of age compared to 17% in patients < 65 years of age *[see Warnings and Precautions (5.5)]*.

9. Advisory Committee Meeting

This efficacy supplement was not referred to a meeting of the Oncologic Drugs Advisory Committee. However, application was discussed with an SGE with expertise in breast cancer who concurred with the approval action and the PMC for a 3-arm trial of everolimus plus exemestane vs. everolimus vs. capecitabine.

10. Pediatrics

A pediatric waiver was granted by the PeRC.

11. Other Relevant Regulatory Issues

The OSI inspections and financial disclosure were found to be acceptable.

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: N/A
- Physician labeling: Agreement has been reached on the physician labeling. The major issues that were discussed include (b) (4) [redacted]

  The final indication is "AFINITOR® is indicated for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole."

- Carton and immediate container labels: N/A

- Patient labeling/Medication guide: Patient labeling was updated to include the new indication.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Approval

- Risk Benefit Assessment

  I concur with the Clinical Review team's rationale for approval as modified below.

  The recommendation for approval is based upon the results of a randomized, double-blind, placebo-controlled trial (BOLERO 2), which compared everolimus 10 mg/day plus exemestane 25 mg/day to placebo plus exemestane 25 mg/day. This trial demonstrated a statistically significant improvement in progression-free survival (PFS) by investigator assessment with a 4.6 month absolute difference in median PFS [HR 0.45 (95% CI 0.38, 0.54)]. The analysis of median PFS by independent review committee (IRC) was consistent with the primary efficacy analysis [HR of 0.38 (95% CI 0.31, 0.48)], corresponding to an improvement in median PFS of 6.9 months. The improvement in efficacy was associated with an increase in toxicity, manifested as a higher rate of serious adverse events, grade 3/4 adverse events, permanent treatment discontinuations, dose interruptions, dose reductions, and on-treatment deaths in the combination arm compared to endocrine monotherapy. As of the interim analysis with 46% of events, overall survival (OS) numerically favors the everolimus plus exemestane arm with a hazard ratio of 0.77 (95% CI: 0.57, 1.04), suggesting that, despite the added toxicity of this combination, addition of everolimus to exemestane provides a net benefit to patients with advanced hormone receptor positive breast cancer.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

  None

- Recommendation for other Postmarketing Requirements and Commitments

  The applicant has agreed to the following Postmarketing Commitments.

1899-1: Submit a final report, including datasets, for the final overall survival results from trial CRAD001Y2301 (BOLERO-2).

Final Protocol Submission:	December 2011
Trial Completion:	June 2014
Final Report Submission:	June 2015

The rationale for this PMC is self-evident. The OS results were not mature at the interim analysis but the hazard ratio was 0.77 (95% CI: 0.57, 1.04).

1899-2: Conduct a 3-arm randomized trial 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 anastrazole.

Final Protocol Submission:	November 2012
Trial Completion:	August 2016
Final Report Submission:	August 2017

The rationale for this trial is stated in the Clinical Review:

> The pivotal trial that led to the approval of everolimus in combination with exemestane for postmenopausal women with advanced hormone receptor positive breast cancer, did not address the contribution of exemestane to the treatment regimen. The everolimus monotherapy arm will address the contribution of exemestane to the treatment combination. The third treatment arm will compare the efficacy and safety of capecitabine monotherapy, a treatment regimen frequently used after progression on hormonal therapies, to the everolimus plus exemestane combination.

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/s/

ROBERT L JUSTICE
07/20/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-334/S-016

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: NDA 022334/SE1-016
Afinitor (everolimus) Tablets
Novartis Pharmaceuticals Corporation

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Chikhale, Elsbeth
Cortazar, Patricia
Cottrell, Christy
Dorantes, Angelica
Fuller, Barbara
Garnett, Christine
Griffiths, LaShawn
Gwise, Thomas
Ibrahim, Amna
Justice, Robert
Kacuba, Alice
Kim, Geoffrey
Liu, Qi
Mills, Sharon
Pilaro, Anne
Prowell, Tatiana
Safarik, Michelle
Tang, Jean
Yu, Jingyu
Zhang, Lijun

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-334/S-016

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	July 16, 2012
DOP1 Clinical Team Leader	Patricia Cortazar, M.D.
sNDA	022334
Applicant	Novartis Pharmaceuticals Corporation
Date of Submission	November 2, 2011
PDUFA Goal Date	September 2, 2012
Proprietary Name / Established (USAN) names	Afinitor® /everolimus
Dosage forms / Strength	2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets
Proposed Indication(s)	"indicated for the treatment of postmenopausal women with advanced hormone receptor-positive breast cancer (advanced HR+ BC) in combination with exemestane after failure of treatment with letrozole or anastrozole"
Recommended:	*Approval*

Review Disciplines	Names of discipline reviewers/ Team Leaders
Regulatory Project Manager	Christy Cottrell/Alice Kacuba
Medical Officer Reviewers	Tatiana Prowell, M.D. (efficacy) Geoffrey Kim, M.D. (safety)
Statistical Review	Lijun Zhang/ Shenghui Tang
Clinical Pharmacology	Jingyu Yu, Elimika Pfuma, Christine Garnett/Qi Liu
Pharmacology Toxicology	Mary Jane Hinrichs/ Anne Pilaro
DDMAC	Mary Beth Toscano/ Michelle Safarik
OSI	Robert Young/ Janice Pohlman
DMPP	Sharon Mills/Barbara Fuller

Introduction

Novartis submitted a supplemental NDA to support marketing approval of Afinitor® (everolimus) for the treatment of postmenopausal women with advanced hormone receptor-positive breast cancer (advanced HR+ BC) in combination with exemestane after failure of treatment with letrozole or anastrozole. This document summarizes the reviews and conclusions of the review team.

The approval is based on a randomized, double-blind, multicenter trial conducted in 724 postmenopausal women with estrogen receptor-positive, HER2-negative, advanced breast cancer with recurrence or progression following prior therapy with letrozole or anastrozole. Patients were randomly allocated (2:1) to everolimus 10 mg/day plus exemestane 25 mg/day (n=485) or to placebo plus exemestane 25 mg/day (n=239). Patients were not permitted to cross over to everolimus at the time of disease progression.

The median progression-free survival (PFS) by investigator assessment at the time of the final PFS analysis was 7.8 and 3.2 months in the everolimus and placebo arms, respectively [HR 0.45 (95% CI: 0.38, 0.54), $p < 0.0001$]. The results of the PFS analysis based on independent central radiological assessment were consistent with the investigator assessment. PFS results were also consistent across the subgroups of age, race, presence and extent of visceral metastases, and sensitivity to prior hormonal therapy. The objective response rates were 12.6% and 1.7% in the everolimus and placebo arms, respectively. An interim analysis of overall survival (OS) conducted at 46% of expected events was not statistically significant [HR=0.77 (95% CI: 0.57, 1.04)]. The final analysis of OS is expected to occur in June 2014.

Safety was evaluated in 720 patients enrolled in the randomized trial. The most common grade 1-4 adverse reactions (incidence ≥ 30%) in patients receiving everolimus plus exemestane were stomatitis, infections, rash, fatigue, diarrhea, and decreased appetite. The most common grade 3-4 adverse reactions (≥ 2%) were stomatitis, infections, hyperglycemia, fatigue, dyspnea, pneumonitis, and diarrhea. The most common grade 3-4 laboratory abnormalities (≥ 3%) were lymphopenia, hyperglycemia, anemia, decreased potassium, increased AST, increased ALT, and thrombocytopenia.

Fatal adverse reactions occurred in 2% of patients on everolimus arm compared to 0.4% of patients on the placebo arm. Adverse reactions resulting in permanent discontinuation occurred in 24% and 5% of patients in the everolimus and placebo arms, respectively. Dose interruptions or reductions were necessary in 63% of patients on the everolimus arm compared to 14% on the placebo arm.

1. Background

Everolimus is an inhibitor of mammalian target of rapamycin (mTOR), a serine-threonine kinase, downstream of the PI3K/AKT pathway. The mTOR pathway is dysregulated in several human cancers. Constitutive activation of the PI3K/Akt/mTOR pathway can

contribute to endocrine resistance in breast cancer. In vitro studies show that estrogen-dependent and HER2+ breast cancer cells are sensitive to the inhibitory effects of everolimus, and that combination treatment with everolimus and Akt, HER2, or aromatase inhibitors enhances the anti-tumor activity of everolimus in a synergistic manner.

Everolimus clinical development supporting the prophylaxis of organ transplant rejection was started in 1996. On 04-20-2010 received marketing approval in the US as Zortress, for prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a renal transplant.

Everolimus clinical development for oncologic indications started in 2002 and is currently marketed in the US under the trade name of Afinitor at a daily dose of 10 mg for the following indications:

- Treatment of advanced renal cell carcinoma after failure of sunitinib or sorafenib (03-30-2009)
- Treatment of subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) in patients who require therapeutic intervention but are not candidates for curative surgical resection (10-29-2010)
- Treatment of progressive neuroendocrine tumors of pancreatic origin (PNET) in patients with unresectable, locally advanced, or metastatic disease (05-05-2011)
- Treatment of renal angiomyolipomas not requiring immediate surgery in patients with tuberous sclerosis complex (04-26-2012)

The everolimus development program in support of the current indication was discussed with FDA at a pre sNDA meeting held on October-11-2011. There was no End of Phase II meeting (EOP2) held with the FDA nor any special protocol assessment requested for Study Y2301 (BOLERO 2) supporting the current sNDA submission.

In this meeting, FDA recommended that Novartis submit the sNDA with the final PFS analysis, not the interim PFS analysis as proposed. In addition, FDA recommended that the statistical analysis plan be revised to include an interim analysis of OS at the time of the final analysis of PFS. The Sponsor provided compelling clinical and statistical arguments in favor of their strategy to base submission upon the interim PFS analysis. The Agency stated that sNDA submission based upon the interim analysis of PFS and first interim analysis of OS was acceptable to support the sNDA submission and that a second interim analysis of OS was to be submitted during the review cycle. The sponsor's decision to submit the sNDA based upon the interim analysis of PFS was the basis for FDA's decision to grant the application a standard review rather than a priority review.

2. CMC/Device

There are no new CMC issues to review with this sNDA.

3. Nonclinical Pharmacology/Toxicology

There are no new nonclinical pharmacology/toxicology issues to review with this sNDA.

4. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology/biopharmaceutics reviewer (Jingyu Yu) and team leader (Qi Liu) concluded that there are no outstanding clinical pharmacology issues that preclude approval of this supplement.

In Study Y2301, there was a 45 – 64% mean increase in exemestane exposure when given in combination with everolimus. The reviewers believe that it is unclear if the increase in exemestane exposure has an effect on efficacy or safety in the combination arm. The exemestane exposure-response relationship for efficacy and safety could not be established due to limited PK data (10% of patients). The estradiol levels at steady state (4 weeks) were similar between the two treatment arms; however, estradiol levels may not be directly related to PFS.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical- Efficacy

This NDA is primarily supported by results from a single industry-sponsored study, BOLERO 2 (Y2301), entitled:

> "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."

Study Design:

BOLERO 2 (Y2301) was a randomized, multicenter, double-blind, placebo-controlled trial of 724 postmenopausal women with advanced hormone receptor-positive, HER 2/neu-negative breast cancer who had progressed on either anastrozole or letrozole. Key eligibility criteria included confirmed estrogen receptor-positive (ER+) metastatic or locally advanced if not amenable to curative surgery or radiotherapy, breast cancer whose disease was refractory to non-steroidal aromatase inhibitors (NSAI). Randomization was stratified by documented sensitivity to prior hormonal therapy (yes vs. no) and by the presence of visceral metastasis (yes vs. no). Sensitivity to prior hormonal therapy was defined as either (1) documented clinical benefit (complete response [CR], partial response [PR], stable disease ≥ 24 weeks) to at least one prior hormonal therapy in the advanced setting or (2) at least 24 months of adjuvant hormonal therapy prior to recurrence. Patients were permitted to have received 0-1 prior lines of chemotherapy for advanced disease.

Patients were randomly allocated in a 2:1 ratio to everolimus 10 mg/day plus exemestane 25 mg/day or to placebo plus exemestane 25 mg/day. Patients were not permitted to cross over to the everolimus treatment arm at the time of disease progression.

The primary endpoint for the trial was progression-free survival (PFS) evaluated by RECIST (Response Evaluation Criteria in Solid Tumors), based on investigator (local radiology) assessment. PFS was defined as the time from the date of randomization to the date of disease progression or death (from any cause). Secondary endpoints included overall survival (OS), PFS (investigator-assessed), objective response rate (ORR) and duration of response. Secondary endpoints included overall survival (OS), objective response rate (ORR), and safety.

Statistical Analysis Plan:

The statistical analysis plan specified a sample size of 705 patients needed to provide 90% power to detect a 35% improvement in PFS (3.7 months median placebo vs. 5 months median everolimus; HR=0.74) at the two sided significance level of 5%. Subjects were to be followed until 398 deaths had occurred, which provided 80% power to detect a 35% improvement in median OS (24 versus 32.4 months), corresponding to a HR of 0.74 with a two-sided alpha of 0.05.

There was a pre-specified interim analysis of PFS to be conducted after 359 (68%) events had been reported by the investigator and 218 (41%) events had been reported by the IRC. A final PFS analysis by investigator was to be conducted after 510 (97%) events had been observed. These data were submitted to FDA during the current review cycle and, as the most mature data, were used to generate the product labeling. Three interim and a final analyses of OS were planned. The first interim OS analysis was performed concurrent with the interim analysis of PFS and accompanied the original sNDA submission. The second interim analysis of OS was performed during the sNDA review cycle and has also been reviewed by FDA. The third interim and final analyses of OS were pending at the time of regulatory action. The second interim analysis of OS with 46% of events, which represent the most mature OS data available, was used for review and product labeling.

BOLERO Efficacy Results:

The trial randomized 724 patients, 485 to the everolimus arm and 239 to the placebo arm, comprising the ITT population. Patients were recruited at 196 centers in 24 countries. The US sites contributed 31% of the total trial population.

Baseline demographics and treatment characteristics were well balanced between treatment arms. Approximately 59% of patients had visceral involvement and 76% had bone involvement as would be expected in a population of hormone receptor-positive breast cancer patients. Less than 1% of patients had central nervous system involvement. All patients had previously been treated with either letrozole or anastrozole; only 57 patients (8%) had previously received both aromatase inhibitors. For 68% of patients, a NSAI had been used only in the metastatic setting, and for three-quarters, the NSAI was their last treatment prior to study entry. Approximately 70% of patients had received prior chemotherapy, either in the neo/adjuvant setting (42%), the metastatic setting (12%), or both (13%).

Primary Endpoint

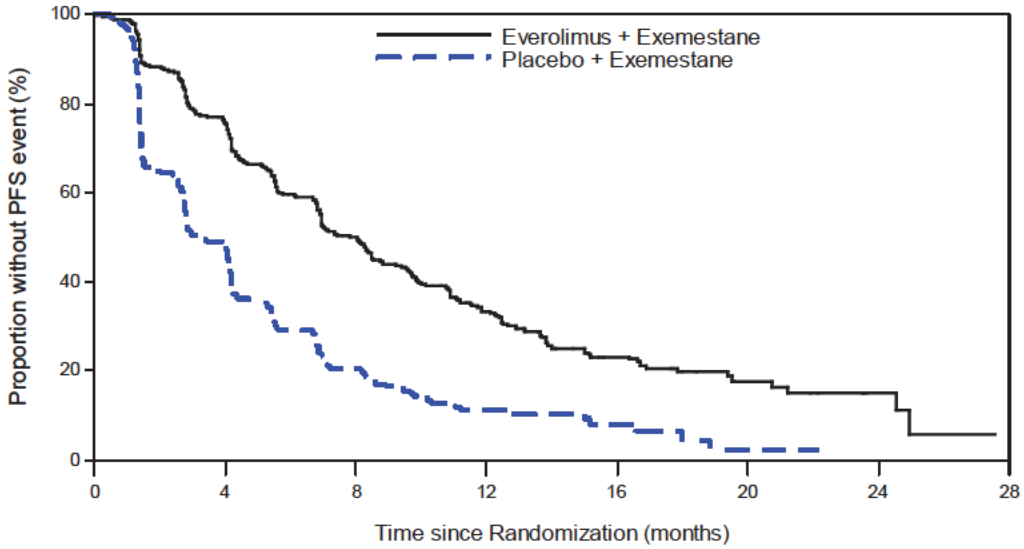
PFS Results:

At the time of the final PFS analysis, the median progression-free survival by investigator assessment was 7.8 and 3.2 months in the everolimus and placebo arms, respectively [HR = 0.45 (95% CI: 0.38, 0.54), one-sided log-rank $p < 0.0001$] (see Table 1 and Figure 1). The results of the PFS analysis based on independent central radiological assessment were consistent with the investigator assessment. PFS results were also consistent across the subgroups of age, race, presence and extent of visceral metastases, and sensitivity to prior hormonal therapy.

Table 1 Study Y2301 Final Analysis of PFS by Investigator (ITT Population)

	Everolimus + Exemestane **N=485** **N (%)**	**Placebo + Exemestane** **N=239** **N (%)**
PFS events Disease Progression Death	310 (64) 294 (61) 16 (3)	200 (84) 198 (83) 2 (1)
Median PFS, months [95% CI]	7.8 [6.9, 8.5]	3.2 [2.8, 4.1]
HR [95% CI]	0.45 [0.38, 0.54]	
p-value	P<0.0001	

Figure 1 Study Y2301 Final Analysis of OS by Investigator (ITT Population)



During FDA's review of the PFS data using patient-level investigator raw lesion data, 29 patients with discrepancies in the date or nature of PFS event were identified. The FDA clinical and statistical review teams conducted their own PFS analysis using the case report forms to amend the dataset per RECIST criteria for these 29 patients. The results were consistent with the primary analysis. Per FDA's analysis, the median PFS was 6.9 months in the everolimus plus exemestane arm and 2.8 months in the exemestane plus placebo arm, corresponding to a 56% reduction in the risk of progression or death [HR 0.44 (95% CI 0.35, 0.54)]. These results are consistent with the primary analysis of the endpoint by investigator assessment.

Secondary Endpoints

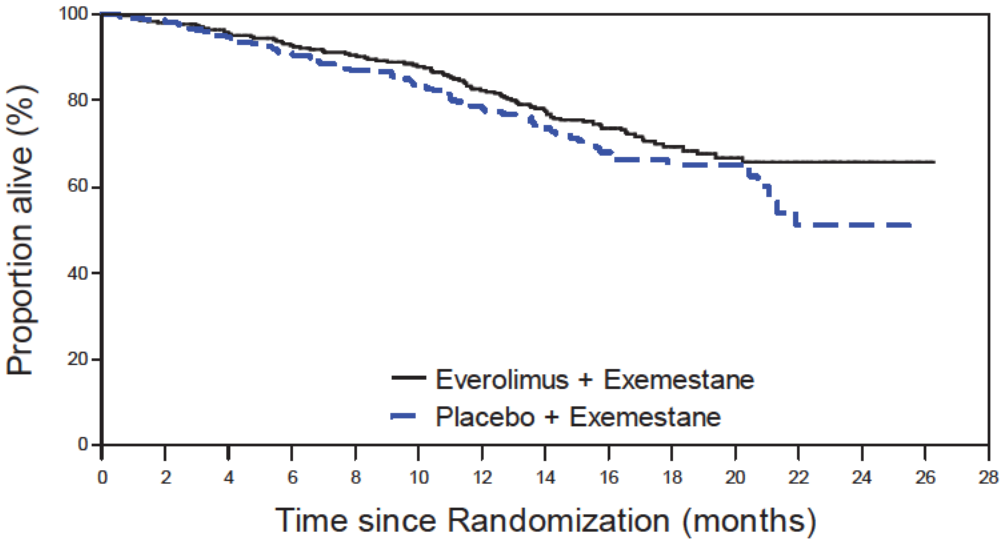
OS Results:

The overall survival results were not mature at the time of the interim analysis, and no statistically significant treatment-related difference in OS was noted. The first interim OS analysis was conducted at the time of the interim PFS analysis, when 83 (21%) of 398 required death events for the final OS analysis occurred. The second interim OS analysis was conducted when 182 (46%) deaths events occurred. The results of the 1st and 2nd OS interim analyses are presented in Table 2. There was no statistically significant difference between the two treatment arms with respect to OS at both interim analyses (one-sided p-value of 0.15 at the first interim analysis and 0.046 at the second interim analysis). The hazard ratio for OS was 0.79 (95% CI: 0.50, 1.24) at the first interim analysis and 0.77 (95% CI: 0.57, 1.04) at the second interim analysis.

Table 2 Summary of OS Interim Analysis (sponsor's efficacy results)

	Everolimus + Exemestane N=485	**Placebo + Exemestane N=239**
	First Interim Analysis	
Number of Deaths, n(%)	52 (11%)	31 (13%)
HR	0.79 (0.50, 1.24)	
P-value, one-sided*	0.15	
	Second Interim Analysis	
# of Deaths, n(%)	112 (23%)	70 (29%)
HR	0.77 (0.57, 1.04)	
P-value, one-sided*	0.046	

Figure 2 Study Y2301 Kaplan-Meier Plot of OS in the ITT Population at the Second Interim Analysis



Objective Response Rate:

At the time of the final PFS analysis, objective response rate was 12.6% (95% CI: 9.8, 15.9) in the everolimus plus exemestane arm vs. 1.7% (95% CI: 0.5, 4.2) in the placebo plus exemestane arm. There were 3 complete responses (0.6%) and 58 partial responses (12.0%) in the everolimus plus exemestane arm. There were no complete responses and 4 partial responses (1.7%) in the placebo plus exemestane arm. Similarly, objective response rate per central radiology review was 12.6% in the everolimus arm vs. 2.1% in the placebo arm. Due to the small response rate, duration of response and time to response were not calculated.

Table 3 Study Y2301 ORR

	Everolimus + Exemestane **N=485** **N (%)**	**Placebo + Exemestane** **N=239** **N (%)**
Objective Response Rate (ORR)	61 (12.6)	4 (1.7)
Complete Response (CR)	3 (0.6)	0 (0)
Partial Response (PR)	58 (12)	4 (1.7)
Clinical Benefit Rate (CBR)	249 (51)	63 (26)

7. Safety

The safety database for everolimus was adequate to characterize the safety of this product for the proposed indication. Everolimus was administered in combination with exemestane with acceptable toxicity. Overall toxicities, are consistent with the known safety profile of everolimus in other advanced cancers in the adult population. There was an increased rate of on-treatment mortality seen on everolimus therapy in patients ≥ 65 years of age. The rate of treatment discontinuations, dose interruptions, and dose reductions seen with the combination of everolimus plus exemestane was comparable in both treatment arms.

The most common adverse reactions (incidence ≥ 30%) were stomatitis, infections, rash, fatigue, diarrhea, and decreased appetite. The most common grade 3/4 adverse reactions (incidence ≥ 2%) were stomatitis, infections, hyperglycemia, fatigue, dyspnea, pneumonitis, and diarrhea. The most common laboratory abnormalities (incidence ≥ 50%) were hypercholesterolemia, hyperglycemia, increased AST, anemia, leukopenia, thrombocytopenia, lymphopenia, increased ALT, and hypertriglyceridemia. The most common grade 3/4 laboratory abnormalities (incidence ≥ 3%) were lymphopenia, hyperglycemia, anemia, decreased potassium, increased AST, increased ALT, and thrombocytopenia.

Fatal adverse reactions occurred more frequently in patients who received everolimus plus exemestane (2%) compared to patients on the placebo plus exemestane arm (0.4%). The rates of treatment-emergent adverse events resulting in permanent discontinuation were 24% and 5% for the everolimus plus exemestane and placebo plus exemestane treatment groups, respectively. Dose adjustments (interruptions or reductions) were more frequent among patients in the everolimus plus exemestane arm than in the placebo plus exemestane arm (63% versus 14%).

Forty percent of patients on the everolimus arm were ≥ 65 years of age and 15% were ≥ 75 years of age. The incidence of deaths due to any cause within 28 days of the last everolimus

dose was 6% in patients ≥ 65 years of age compared to 2% in patients < 65 years of age. Adverse reactions leading to permanent treatment discontinuation occurred in 33% of patients ≥ 65 years of age compared to 17% of patients < 65 years of age.

The safety data from the BOLERO 2 study are provided in the table below.

Table (b) (4) Adverse Reactions Reported ≥ 10% of Patients with Advanced HR+ BC

	AFINITOR (10 mg/day) + exemestane[a] N=482			Placebo + exemestane[a] N=238		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Any adverse reaction	**100**	**41**	**9**	**90**	**22**	**5**
Gastrointestinal disorders						
Stomatitis[b]	67	8	0	11	0.8	0
Diarrhea	33	2	0.2	18	0.8	0
Nausea	29	0.2	0.2	28	1	0
Vomiting	17	0.8	0.2	12	0.8	0
Constipation	14	0.4	0	13	0.4	0
Dry mouth	11	0	0	7	0	0
General disorders and administration site conditions						
Fatigue	36	4	0.4	27	1	0
Edema peripheral	19	1	0	6	0.4	0
Pyrexia	15	0.2	0	7	0.4	0
Asthenia	13	2	0.2	4	0	0
Infections and infestations						
Infections[c]	50	4	1	25	2	0
Investigations						
Weight decreased	25	1	0	6	0	0
Metabolism and nutrition disorders						
Decreased appetite	30	1	0	12	0.4	0
Hyperglycemia	14	5	0.4	2	0.4	0
Musculoskeletal and connective tissue disorders						

	AFINITOR (10 mg/day) + exemestane[a] N=482			Placebo + exemestane[a] N=238		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Arthralgia	20	0.8	0	17	0	0
Back pain	14	0.2	0	10	0.8	0
Pain in extremity	9	0.4	0	11	2	0
Nervous system disorders						
Dysgeusia	22	0.2	0	6	0	0
Headache	21	0.4	0	14	0	0
Psychiatric disorders						
Insomnia	13	0.2	0	8	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	24	0.6	0	12	0	0
Dyspnea	21	4	0.2	11	0.8	0.4
Epistaxis	17	0	0	1	0	0
Pneumonitis[d]	19	4	0.2	0.4	0	0
Skin and subcutaneous tissue disorders						
Rash	39	1	0	6	0	0
Pruritus	13	0.2	0	5	0	0
Alopecia	10	0	0	5	0	0
Vascular disorders						
Hot flush	6	0	0	14	0	0
Median Duration of Treatment[e]	**23.9 weeks**			**13.4 weeks**		

CTCAE Version 3.0

*160 patients (33.2%) were exposed to AFINITOR therapy for a period of ≥ 32 weeks)

[a] Exemestane (25 mg/day)

[b] Includes stomatitis, mouth ulceration, aphthous stomatitis, glossodynia, gingival pain, glossitis and lip ulceration

[c] Includes all preferred terms within the 'infections and infestations' system organ class, the most common being nasopharyngitis (10%), urinary tract infection (10%), upper respiratory tract infection (5%), pneumonia (4%), bronchitis (4%), cystitis (3%), sinusitis (3%), and also including candidiasis (<1%), and sepsis (<1% and hepatitis C (<1%).

[d] Includes pneumonitis, interstitial lung disease, lung infiltration, and pulmonary fibrosis

[e] Exposure to AFINITOR or placebo

8. Advisory Committee Meeting

There were no controversial issues identified by the review team that would have benefitted from an advisory committee discussion.

9. Pediatrics

No new pediatric or growth assessment data were provided with this sNDA. There is clinical experience with everolimus in pediatric patients, including a labeled indication for pediatric patients age ≥ 3 years old with tuberous sclerosis and subependymal giant cell astrocytoma who are not candidates for surgical intervention.

10. Other Relevant Regulatory Issues

The OSI inspected three of the highest accruing sites in the US. The inspectional findings revealed no significant deviations that would preclude the use of the clinical data provided in support of this NDA.

According to the Applicant, the study was conducted in full conformance with the principles of the Declaration of Helsinki or with the laws and regulations of the country where the research was conducted, whichever provided greater protection to the individual. The study adhered to the January 1997 ICH Guideline for Good Clinical Practice. Written informed consent was obtained from each participant in the study. The protocol and subsequent amendments were approved by local Independent Ethics Committees (IEC) or Institutional Review Boards (IRB).

There were no financial conflicts of interest identified by any investigator as defined in 21 CFR 54.2(a), (b), and (f).

11. Labeling

The following major labeling issues in clinical labeling were identified:

(b) (4)

(b) (4)

- The final PFS results by IRC and 2 interim analysis of OS are supportive of the primary endpoint and may be of importance to patients and clinicians; however, they are secondary endpoints. As a result, they should be included in the text of the package inser (b) (4)

(b) (4)

- New listings in the Warnings & Precautions and Geriatric Use were added to highlight the different safety profiles seen in the elderly advanced breast cancer population and to encourage closer monitoring of these patients.

12. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

We recommend that this NDA be approved for the following indication:

"AFINITOR® is indicated for the treatment of postmenopausal women with advanced hormone receptor-positive breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole."

- Risk Benefit Assessment

The current recommendation for full approval is based upon a statistically significant and clinically meaningful, 4.6 month improvement in median progression-free survival (PFS) observed in patients receiving everolimus compared to those receiving placebo [HR 0.45 (95% CI: 0.38, 0.54; p< 0.0001)]. The magnitude of PFS improvement is robust based on the consistency of the finding across relevant subgroups supported by patient demographics and tumor prognostic characteristics. As of the interim analysis with 46% of events, overall survival (OS) numerically favors the everolimus plus exemestane arm with a [HR=0.77 (95%

CI: 0.57, 1.04)]. Although the response rates were relatively low in both arms (13% versus 2%), they were higher in the everolimus arm.

The improvement in efficacy was associated with an increase in toxicity, manifested as a higher rate of serious adverse events, grade 3/4 adverse events, permanent treatment discontinuations, dose interruptions, dose reductions, and on-treatment deaths in the combination arm compared to endocrine monotherapy. There were no new toxicity signals in the BOLERO 2 trial. The adverse events associated with everolimus are consistent with the known safety profile of mTOR inhibitors found in the other approved advanced cancer populations. Patients over the age of 65 on the everolimus arm experienced higher rates of on-treatment mortality (6% versus 2%), serious adverse events (32% versus 23%), grade 3 and 4 adverse events (57% versus 45%), and permanent treatment discontinuations (33% versus 17%) compared to patients younger than 65. In spite of the difference in the everolimus toxicity profile seen in the elderly and compared to the younger population, the improvement of progression free survival remained consistent.

In conclusion, everolimus when added to exemestane in treatment of postmenopausal women with advanced hormone receptor-positive breast cancer after failure of treatment with letrozole or anastrozole, demonstrates a favorable risk-benefit profile.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  The clinical review team believes that a REMS is not required for this product for the requested indication. When administered in accordance with product labeling, it is anticipated that the risks of everolimus will be tolerable and manageable. There are no unusual risks which required training to assure safe use, given that this therapy is generally prescribed and administered only by healthcare professionals with specific training and experience in medical oncology and use of agents with similar toxicities.

- Recommendation for other Postmarketing Requirements and Commitments

Post-Marketing Commitments

The clinical team recommends the following Postmarketing Commitments (PMCs):

1. Submit a final report, including datasets, for the final overall survival results from trial CRAD001Y2301 (BOLERO-2)
   The timetable you submitted states that you will complete this plan according to the following schedule:

Final Protocol Submission:	12/2011
Trial Completion:	06/2014
Final Report Submission:	06/2015

   Rationale for PMC:
   Overall survival is a key secondary endpoint of the applicant's pivotal study. At the time of approval, the overall survival data were not mature, and longer follow-up is needed to determine whether there is a survival advantage of the use of everolimus in conjunction with exemestane as compared to placebo plus exemestane in advanced hormone receptor positive breast cancer.

2. Conduct a 3-arm randomized trial 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 timetable you submitted states that you will conduct this study according to the following schedule:

Final Protocol Submission:	11/2012
Trial Completion:	08/2016
Final Report Submission:	08/2017

   Rationale for PMC:
   The pivotal trial that led to the approval of everolimus in combination with exemestane for postmenopausal women with advanced hormone receptor positive breast cancer, did not address the contribution of exemestane to the treatment regimen. The everolimus monotherapy arm will address the contribution of exemestane to the treatment combination. The third treatment arm will compare the efficacy and safety of capecitabine monotherapy, a treatment regimen frequently used after progression on hormonal therapies, to the everolimus plus exemestane combination.

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/s/

PATRICIA CORTAZAR
07/19/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-334/S-016

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Supplement
Application Number(s)	022334
Priority or Standard	Standard
Submit Date(s)	November 3, 2011
Received Date(s)	November 4, 2011
Goal Date	September 2, 2012
Division / Office	CDER/OHOP/DOP1
Reviewer Name(s)	Tatiana Prowell, MD and Geoffrey Kim, MD
Review Completion	June 18, 2012
Established Name	Everolimus
Trade Name	Afinitor
Therapeutic Class	Kinase inhibitor
Applicant	Novartis
Formulation(s)	2.5 mg, 5 mg, 7.5 mg and 10 mg tablets
Dosing Regimen	10 mg once daily with or without food
Indication(s)	Metastatic breast cancer
Intended Population(s)	“postmenopausal women with advanced hormone receptor-positive breast cancer (advanced HR+ BC) in combination with exemestane

after failure of treatment with letrozole or anastrozole”

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical team recommends regular approval of the supplemental new drug application (sNDA) for everolimus 10 mg orally daily in combination with exemestane 25 mg orally daily for the following indication:

"AFINITOR® is indicated for the treatment of postmenopausal women with advanced hormone receptor-positive breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole"

The recommendation for approval is based upon the results of a randomized, double-blind, placebo-controlled trial (BOLERO 2), which compared everolimus 10 mg/day plus exemestane 25 mg/day to placebo plus exemestane 25 mg/day. This trial demonstrated a statistically significant improvement in progression-free survival (PFS) by investigator assessment with a 4.6 month absolute difference in median PFS [HR 0.45 (95% CI 0.38, 0.54)]. The analysis of median PFS by independent review committee (IRC) was consistent with the primary efficacy analysis [HR of 0.38 (95% CI 0.31, 0.48)], corresponding to a median improvement in PFS of 6.9 months. The improvement in efficacy was associated with an increase in toxicity, manifested as a higher rate of serious adverse events, grade 3/4 adverse events, permanent treatment discontinuations, dose interruptions, dose reductions, and on-treatment deaths in the combination arm compared to endocrine monotherapy. As of the interim analysis with 46% of events, overall survival (OS) numerically favors the everolimus plus exemestane arm with a [HR=0.77 (95% CI: 0.57, 1.04)]. suggesting that, despite the added toxicity of this combination, addition of everolimus to exemestane provides a net benefit to patients with advanced hormone receptor positive breast cancer.

1.2 Risk Benefit Assessment

The foundation of the sNDA submission was the Y2301 (BOLERO2) trial, a randomized controlled trial in 724 postmenopausal women with estrogen receptor-positive advanced breast cancer that had either recurred while on, or within 12 months of completion of, adjuvant letrozole or anastrozole or had progressed while on, or within 1 month of discontinuing, letrozole or anastrozole in the advanced setting. Subjects were randomly assigned in a 2:1 ratio to receive either everolimus 10 mg/day plus exemestane 25 mg/day (n=485) versus placebo plus exemestane 25 mg/day (n=239). The primary endpoint was PFS by investigator assessment.

This trial demonstrated a statistically significant improvement in median progression-free survival (PFS) with a HR of 0.43 at the interim analysis ($p<0.0001$) and a HR of 0.45 (95% CI 0.38, 0.54) at the final analysis of PFS. This translated, at the time of the final PFS analysis, into a 4.6 month absolute improvement in median PFS [7.8 months (95% CI 6.9, 8.5) versus 3.2 months (95% CI 2.8, 4.1)] for the everolimus plus exemestane arm versus the exemestane plus placebo arm, respectively. All secondary endpoint analyses were supportive of the primary endpoint findings. These included the final analysis of PFS by independent review committee (IRC), which similarly reported a HR for PFS of 0.38 (95% CI 0.31, 0.48), corresponding to an absolute median PFS difference of 6.9 months, as well as the interim analysis of overall survival (OS), in which a HR of 0.77 (one-sided $p=0.046$), favoring the combination, was observed. Although the response rates were relatively low in both arms (13% versus 2%), they were higher in the everolimus arm. Importantly in a population of hormone receptor-positive breast cancer patients, in whom much of an observed improvement in PFS may due to prolonged periods of stable disease, the clinical benefit rate (CBR) was approximately doubled by the addition of everolimus (51% versus 26%).

The improvement in efficacy was associated with a clinically significant increase in toxicity, manifested as a higher rate of grade 3/4 adverse events (50% versus 29%), treatment discontinuations (24% versus 5%), dose interruptions/reductions (64% versus 21%), and on-treatment deaths (4% versus 2%) in the combination arm compared to endocrine monotherapy. Despite an increase in the number of on-treatment deaths on the everolimus plus exemestane arm, there remains a trend for an improvement in overall survival (OS) with a HR of 0.77 (one-sided $p=0.046$) at the time of interim analysis with 46% of events, suggesting that, despite the added toxicity of this combination, a net benefit to the patients receiving the combination is present. The rates of toxicity of notable adverse events associated with the use of mTOR inhibitors are consistent with the known safety profile of everolimus in the other approved advanced cancer populations and no new notable toxicities were identified. Patients over the age of 65 on the everolimus arm did experience higher rates of on-treatment mortality (6% versus 2%), serious adverse events (32% versus 23%), grade 3 and 4 adverse events (57% versus 45%), and permanent treatment discontinuations (33% versus 17%) compared to patients younger than 65. There were no major differences seen in the toxicity profile of exemestane monotherapy in terms of age group. In spite of the difference in the toxicity profile seen in the elderly versus younger population in patients treated with everolimus, the improvement of progression free survival as compared to placebo remained consistent.

The review team considered the appropriateness of exemestane plus placebo as a control arm in view of the response rate of <2% in that arm. In U.S. clinical practice, exemestane or fulvestrant are commonly recommended to postmenopausal women with ER+ breast cancer after failure of a nonsteroidal aromatase inhibitor (NSAI). The 2012 NCCN guidelines state, "…postmenopausal women with hormone-responsive

breast cancer benefit from sequential use of endocrine therapies at the time of disease progression. Therefore women with breast cancers who respond to an endocrine maneuver with either shrinkage of the tumor or long-term disease stabilization (clinical benefit) should receive additional endocrine therapy at the time of disease progression." Chia and colleagues reported the results of a randomized, double-blind, placebo-controlled trial of fulvestrant versus exemestane in 693 postmenopausal women with ER-positive breast cancer after failure of a NSAI. (Chia et al. J Clin Oncol 2008; 26: 1664-1670). The investigators observed no difference between arms in terms of median time to progression (TTP), objective response rate (ORR), or clinical benefit rate (CBR). Of note, the median TTP of both the exemestane and the fulvestrant arms in the trial was 3.7 months, very similar to the median PFS of 3.2 months for the exemestane plus placebo arm in Study Y2301. Likewise, the CBR was 32% in both arms, again quite similar to the 26% CBR for the exemestane arm in Study Y2301. These results suggest that the control arm in Study Y2301 did not "underperform" relative to what one would predict and that, if endocrine therapy constitutes an appropriate control arm for the trial, either exemestane or fulvestrant monotherapy could have reasonably served as the comparator to everolimus plus exemestane.

The reviewers also considered whether a comparison to chemotherapy rather than endocrine therapy would have been a more appropriate in view of the toxicities of everolimus. As stated above, the current standard of care in the US for postmenopausal women with HR+ advanced breast cancer is to utilize sequential lines of endocrine therapy. Chemotherapy, most often using a single agent, is generally reserved for disease that is rapidly progressive, highly symptomatic, or resulting in visceral crisis, and for disease that has become refractory to available endocrine therapy. Despite the fact that most patients in Study Y2301 had visceral involvement at study entry, it is noteworthy that the majority of women in both arms of Study Y2301 in fact received another line of endocrine therapy as their first off-study treatment. Nonetheless, there is a substantial increase in toxicity associated with the addition of everolimus to exemestane. A postmarketing trial comparing the efficacy and safety of everolimus plus exemestane to single-agent chemotherapy is recommended to place in context the risks and benefits of this novel combination and to help clinicians and patients determine the most appropriate way to sequence it in the U.S. breast cancer armamentarium. A comparison of everolimus plus exemestane to single-agent chemotherapy may be of particular relevance for advanced breast cancer patients greater than 65 years of age, who appear to be at increased risk of everolimus-related toxicity.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No additional postmarketing risk evaluation and mitigation strategies are being recommended. Note that everolimus is already marketed at the same dose for other malignancies.

1.4 Recommendations for Postmarket Requirements and Commitments

The clinical team recommends the following Postmarketing Commitments (PMCs):

1) Submit a final report, including datasets, for the final overall survival results from trial CRAD001Y2301 (BOLERO-2).

Rationale:
Overall survival is a key secondary endpoint of the applicant's pivotal study. At the time of approval, the overall survival data were not mature, and longer follow-up is needed to determine whether there is a survival advantage of the use of everolimus in conjunction with exemestane as compared to placebo plus exemestane in advanced hormone receptor positive breast cancer.

2) Conduct a 3-arm randomized trial 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.

Rationale:
The pivotal trial that led to the approval of everolimus in combination with exemestane for postmenopausal women with advanced hormone receptor positive breast cancer, did not address the contribution of exemestane to the treatment regimen. The everolimus monotherapy arm will address the contribution of exemestane to the treatment combination. The third treatment arm will compare the efficacy and safety of capecitabine monotherapy, a treatment regimen frequently used after progression on hormonal therapies, to the everolimus plus exemestane combination.

2 Introduction and Regulatory Background

2.1 Product Information

Everolimus (IND 66, 279) is a rapamycin derivative and kinase inhibitor that inhibits mammalian target of rapamycin (mTOR) through allosteric binding to mTORC1. Everolimus entered clinical development for prophylaxis of organ transplant rejection in

1996 and has been marketed in the US since 04-20-2010 as Zortress, for prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a renal transplant.

Everolimus entered clinical development for oncologic indications in 2002 and received initial US approval in 2009 for treatment of advanced renal cell carcinoma. It is currently marketed in the US under the trade name of Afinitor at a dose of 10 mg by mouth once daily for the following indications:

- Treatment of advanced renal cell carcinoma after failure of sunitinib or sorafenib (03-30-2009)
- Treatment of subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) in patients who require therapeutic intervention but are not candidates for curative surgical resection (10-29-2010)
- Treatment of progressive neuroendocrine tumors of pancreatic origin (PNET) in patients with unresectable, locally advanced, or metastatic disease (05-05-2011)
- Treatment of renal angiomyolipomas not requiring immediate surgery in patients with tuberous sclerosis complex (04-26-2012)

2.2 Tables of Currently Available Treatments for Proposed Indications

Available Therapy for All Patients with Advanced Breast Cancer	
Paclitaxel§	Docetaxel†
Cyclosphosphamide, methotrexate, fluorouracil (CMF)	Capecitabine†
(b) (4)	Ixabepilone
Gemcitabine§	Eribulin
Hormone Receptor Positive Subset Only	
Tamoxifen	Anastrozole or Letrozole
Exemestane	Fulvestrant
Toremifene	

†§Note: Cytotoxics for metastatic breast cancer are most often used as sequential monotherapy rather than combination therapy. The symbol indicates agents that may be used as FDA-approved combinations for treatment of advanced breast cancer.

Note that other cytotoxics are available for treatment of metastatic breast cancer such as mitomycin and vinblastine and have indeed served as control arms in previous

registration trials; these agents have been omitted from the table due to the rarity of their use in the United States.

2.3 Availability of Proposed Active Ingredient in the United States

The product under the trade name Afinitor is currently marketed in the United States for four FDA-approved oncologic indications, and the active ingredient is therefore available.

More than 8,000 patients have been treated with everolimus in oncology clinical trials and 3 healthy volunteer studies. The largest completed phase 3 trial, other than the trial under consideration in this sNDA, is C2240, a randomized, double-blind trial comparing RAD-001 versus placebo in 411 patients with metastatic renal cell carcinoma who had progressed on a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF TKI). The most common adverse reactions, observed in $\geq$ 10% of participants, included stomatitis, rash, fatigue, asthenia, diarrhea, anorexia, nausea, mucosal inflammation, vomiting, cough, peripheral edema, infections, dry skin, epistaxis, pruritus, and dyspnea. The most common grade 3-4 adverse reactions, reported in $\geq$ 2%, were infections, stomatitis, fatigue, and pneumonitis.

2.4 Important Safety Issues with Consideration to Related Drugs

Other approved mTOR inhibitors include sirolimus and temsirolimus. Known associated risks associated with these agents include: infections, pneumonitis, stomatitis, renal failure, hyperglycemia, and fatigue. Other notable risks include: thrombosis, bleeding, rash, and hypersensitivity reactions.

See Section 7.3 for a detailed discussion of the safety of everolimus in combination with exemestane in the proposed patient population.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

There was no End of Phase II meeting (EOP2) held with the FDA nor any special protocol assessment requested for Study Y2301 (BOLERO 2) supporting the current sNDA submission.

The protocol for Study Y2301 was submitted to the IND on 03-25-2009 (SN 806). Amendment 1 to the protocol was submitted to the IND on 02-17-2010 (SN 1046). This amendment, which became effective on 02-17-2010 prior to any unblinding of efficacy data, changed the primary endpoint from PFS by independent central radiographic review to PFS by investigator assessment. Per the Sponsor, the change in primary endpoint was made due to concerns for the high level of informative censoring that may

be present in the independent radiographic review. The statistical analysis plan was submitted to the IND on 03-31-2011 (SN 1269).

A Type B pre-sNDA meeting was requested by Novartis on 07-19-2011 and held on 10-11-2011 to discuss the current sNDA for treatment of patients with advanced hormone receptor-positive breast cancer. In this meeting, FDA recommended that Novartis submit the sNDA with the final PFS analysis, not the interim PFS analysis as proposed. In addition, FDA recommended that the statistical analysis plan be revised to include an interim analysis of OS at the time of the final analysis of PFS. The Sponsor provided compelling clinical and statistical arguments in favor of their strategy to base submission upon the interim PFS analysis. The Agency stated that sNDA submission based upon the interim analysis of PFS and first interim analysis of OS by a Data Monitoring Committee (DMC), with a PFS update at 85% of events and second interim analysis of OS by the DMC submitted during the review cycle, would not result in a refusal to file. Note that the sponsor's decision to submit the sNDA based upon the interim analysis of PFS did, in part, inform our decision to grant the application a standard review rather than a priority review.

The sNDA was submitted on 11-04-2011 and assigned a standard review with a PDUFA goal date of 09-02-2012.

2.6 Other Relevant Background Information

(b) (4)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The sNDA submission was generally well-organized and complete. All of the datasets required for efficacy and safety analyses were navigable and functional. Requests for additional information from the Sponsor throughout the review process were addressed in a timely fashion.

3.2 Compliance with Good Clinical Practices

Novartis affirms that the trial was conducted in full compliance with Good Clinical Practices. The study protocol and amendments were reviewed by an Institutional Review Board or Independent Ethics Committee. Novartis has provided certification that it did not use in any capacity the services of any debarred individuals in the conduct of trial Y2301. All subjects were to provide written informed consent prior to study enrollment.

The number of major protocol deviations was low overall (1.5% of subjects) and similar between arms (0.8% exemestane arm, 1.9% exemestane + everolimus arm). The nature and distribution of the protocol violations is such that the efficacy outcomes are unlikely to have been significantly affected. The details of major protocol deviations are shown in Table 1 below, provided by the Sponsor.

Table 1: Protocol Deviations, Y2301 Full Analysis Set

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
Source: Table 14.1-1.3

An Office of Scientific Investigations (OSI) audit was requested for this supplemental NDA due to the following concern:

- There is a large difference in the censoring pattern between investigator and independent central review of the radiographic findings. Many patients were discontinued from study treatment for clinical progression without documented radiographic progression. It is necessary to determine whether the findings noted by the investigator and what is documented on the case report forms are consistent.

The sites selected for inspection reflect those having enrolled the greatest number of subjects. These sites are shown in Table 2 below.

Table 2: Sites Selected for Inspection

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site 545 PI: Dr. Denise Yardley Sarah Cannon Research Institute 250 25th Avenue North, Suite 110 Nashville, TN 37203 P: 615-329-7274	RAD001Y2301	12	HR+ breast cancer
Site 540 PI: Dr. Mikhail Shtivelband Ironwood Cancer and Research Centers 695 South Dobson Road Chandler, AZ 85224	RAD001Y2301	11	HR+ breast cancer
Site 534 PI: Dr. Thaddeus Beck Highlands Oncology Group 3232 N. North Hills Blvd. Fayetteville, AR 72703 P: 479-587-1700	RAD001Y2301	14	HR+ breast cancer

There were no significant data integrity issues identified. The summary results of the inspection by Robert Young and Janice Pohlman from OSI were communicated to the review team on May 25, 2012 as follows: "The clinical data from the inspected sites appear reliable based on available information and may be used in assessment of the pending application."

3.3 Financial Disclosures

Disclosure of financial arrangements were requested from all clinical investigators who participated in Y2301. Overall, 99.5% (604 out of 607) of clinical investigators from US

sites and 99.8% (812 out of 814) of non-US clinical investigators responded to repeated inquiries.

A total of 5 investigators had financial disclosures to report. One reported having received (b) (6) from Novartis (undisclosed amount), one reported having received > $25,000 for (b) (6); one reported holding >$50,000 in stock; one reported having (b) (6) (undisclosed amount); and one reported having received > $25,000 in (b) (6) These individuals were at 5 different clinical sites.

Given the large number of clinical investigators (N=1,421) who participated in the Y2301 trial, the potential bias resulting from patients enrolled by these 5 investigators (0.35%) who disclosed financial interests is unlikely to have substantially altered the findings of the trial.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

No new chemistry manufacturing and controls (CMC), clinical microbiology, or preclinical pharmacology/toxicology (PT) data were submitted in support of this sNDA.

4.1 Chemistry Manufacturing and Controls

No new Chemistry Manufacturing and Controls (CMC) data were submitted for review.

4.2 Clinical Microbiology

No new Clinical Microbiology data were submitted for review.

4.3 Preclinical Pharmacology/Toxicology

No new Preclinical Pharmcology/Toxicology data were submitted for review.

4.4 Clinical Pharmacology

The information in Section 4.4.3 is taken from the Clinical Pharmacology review authored by Jingyu Yu, Elimika Pfuma, Christine Garnett, and Qi Liu.

4.4.1 Mechanism of Action

Everolimus is an inhibitor of the human kinase mammalian target of rapamycin (mTOR). The exact mechanism by which mTOR inhibitors mediate their anti-cancer activity remains unclear. In normal cells, mTORC1 is a key sensor of nutritional status and regulates protein and lipid synthesis accordingly (reviewed by Laplante and Sabbatini 2012). In addition, mTORC1 negatively regulates autophagy and promotes cell proliferation and survival in response to various cellular growth factors. Inhibition of mTORC1 by rapamycin and rapamycin analogues thereby inhibits protein synthesis and cellular proliferation and may promote autophagy. The net result of these cellular processes is the inhibition of tumor growth without apoptosis or direct cytotoxicity. Instead, the tumor may remain senescent in the presence of constitutive mTOR inhibition. This may explain why there is an improvement of progression free survival seen in the RCC and PNET trials in the absence of robust objective response rates (2.2% and 4.8% respectively). In the advanced breast cancer population, there was a relatively higher response rate of 13% seen which may be due to the addition of exemestane and is supported by non-clinical studies which suggest that there may be a synergistic effect of using the 2 agents together.

4.4.3 Pharmacokinetics

In Study Y2301, patients were randomized to receive everolimus (10 mg/day) plus exemestane (25 mg/day) or placebo plus exemestane (25 mg/day). There was a 45 – 64% mean increase in exemestane exposure when given in combination with everolimus. It is unclear if this mean increase in exemestane exposure has an effect on efficacy or safety in the combination arm. The exemestane exposure-response relationship for efficacy and safety could not be established due to limited PK data (10% of patients). The estradiol levels at steady state (4 weeks) were similar between the two treatment arms; however, estradiol levels may not be directly related to PFS.

The sponsor proposed labeling language stating that no increase in adverse events related to exemestane were observed in patients receiving the combination. The clinical safety reviewer agreed that the sponsor's statement was acceptable.

In the combination arm, on-treatment deaths in elderly patients ($\geq$ 65 yrs) were higher than younger patients (< 65 yrs). Based on the original NDA review of everolimus, age, weight, gender and renal function have no effect on PK. It is known that hepatic impairment and co-administration of CYP3A4 inhibitors increase everolimus exposure; however, the elderly patients who died on-treatment in Study Y2301 had normal baseline bilirubin and serum albumin levels, and only one of these patients had a strong CYP3A4 inhibitor as a concomitant medication. Therefore, the clinical pharmacology team could not conclude that the higher on-treatment deaths in elderly patients were due to higher exposures.

5 Sources of Clinical Data

The primary assessment of the efficacy and safety of everolimus in combination with exemestane is derived from the original submission, safety update, and final PFS analysis of the Y2301 (BOLERO 2) trial. Y2301 was a randomized, multinational, double blind trial that enrolled 724 postmenopausal women with advanced breast cancer who had previously received a non-steroidal aromatase inhibitor. After stratification by documented sensitivity to prior endocrine therapy (yes, no) and presence of visceral disease (yes, no), subjects were randomly assigned in a 2:1 allocation to receive either exemestane 25 mg po daily plus everolimus 10 mg po daily (investigational arm) or exemestane 25 mg po daily plus oral placebo (control arm) until disease progression or unacceptable toxicity.

5.1 Tables of Studies/Clinical Trials

A single clinical trial, Study Y2301, was submitted in support of this sNDA. The summary of the design of this trial are shown in Table 3, modified from Sponsor's Table 4-1 from the Clinical Study Report, below.

Table 3: Summary of Design of Study Y2301

Study No.	Design	Population	Patients and treatments	Treatment duration	Endpoints
[Y2301] 196 centers 24 countries	Multicenter, double-blind, randomized (2:1), parallel-group, Phase III Efficacy and safety	Postmenopausal women with ER+, HER2/neu non-amplified advanced/ metastatic breast cancer who relapsed or progressed on letrozole or anastrozole	Everolimus 10 mg/day plus exemestane 25 mg/day (n=485) Placebo plus exemestane 25 mg/day (n=239)	Until disease progression, unacceptable toxicity, or withdrawal of consent	Primary: PFS Key secondary: OS Other secondary: ORR, time to response, duration of response, CBR, QoL Exploratory: bone turnover markers

CBR Clinical benefit rate; ER+ Estrogen-receptor-positive; HER2 Human epidermal growth factor receptor 2; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; QoL Quality of life

5.2 Review Strategy

The clinical review was conducted jointly by Drs. Tatiana Prowell and Geoffrey Kim and compiled into a single review document. Study Y2301 formed the basis of both the efficacy and safety review of everolimus in combination with exemestane for treatment of advanced breast cancer. The Sponsor's electronic submissions, including the original Clinical Study Report (CSR), Safety Update, and updated analyses of PFS and OS, were reviewed. The principal review activities for this sNDA included:

- Review of the original electronic submission of the sNDA, including the Sponsor's CSR;
- Review of electronic submissions from the Sponsor in response to clinical and biostatistical queries;
- Review of Sponsor presentation slides to FDA 01/05/2012;
- Review of additional efficacy submissions including an unplanned PFS update requested by FDA, the 2nd interim analysis of overall survival (OS), and the final analysis of PFS;
- Reproduction/auditing of key efficacy and safety analyses with JMP using raw and derived datasets provided by the applicant;
- Performance of sensitivity analyses and exploratory subgroup analyses;
- Review of relevant case report forms and patient narratives;
- Consultation with other disciplines, including Biostatistics and Clinical Pharmacology

It is of note that everolimus has been approved and marketed in the United States for other oncology indications since 2009 and generally has a well-established safety profile, though not when given in combination with exemestane and not when used in an advanced breast cancer patient population. There is one randomized study submitted to this sNDA using this combination (Study Y2301). Thus, study Y2301 served as the primary source of data for the efficacy and safety review of this sNDA. Details of the trial design, demographics, etc. for Study Y2301 may be found in Section 6.1.

No new chemistry manufacturing and controls (CMC), clinical microbiology, or preclinical pharmacology/toxicity (PT) data were included in the sNDA submission.

5.3 Discussion of Individual Studies/Clinical Trials

Given that a single clinical trial, Study Y2301, was submitted to support this sNDA in advanced breast cancer, this trial will be discussed in detail in Section 6 below.

A phase II open-label, randomized trial of tamoxifen or without everolimus (TAMRAD) has previously been conducted, although the data were not submitted to the sNDA. This trial enrolled 111 postmenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer who had previously received an aromatase inhibitor and randomized them to tamoxifen 20 mg po daily with or without everolimus 10 mg po daily. Patients were stratified by primary hormone resistance (defined as relapsing during or ≤ 6 months after stopping adjuvant AI or progressing within 6 months of starting AI for advanced disease) and secondary hormone resistance (defined as relapsing > 6 months after stopping adjuvant AI or responding for ≥ 6 months to AIs in the metastatic setting). The primary endpoint was clinical benefit rate (CBR), defined as

the percentage of all patients with complete or partial response or stable disease at 6 months. In the intent to treat (ITT) population, the CBR was 61% in the combination arm (95% CI 47-77%) compared with 42% (95% CI 29-56%) for tamoxifen alone. Time to progression favored the everolimus plus tamoxifen arm with a HR of 0.54 (95% CI 0.36-0.81), corresponding to a 4.1 month prolongation of median TTP from 4.5 to 8.6 months. An analysis of OS similarly favored the everolimus plus tamoxifen arm with a HR of 0.45 (95% CI 0.24-0.81). In exploratory subgroup analyses, patients with secondary hormone resistance appeared to benefit to a greater degree from the addition of everolimus to tamoxifen than patients with primary hormone resistance. The most prominent toxicities of the combination were fatigue, stomatitis, rash, anorexia, and diarrhea.

Two small trials combining everolimus with another aromatase inhibitor, letrozole, have also been completed and were submitted to the original everolimus NDA in renal cell cancer, but have not been submitted to the current everolimus sNDA. These included Study C2108, an open-label phase 1 dose-escalation trial that included 18 post-menopausal women with advanced breast cancer, and Study C222, a randomized phase 2 trial in 270 post-menopausal women with ER+ early breast cancer who received up to 16 weeks of everolimus in combination with letrozole in the neoadjuvant setting. Due to the differences in the treatment regimens and patient populations or limited sample sizes, these trials are of limited relevance for the current sNDA review and will not be discussed further.

6 Review of Efficacy

Efficacy Summary

The single phase 3 trial supporting this sNDA was Y2301 (BOLERO 2). This was a randomized, double-blind multi-national trial with an add-on design that enrolled 724 postmenopausal women with advanced breast cancer who had progressed on a non-steroidal aromatase inhibitor. After stratification by documented sensitivity to prior endocrine therapy (yes, no) and presence of visceral disease (yes, no), subjects were randomly assigned in a 2:1 allocation to receive either exemestane 25 mg po daily plus everolimus 10 mg po daily (investigational arm) or exemestane 25 mg po daily plus oral placebo (control arm). Treatment was to continue until disease progression or unacceptable treatment-related toxicity.

The primary endpoint of the trial was progression-free survival by investigator assessment [(PFS), defined as the interval from date of randomization to date of disease progression or death from any cause, whichever occurred first]. Key secondary endpoints included PFS by independent radiographic review; overall survival [(OS), defined as the interval from date of randomization to date of subject's death from any cause]; and objective response rate [(ORR), the proportion of subjects in the evaluable

population, defined as all randomized subjects who received at least one dose of study drug and who had at least one post-baseline tumor assessment, who achieved a complete or partial response by RECIST v. 1.1 criteria].

Radiographic assessments were scheduled to occur every 6 weeks throughout trial participation. Subjects who discontinued study treatment prior to disease progression were to continue to undergo radiographic assessments every 6 weeks until disease progression.

Patients randomized to the control arm were not permitted to cross over to receive everolimus at the time of disease progression, even if the study was stopped at the time of the interim analysis for crossing the pre-specified efficacy boundary.

6.1 Indication

Breast Cancer: The sponsor's proposed indication is: Afinitor is indicated for treatment of postmenopausa (b) (4) Please see Section 9.2 for a discussion of the reviewers' modifications to the proposed indication.

6.1.1 Methods

Study Title: 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

Protocol Number: CRAD001Y2301

6.1.1.1 Study Objectives:

Primary Objective:

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

Key Secondary Objective:

- To compare overall survival (OS) between the two treatment arms

Other Secondary Objectives:

- To summarize time to response and duration of response in the two treatment arms

- To characterize a subgroup of patients the pharmacokinetics (PK) of everolimus when administered in combination with exemestane
- To compare the two treatment arms with respect to pre-dose concentration (C_{min}) and concentration at 2 hours post-dose (C_{2h}) of exemestane and to compare in a subgroup of patients the two treatment arms with respect to estradiol (E_2) changes from baseline.
- To evaluate the treatment arms with respect to:
    - Overall response rate (ORR)
    - Time to deterioration of ECOG performance status (ECOG PS)
    - Safety
    - Change in quality-of-life (QoL) scores over time
    - Clinical benefit rate (CBR)

Landmark events in the conduct of Study Y2301 are shown in Table 4 below.

Table 4: Landmark Events in Study Y2301

Date	Landmark events
June 3, 2009	First subject randomized
February 17, 2010	Amendment 1: major changes included a change in the primary endpoint from PFS by independent review committee to PFS by investigator assessment; exclusion of patients with CNS metastases; and inclusion of guidelines for management of various adverse events including hyperglycemia and reactivation of viral hepatitis
February 11, 2011	Data cutoff date for PFS interim analysis
July 8, 2011	Data cutoff date for 45-day safety and efficacy update
October 31, 2011	Data cutoff date for 2nd OS interim analysis
November 3, 2011	Original sNDA submission
December 14, 2011	Amendment 2: major changes included addition of a third interim OS analysis to take place after approximately 275 deaths (70% of total targeted)
December 15, 2011	Data cutoff date for final PFS analysis
December 21, 2011	45-day safety and efficacy update submitted (87% PFS events by investigator; 35% OS events)

Date	Landmark events
December 22, 2011	2nd OS interim analysis submitted (PFS events N/A; 46% OS events)
March 21, 2012	Final PFS analysis submitted (OS events N/A; 97% PFS events)
June 2014	Final OS analysis to be conducted
June 2015	Final OS results and datasets to be submitted to FDA

6.1.1.2 Study Endpoints

Primary Endpoint:

The primary endpoint of the study was progression-free survival (PFS), defined as time from date of randomization to date of the first documented progression or death due to any cause, whichever occurred first, as assessed by local investigator.

Subjects who were progression-free at the time of the data cutoff for analysis were to be censored for PFS at the date of the last adequate tumor assessment. PFS was also censored at the last adequate tumor assessment if an event occurred after a new anti-cancer therapy had been started or if an event occurred after 2 or more consecutive missing tumor assessments. Discontinuation of study treatment for any reason was not treated as a reason for censoring.

Secondary Endpoints:

Key secondary efficacy endpoints, per the amended protocol, included:

- Overall survival (OS), defined as time from date of randomization to date of death due to any cause. Patients who were not known to have died were censored at the last date of contact. OS was to be tested in a hierarchical fashion, only if the primary endpoint had been met, in order to control the overall type I error rate.
- Progression-free survival (PFS), as defined above, by independent central radiographic review. Subjects who were progression-free at the time of the data cutoff for analysis were to be censored for PFS at the date of the last adequate tumor assessment.

6.1.1.3 Study Design

Y2301 was a randomized, double-blind, placebo-controlled, multinational phase 3 trial comparing treatment with exemestane with or without the addition of everolimus. The trial enrolled 724 postmenopausal women with advanced hormone receptor-positive breast cancer who had progressed on either anastrozole or letrozole. The trial was conducted at 196 centers in 24 countries worldwide. The US sites contributed 31% of the total trial population.

Subjects were stratified by:

- presence of visceral disease (yes, no)

and

- documented sensitivity to prior hormonal therapy (yes, no), with hormonal sensitivity defined as either:
    - documented clinical benefit to at least one prior hormonal therapy in the advanced setting *or*
    - at least 24 months of adjuvant hormonal therapy prior to recurrence;

Following stratification, subjects were randomized in a 2:1 allocation to one of two treatment arms:

- Exemestane 25 mg po daily plus everolimus 10 mg po daily (n=485)
- Exemestane 25 mg po daily plus oral placebo (n=239)

Patients were to continue treatment until disease progression, unacceptable treatment-related toxicity, or study withdrawal.

Tumor assessments were performed every 6 weeks until disease progression. Patients who discontinued both study drugs for reasons other than progression were to continue to follow the scheduled tumor assessments every 6 weeks until disease progression. All patients were followed for safety for 28 days after discontinuation of study drug, and all patients were to be contacted for survival data every 90 days until 392 events had been observed.

Table 5: Study Calendar

				Week								
	Screening / Baseline	Day 1	Day 15	4	6	12	18	24	Every 6 wk	EOT	Follow-up[25]	Survival[20]
Visit number	1	2	3	4	5	6	7	8	9, 10 etc…		EOT + 28 d / SEC	
Treatment days	-21 to -1	1	15	28	42	84	126	168				
Demography/informed consent	X											
Inclusion/exclusion criteria	X											
IVRS/IWRS	X[1]	X[1]								X[1]		
Relevant medical history/current medical conditions	X											
Diagnosis and extent of cancer	X											
Prior/post antineoplastic therapy	X										X	
HIV history	X											
Vital signs	X	X	X	X	X	X	X	X	X	X		
Height	X											
Weight	X	X	X	X	X	X	X	X	X	X		
Physical examination	X	X	X	X	X	X	X	X	X	X		
ECOG performance status	X	X			X	X	X	X	X		X[26]	
ECG[2]	X											
Pulmonary function tests (PFTs)[3]	As clinically indicated											
Hematology[4]	X	X	X	X	X	X	X	X	X	X		
Coagulation	X	As clinically indicated										
Biochemistry[5]	X	X	X	X	X	X	X	X	X	X		
Serum lipid profile[6]	X				X	X	X	X	X	X		
Urinalysis[7]	X											
Prior/concomitant medications	X	Continuous during the study, up to 28 days after the last treatment										
Adverse events	X	Continuous during the study, up to 28 days after the last treatment										
Tumor evaluation												
CT or MRI for chest, abdomen, pelvis[8]	X				X	X	X	X	X	X[9]	X[10] / X[10]	

				Week								
	Screening / Baseline	Day 1	Day 15	4	6	12	18	24	Every 6 wk	EOT	Follow-up[25]	Survival[20]
Visit number	1	2	3	4	5	6	7	8	9, 10 etc…		EOT + 28 d / SEC	
Treatment days	-21 to -1	1	15	28	42	84	126	168				
CT or MRI for brain[11]	X											
Bone scan or skeletal survey[12]	X											
Bone X-Ray, CT or MRI[12]	X				X	X	X	X	X	X[9]	X[10] / X[10]	
PK blood sampling[13]	X[14]			X								
Blood samples for plasma and serum soluble biomarkers[15]	X		X[15]	X[15]		X				X		
Blood samples for biomarkers of bone resorption and formation[16]	X				X	X						
Collection of archival tumor block/slides[17]	X											
Blood samples for DNA extraction[18]	X											
EORTC QLQ-C30 (module BR-23)[19]		X			X	X	X	X	X		X[19]	
Follow up survival contact												X[20]
HBV-DNA, HBsAg, HBs Ab, HBc Ab, HCV-RNA-PCR[21] (D)	X											
HBV-DNA, HCV-RNA-PCR		X		X[23]	X[22]	X[22]	X[22]	X[22]	X[22]	X	X	

EOT: End of treatment; SEC: Study Evaluation Completion; EORTC; European Organisation for Research and Treatment of Cancer
All attempts were to be made to complete the visits within 48 hours of the day indicated on the evaluation schedule. Visit 2 was required to be conducted **no more than** 21 days after the screening visit and 28 days for patient positive for hepatitis B and C.
[1] Treatment was to start no more than 7 days after randomization.
[2] Baseline electrocardiogram (ECG) was performed within 14 days of the first dose for patients enrolled and could be repeated at the investigator's discretion if clinically indicated.
[3] Pulmonary function tests (PFTs) could be performed at screening or Treatment Day 1 (prior to administration of the study drug) and during the trial if clinically indicated and if warranted to exclude or manage non-infection pneumonitis (Appendix 16.1.1 - Protocol Table 6-4).
[4] Information on the hematology tests performed is found in Appendix 16.1.1 - Protocol Table 7-1.
[5] Information on the serum chemistry tests performed is found in Appendix 16.1.1 - Protocol Table 7-1.
[6] Serum fasting lipid profile included total cholesterol and triglycerides. Patients were to be in fasting state.
[7] Standard urinalysis dipstick assessments included those described in Appendix 16.1.1 - Protocol Table 7-1. This could be repeated and be supplemented with laboratory quantification of any potentially relevant abnormalities after baseline as per investigator's discretion if clinically indicated.
[8] Chest, abdomen, pelvis scans were repeated at each tumor assessment visit (including if negative at baseline). Scans for complete and partial responses were

repeated at least at 4 weeks but no later than the next scheduled tumor assessment following the first documented response.
[9] Except in case of discontinuation from treatment due to progression, tumor assessment at EOT was not necessary if the previous evaluation was done within 6 weeks of EOT.
[10] Patients were followed with tumor assessments every six weeks until disease progression. During this follow-up period, the site was to continue sending radiological scans for central review. Additional tumor assessments performed prior to starting further anticancer therapy were also to be sent within 2 weeks for central review.
[11] Brain scan (CT scan or MRI with intravenous contrast) was performed if CNS symptoms were present.
[12] A bone scan or skeletal survey was to be performed at baseline only (within 6 weeks before randomization). Positive areas on bone scans were assessed by X-ray, CT scan with bone windows or MRI, prior to randomization and were to continue to be assessed using the same modality (X-ray, CT scan with bone windows or MRI) every 6 weeks until disease progression and new anticancer therapy is started. Additional tumor assessments performed prior to starting new anticancer therapy were also sent within 2 weeks for central review. Additional bone scans or skeletal surveys were to be performed if clinically indicated.
[13] Blood samples for everolimus and exemestane levels were collected **pre-dose and 2 hours post dose** on Visit 4 (Week 4); Blood levels were to be analyzed for the first 60 patients with evaluable PK samples.
[14] A blood sample for estrogen (E_2) was to be collected at screening or Day 1 before study treatment and at Week 4 (Visit 4).
[15] Plasma samples were collected at screening, at pre-dose of Visit 4, Visit 6, and EOT. Serum samples were collected at screening, at pre-dose of Visit 3 (Day 15), Visit 6 and EOT.
[16] Biomarkers of bone turnover were collected at screening/baseline, Week 6 and Week 12There can be an important circadian rhythm variation of these markers, samples were thus optimally to be collected fasting in the morning and specimen collection was to be consistent during study visits.
[17] The most recent biopsy was to be provided.
[18] One 4 ml blood sample for DNA extraction was collected at baseline from all patients.
[19] Quality-of-life (QoL) questionnaire (EORTC QLQ C30 BR23) was administered at screening/baseline or Day 1, before or within 7 days prior to first study treatment. It was completed at Week 6, 12, 18, and 24 as well as every 6 weeks thereafter until progression.
[20] After progression, patients continued to be followed for survival every three months until 392 events were observed (expected to be 50.5 months from date of randomization of the first patient).
[21] It was highly recommended that patients with positive HBV-DNA or HBsAg were to be treated prophylactically with an antiviral for 1-2 weeks prior to receiving study drug (Appendix 16.1.1 - Protocol Section 6.7.3). Antiviral treatment was to continue throughout the entire study period and for at least 4 weeks after the last dose of study drug.
[22] Patient positive for HBV-DNA or/and HBsAg should have HBV-DNA monitored every 6 weeks, at end of treatment, and until EOT+28 days (Appendix 16.1.1 - Protocol Table 6-1). Patients with positive HCV-RNA PCR or a history of past infection, even if treated and considered 'cured' should have HCV-RNA monitored every 6 weeks, at end of treatment and until EOT+28 days.
[23] Patient positive for HBs Ab or/and HBc Ab should have HBV-DNA monitored every 4 weeks, at end of treatment and until EOT+28 days (Appendix 16.1.1 - Protocol Table 6-1).
[24] ECOG PS was to be assessed every six weeks until progression.
[25] Follow-up visits conducted between the EOT+28 days visit; the SEC visit were numbered 502, 503, 504, etc.

6.1.1.4 Study Eligibility Criteria

Postmenopausal women with estrogen receptor-positive (ER+) metastatic, or locally advanced if not amenable to curative surgery/radiotherapy, breast cancer whose disease was refractory to non-steroidal aromatase inhibitors (NSAI) and who had had a documented recurrence or progression on last therapy for breast cancer prior to randomization were eligible for the trial. Refractory disease to NSAI was 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 one month of the end of, letrozole or anastrozole for locally advanced or metastatic breast cancer.

There were no restrictions regarding the category of the last anticancer treatment prior to randomization. Any prior use of exemestane or mTOR inhibitors was prohibited. Patients were permitted to have received neo/adjuvant chemotherapy and any number of prior lines of endocrine therapy and were allowed 0-1 prior lines of chemotherapy for advanced disease. Concurrent bisphosphonate use was permitted for management of bone metastases, as was local radiotherapy for pain control or for lytic lesions at acute risk of fracture.

Complete inclusion and exclusion criteria are shown below.

Inclusion Criteria:

- Adult women (≥ 18 years of age) 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. Postmenopausal status is defined either by:
  - Age ≥ 55 years and ≥ 1 year of amenorrhea
  - Age < 55 years and ≥ 1 year of amenorrhea, with an estradiol assay < 20 pg/mL
  - Surgical menopause with bilateral oophorectomy

- 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 randomization

- 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 and coagulation function as shown by:
  - Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
  - Platelets ≥ 100×10^9/L
  - Hemoglobin (Hgb) ≥ 9.0 g/dL
  - International normalized ratio (INR) ≤ 2

- Adequate liver function as shown by:
  - Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × the upper limit of normal (ULN) (or ≤ 5 × ULN if hepatic metastases were present)
  - Total serum bilirubin ≤ 1.5 × ULN (≤ 3 × ULN for patients known to have Gilbert Syndrome)

- Adequate renal function as shown by:

- Serum creatinine ≤ 1.5 × ULN

- Fasting serum cholesterol ≤ 300 mg/dL or 7.75 mmol/L and fasting triglycerides ≤ 2.5 × ULN. In case one or both of these thresholds were exceeded, the patient could only be included after initiation of statin therapy and when the aforementioned values were achieved.

- ECOG performance status ≤ 2

- Written informed consent obtained before any trial-related activity and according to local guidelines

Exclusion Criteria:

- HER2-overexpressing patients by local laboratory testing [immunohistochemistry (IHC) 3+ staining or in situ hybridization positive]

- Patients with only non-measurable lesions other than bone metastasis (e.g., pleural effusion, ascites, etc)

- Patients who received ≥ 1 line of chemotherapy for advanced breast cancer

- Previous treatment with exemestane or mTOR inhibitors

- Known hypersensitivity to mTOR inhibitors, e.g., sirolimus (rapamycin)

- Another malignancy within 5 years prior to randomization, with the exception of adequately treated in-situ carcinoma of the cervix uteri, basal or squamous cell carcinoma, or non-melanomatous skin cancer

- Radiotherapy within 4 weeks prior to randomization except in case of localized radiotherapy for analgesic purposes or for lytic lesions at risk of fracture which could then be completed within 2 weeks prior to randomization. Patients must have recovered from radiotherapy toxicities prior to randomization.

- Currently receiving hormone replacement therapy, unless discontinued prior to randomization

- History of brain or other central nervous system (CNS) metastases

- Patients receiving concomitant immunosuppressive agents or chronic corticosteroid usage at the time of study entry except in the following cases:

  - Topical applications (e.g., rash), inhaled sprays (e.g., obstructive airways diseases), eye drops, or local injections (e.g., intra-articular) were allowed
  - Patients on stable, low doses of corticosteroids for ≥ 2 weeks before randomization were also allowed

- Bilateral diffuse lymphangitic carcinomatosis

- Patients with a known history of human immunodeficiency virus (HIV) seropositivity. Screening for HIV infection at baseline was not required.

- Active bleeding diathesis, or on oral anti-vitamin K medication (except low-dose warfarin, low molecular weight heparin (LMWH), and acetylsalicylic acid or equivalent, as long as INR was ≤ 2.0)

- Any severe and/or uncontrolled medical conditions such as:

  - Unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤ 6 months prior to enrollment, serious uncontrolled cardiac arrhythmia
  - Uncontrolled diabetes as defined by fasting serum glucose > 1.5 × ULN
  - Acute and chronic, active infectious disorders (except for hepatitis B- [HBV] and hepatitis C [HCV]-positive patients) and non-malignant medical illnesses that are uncontrolled or whose control may be jeopardized by the complications of this study therapy
  - Impairment of gastrointestinal function or who have gastrointestinal disease that may significantly alter the absorption of study drugs (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome)
  - Active skin, mucosa, ocular, or gastrointestinal disorders of grade > 1
  - Significant symptomatic deterioration of lung function. If clinically indicated, pulmonary function tests including measures of predicted lung volumes, diffusion capacity (DLco), and O2 saturation at rest on room air, should be considered to exclude restrictive pulmonary disease, pneumonitis, or pulmonary infiltrates.

- Patients being treated with drugs recognized as being strong inhibitors or inducers of the isoenzyme CYP3A (rifabutin, rifampicin, clarithromycin, ketoconazole, itraconazole, voriconazole, ritonavir, telithromycin) within the 5 days prior to randomization

- History of non-compliance to medical regimens

- Patients unwilling or unable to comply with the protocol

6.1.1.5 Study Treatment

Patients received either exemestane 25 mg/day orally in combination with everolimus 10 mg/day orally or an oral placebo in combination with exemestane 25 mg/day orally, given continuously. Treatment was to continue until disease progression, occurrence of unacceptable treatment-related toxicity, study withdrawal, or death, whichever occurred first. In the absence of any of these events, treatment was permitted to continue indefinitely after any maximum objective response (CR, PR, or SD) was achieved.

Dose reductions of everolimus to 5 mg once daily (level -1) or 5 mg every other day (level -2) were permitted for toxicity. Patients who required treatment interruption for longer than 4 weeks had study treatment permanently discontinued.

6.1.1.6 Study Enrollment

A total of 724 patients were randomized to participate in Y2301 at 196 sites with 1,421 investigators in 24 countries. The trial was conducted both in the United States as well as numerous sites abroad. Almost one-third of the trial population (n=223; 31%) was enrolled from the United States. Please refer to Table 2 to see the sites in the United States with the highest enrollment. Other countries that contributed significantly to overall trial enrollment included Japan (n=106; 15%), Canada (n=51; 7%), France (n=51; 7%), and Belgium (n=43; 6%).

6.1.1.7 Statistical Analysis Plan

The primary objective of Y2301 was to compare the combination of everolimus and exemestane versus exemestane alone in postmenopausal women with estrogen receptor positive breast cancer that is refractory to non-steroidal aromatase inhibitors.

Approximately 705 patients were to be randomized to observe 528 events (progression or death). The study had 90% power to detect a 35% improvement in median PFS from 3.7 versus 5 months, corresponding to a hazard ratio (HR) of 0.74 favoring the exemestane and everolimus combination therapy arm with a two-sided alpha of 0.05. Subjects were to be followed until 398 deaths had occurred, which provided 80% power to detect a 35% improvement in median OS (24 versus 32.4 months), corresponding to a HR of 0.74 with a two-sided alpha of 0.05.

There was a pre-specified interim analysis of PFS conducted after 359 (68%) events had been reported by the investigator and 218 (41%) events had been reported by the IRC. A final PFS analysis by investigator was conducted after 510 (97%) events had been observed. These data were submitted to FDA during the current review cycle and, as the most mature data, were used to generate the product labeling.

A total of three interim analyses of OS and a final analysis of OS were planned. The first interim OS analysis was performed concurrent with the interim analysis of PFS and accompanied the original sNDA submission. The second interim analysis of OS was performed during the sNDA review cycle and has also been reviewed by FDA. The third interim and final analyses of OS were pending at the time of regulatory action. These data are shown in Table 6 below. The second interim analysis of OS with 46% of events, which represent the most mature OS data available, was used for review and product labeling.

Table 6: Planned Analyses of Overall Survival

Analysis	Cumulative OS event, n (planned)	Cumulative OS event, n (actual)	Alpha Boundary **	Observed HR (p-value, one-sided)
1*	83	83	<0.0001	0.79 (0.15)
2	173	182	0.002	0.77 (0.046)
3	275			
Final	398			

6.1.2 Demographics

The demographic characteristics of the ITT population are shown in Table 7 below and were generally well-balanced between treatment groups. The median age was 61 years, and 76% of subjects were white. Asians comprised 20% of the study population. African-American patients were under-represented, at only 2% of study subjects.

Table 7: Patient Demographics, 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)

The study population had a favorable performance status; 96% were ECOG 0 or 1. All patients were ER positive, and nearly two-thirds were positive for both ER and PR (72%). No patients were identified as HER2-positive. The majority of patients had invasive ductal carcinoma (77%), although there was significant representation of patients with invasive lobular carcinoma as well (N=104; 14%).

Baseline disease characteristics are shown in Table 8. All but three patients enrolled had distant metastatic disease, and 59% of patients had visceral involvement. Bone involvement was also very common (76%), as would be expected in a population of hormone receptor-positive breast cancer patients; indeed 21% of patients had bone as their only site of metastatic involvement. The extent of disease varied with approximately one-third having a single metastatic site, one-third having two metastatic sites, and one third having three or more sites of metastatic disease. Experience with this combination in patients with brain or leptomeningeal metastases is extremely limited. Fewer than 1% of patients had central nervous system involvement.

Table 8: Baseline Disease Characteristics, ITT Population, Study Y2301

Patient and disease characteristics	Everolimus plus exemestane N=485 n (%)		Placebo plus exemestane N=239 n (%)		All patients N=724 n (%)	
Primary site of cancer						
Breast	485	(100.0)	239	(100.0)	724	(100.0)
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)
Bone only	105	(21.6)	50	(20.9)	155	(21.4)
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)
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

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

As shown in Table 9 below, all patients had previously been treated with either letrozole or anastrozole; only 57 patients (8%) had previously received both NSAIs. For 68% of patients, a NSAI had been used only in the metastatic setting, and for three-quarters, the NSAI was their last treatment prior to study entry.

More than half of patients had received prior endocrine therapy other than an NSAI. Although nearly half had received prior tamoxifen, only 16% had received prior fulvestrant, and only 8% had received both tamoxifen and fulvestrant. As a result, the population enrolled in the trial should not be construed as having exhausted available endocrine therapy; indeed, 49% of subjects in the everolimus plus exemestane arm and 44% of subjects in the exemestane monotherapy arm went on to receive another endocrine therapy as their first off-study treatment. In general, the patient population was not heavily pre-treated. Approximately 60% of patients had received zero or one line of any systemic therapy (endocrine or cytotoxic) in the advanced setting. Only 12% of patients had received more than 2 total lines of any systemic therapy in the advanced setting.

Approximately 70% of patients had received prior chemotherapy, either in the neo/adjuvant setting (42%), the metastatic setting (12%), or both (13%). Per the eligibility criteria, the maximum number of lines of chemotherapy received in the advanced setting was limited to one.

Table 9: Prior Treatment History, ITT Population, 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)

	Everolimus plus exemestane N=485 n (%)		Placebo plus exemestane N=239 n (%)		All patients N=724 n (%)	
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						
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)

[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

6.1.3 Subject Disposition

Please see Section 6.1.1.6 for a discussion of patient enrollment.

Subject disposition as of the February 11, 2011 data cut-off used for the original sNDA submission is detailed in Table 10 below provided by the Sponsor. Approximately 41% of patients remained on at least one study drug at that time. More patients had discontinued treatment on the control arm (71%) than the everolimus plus exemestane arm (53%), due largely to a higher incidence of disease progression in the control arm (66% versus 37%). Approximately 5% of subjects discontinued all study treatment due to an adverse event. Clinically important toxicity was more common in the everolimus plus exemestane arm, as reflected by the greater incidence of discontinuations due to: deaths without documented disease progression (7 cases versus 1 case in the control arm), adverse events (6.6% versus 2.5%), and patient withdrawal of consent (6.8% versus 2%). These safety issues are discussed in detail in Section 7 of this review. Protocol deviations and new cancer therapy as reasons for treatment discontinuation were likewise more common in the everolimus arm but quite rare overall.

Table 10: Patient Disposition, Y2301 Full Analysis Set

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

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint of the study was progression-free survival (PFS), defined as time from date of randomization to date of the first documented progression or death due to any cause, by investigator assessment. If a patient had not had an event, PFS was to be censored at the date of the last adequate tumor assessment. The original protocol specified that PFS by independent central radiographic review would serve as the primary endpoint. A subsequent amendment, enacted prior to unblinding any efficacy

data, specified that PFS by local investigator/radiologist assessment would serve as the primary endpoint with PFS by independent review serving as a secondary endpoint. The Sponsor stated that this amendment was due to concern for the high level of informative censoring anticipated in the independent radiographic review.

For patients with measurable disease at baseline, progression was determined per standard RECIST version 1.0 criteria. The define file from Novartis indicates that worsening of one or more non-target lesions would be deemed disease progression. Patients without measurable disease at baseline who had bone-only lesions (lytic or lytic + sclerotic), were allowed to enter the study. Among the group of patients without measurable disease at baseline, disease progression was defined as: appearance of one or more new lytic bone lesions, appearance of one or more new lesions outside of bones, or unequivocal progression of existing bone lesions. Of note, pathologic fracture, new compression fracture, and complications of bone metastases were not considered evidence of disease progression unless one or more of the preceding criteria for progression was also met. Clinical deterioration without documented disease progression was also not considered evidence of progression.

A single interim analysis was pre-specified to occur when 60% of the total PFS events had been observed per investigator assessment. The interim analysis provided boundaries for stopping the study for superior efficacy, and per IDMC charter amendment, the study would be declared positive at that time only if both the investigator and independent review committee analyses crossed stopping boundaries. A final analysis of PFS was planned once 528 events had been observed.

At a pre-specified interim analysis with 359 (68%) of events by investigator assessment, as of the data cut-off date of 02-11-2011, there was a statistically significant improvement in median PFS of 4.1 months, from a median of 2.8 months for patients receiving exemestane alone to a median of 6.9 months for patients receiving everolimus plus exemestane (HR 0.43; 95% CI: 0.35, 0.54; P<0.0001). These data are shown in Table 11 and in Figure 1 below.

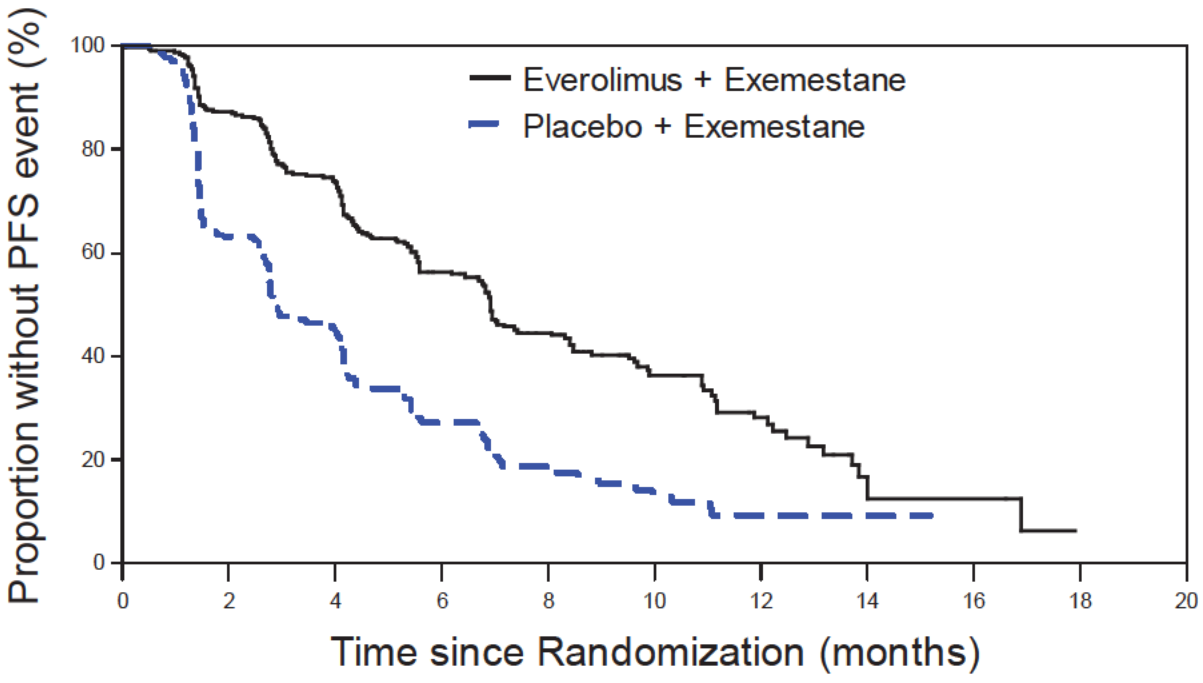
Table 11: Interim Analysis of PFS by Investigator, ITT population, Study Y2301

	Everolimus + Exemestane N=485 **N (%)**	**Placebo + Exemestane N=239** **N (%)**
PFS events	202 (42)	157 (66)
Disease Progression	190 (39)	156 (65)
Death	12 (3)	1 (0.4)
Censored	283 (59)	82 (34)
Median PFS, mos [95% CI]	6.9 [6.4, 8.1]	2.8 [2.8, 4.1]

	Everolimus + Exemestane N=485 N (%)	Placebo + Exemestane N=239 N (%)
HR [95% CI]	0.43 [0.35, 0.54]	
p-value*	<0.0001	

*With 68% events, alpha level is 0.013 (2-sided) per O'Brien-Fleming boundary.

Figure 1: Kaplan-Meier Curve of PFS by Investigator, ITT Population, Study Y2301 Interim Analysis



During FDA's review of the PFS data using patient-level investigator raw lesion data, 29 patients with discrepancies in the date or nature of PFS event were identified. The FDA clinical and statistical review teams conducted their own PFS analysis using the case report forms to amend the dataset per RECIST criteria for these 29 patients. The results were consistent with the primary analysis. Per FDA's analysis, the median PFS was 6.9 months in the everolimus plus exemestane arm and 2.8 months in the exemestane plus placebo arm, corresponding to a 56% reduction in the risk of progression or death [HR

0.44 (95% CI 0.35, 0.54)]. These results are consistent with the primary analysis of the endpoint by investigator assessment.

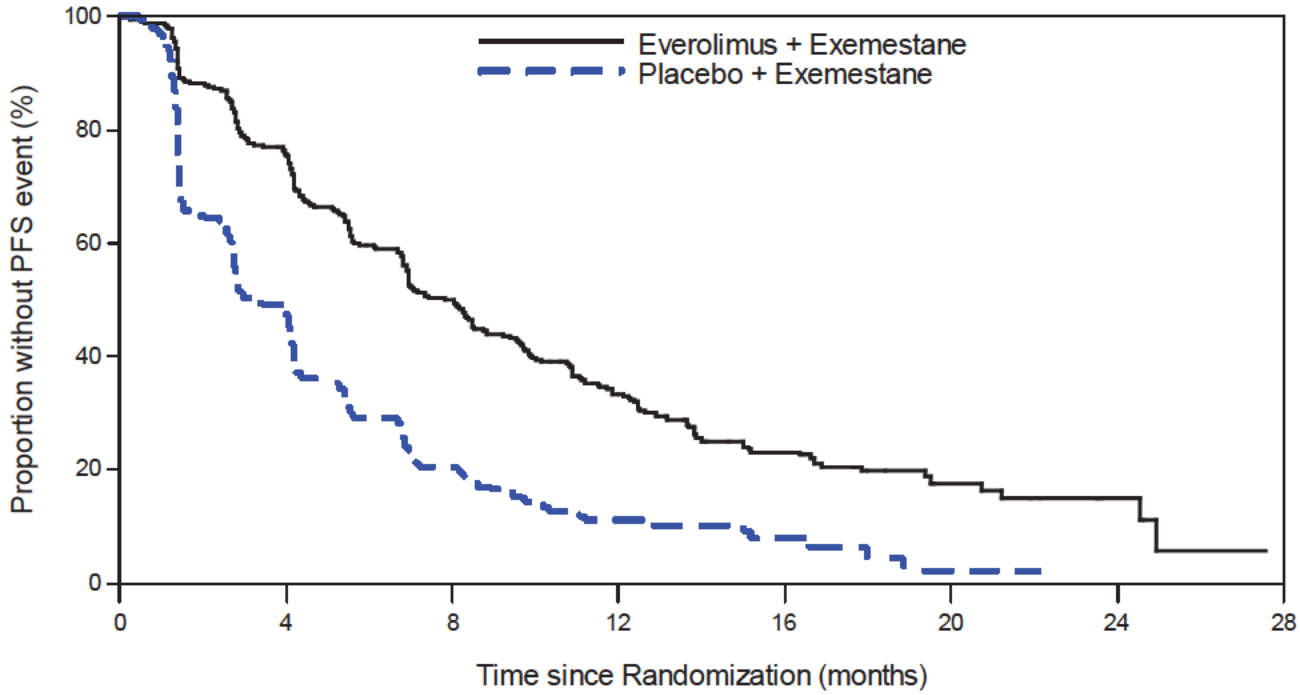
The final analysis of PFS, planned to occur after a total of 528 events had been observed, was performed using a data cutoff date of 12-15-2011 and submitted to the sNDA on 03-21-2012. At this time, a total of 510 events (97% planned) had been reported. The final analysis of PFS by investigator assessment was consistent with the interim analysis. As shown in Table 12, there remained a statistically significant absolute improvement in median PFS of 4.6 months, from a median of 3.2 months for patients receiving exemestane plus placebo to a median of 7.8 months for patients receiving everolimus plus exemestane (HR 0.45; 95% CI: 0.38, 0.54).

Table 12: Final Analysis of PFS by Investigator, ITT Population, Study Y2301

	Everolimus + Exemestane **N=485** **N (%)**	**Placebo + Exemestane** **N=239** **N (%)**
PFS events	310 (64)	200 (84)
Disease Progression	294 (61)	198 (83)
Death	16 (3)	2 (1)
Median PFS, mos [95% CI]	7.8 [6.9, 8.5]	3.2 [2.8, 4.1]
HR [95% CI]	0.45 [0.38, 0.54]	
p-value	P<0.0001	

The Kaplan-Meier curve for the final PFS analysis by investigator assessment is shown in Figure 2 below. The PFS curves begin to separate at the first radiographic assessment, at 6 weeks post-initiation of study treatment, and continue to diverge at later time points. The median PFS difference between arms accurately reflects the effect of the addition of everolimus to exemestane.

Figure 2: PFS by Investigator, ITT Population, Study Y2301, Final Analysis



In summary, the addition of everolimus to exemestane results in a statistically significant and clinically meaningful improvement in PFS of approximately 4.5 months, corresponding to a 55% reduction in the risk of disease progression or death. Key secondary efficacy endpoints, as discussed in Section 6.1.5 in further detail, were uniformly supportive of the primary endpoint.

6.1.5 Analysis of Secondary Endpoints(s)

Analysis of secondary endpoints for Study Y2301 was pre-specified in the protocol's statistical analysis plan. Key secondary efficacy endpoints, per the amended protocol, included:

- Progression-free survival (PFS) by independent central radiographic review, as discussed above
- Overall survival (OS), defined as time from date of randomization to date of death due to any cause. Patients who were not known to have died were censored at the last date of contact.
- Objective response rate, defined as the proportion of patients whose best overall response was either complete response (CR) or partial response (PR) according to RECIST criteria

- Clinical benefit rate (CBR), defined as the proportion of patients with a best overall response of CR, PR, or stable disease (SD) with a duration of 24 weeks or longer per RECIST criteria

The results of these secondary endpoints are supportive of the primary endpoint. Although the analyses were pre-specified, no adjustment has been made for multiplicity, and therefore, the p-values should be interpreted with caution. Secondary endpoints of particular interest are discussed below.

6.1.5.1 Progression-Free Survival by Independent Review Committee (IRC)

Progression-free survival by IRC assessment was the original primary endpoint of the protocol. The protocol was modified by Amendment 1, prior to any unblinding or analysis of data, due to concerns about a significant potential for informative censoring, to make PFS by investigator assessment the primary endpoint and PFS by IRC a secondary endpoint. The results of PFS by IRC were supportive of the primary analysis by investigator assessment.

At the time of the interim analysis using a date cutoff date of 02-11-2011, a total of 41% events had been reported per the IRC assessment. As shown in Table 13 and Figure 3 below, there was a statistically significant median improvement in PFS of 6.5 months, from 4.1 months for patients receiving exemestane alone to 10.6 months for patients receiving everolimus plus exemestane (HR 0.36; 95% CI: 0.27, 0.47; P<0.0001). The hazard ratio for PFS is very similar between the investigator and IRC assessments. The results appear to differ largely due to a much greater degree of censoring for the IRC results. The imbalance in censoring is primarily due to the longer duration of treatment of patients on the everolimus plus exemestane arm, reflecting the superior efficacy of the combination.

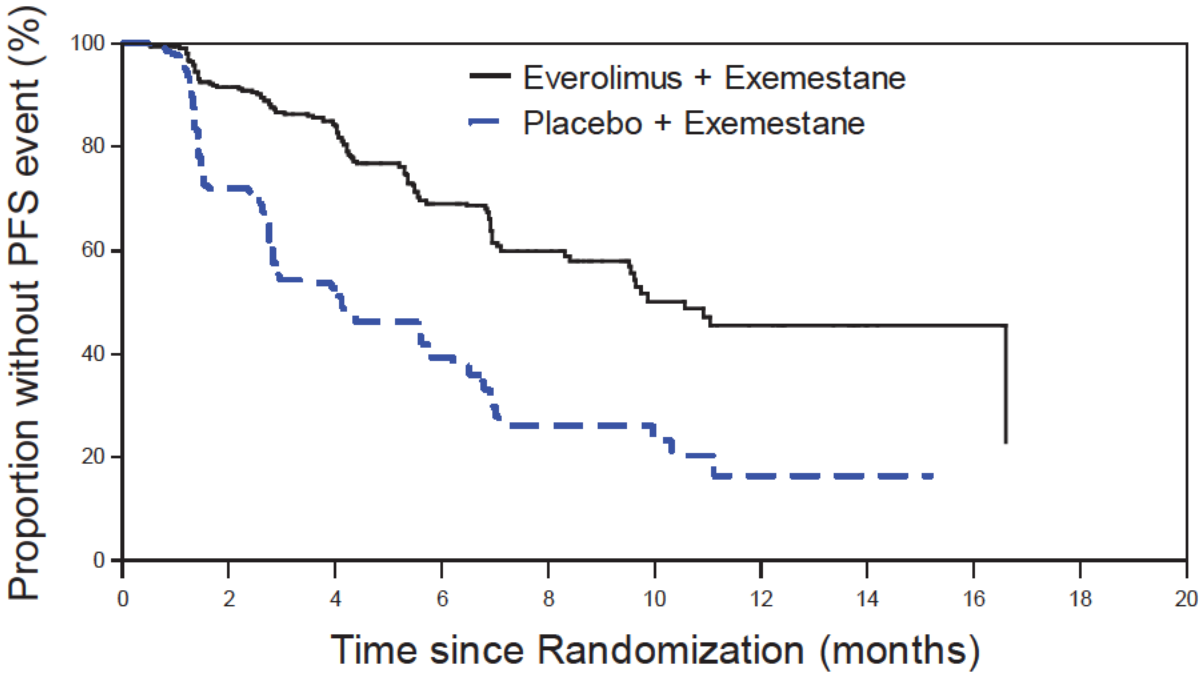
Table 13: Interim Analysis of PFS by Independent Review Committee, ITT Population, Study Y2301

	Everolimus + Exemestane **N=485** **N (%)**	**Placebo + Exemestane** **N=239** **N (%)**
PFS events Disease Progression Death	114 (24) 101 (21) 13 (3)	104 (44) 100 (42) 4 (2)
Censored	371 (77)	135 (357)
Median PFS, mos [95% CI]	10.6 [9.5, NA]	4.1 [2.8, 5.8]
HR [95% CI]	0.36 [0.27, 0.47]	

	Everolimus + Exemestane N=485 N (%)	Placebo + Exemestane N=239 N (%)
p-value*	<0.0001	

*With 218 PFS events (41% total), 2-sided alpha level is 0.001 per O'Brien-Fleming boundary.

Figure 3: Kaplan-Meier Curve of PFS by Independent Review Committee, ITT Population, Study Y2301 Interim Analysis



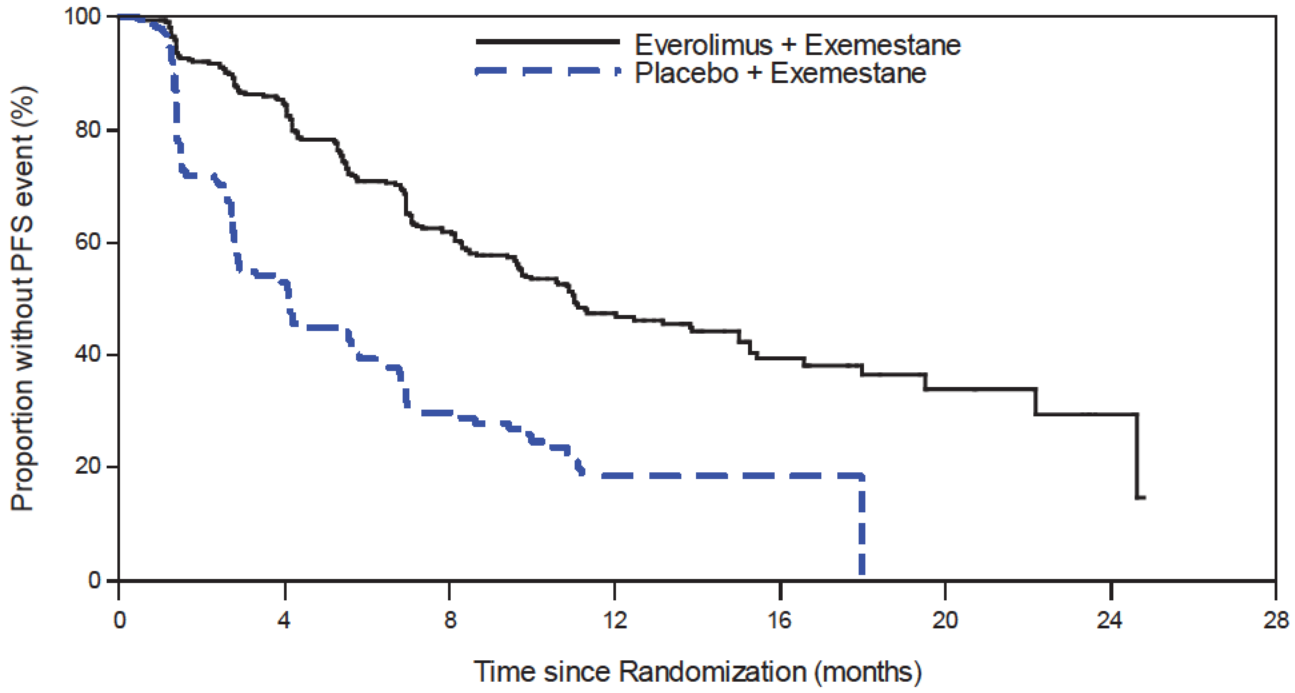
As demonstrated in Table 14 and Figure 4, the results of the final PFS analysis by IRC do not differ meaningfully from what was observed at the time of the interim analysis of PFS by IRC.

Table 14: Final Analysis of PFS by IRC, ITT Population, Study Y2301

	Everolimus + Exemestane N=485 N (%)	Placebo + Exemestane N=239 N (%)
PFS events	188 (39)	132 (55)
Disease Progression	167 (34)	128 (54)
Death	21 (4)	4 (2)
Censored	297 (61)	107 (45)
Median PFS, mos [95% CI]	11.0 [9.7, 15.0]	4.1 [2.9, 5.6]
HR [95% CI]	0.38 [0.31, 0.48]	
p-value*	<0.0001	

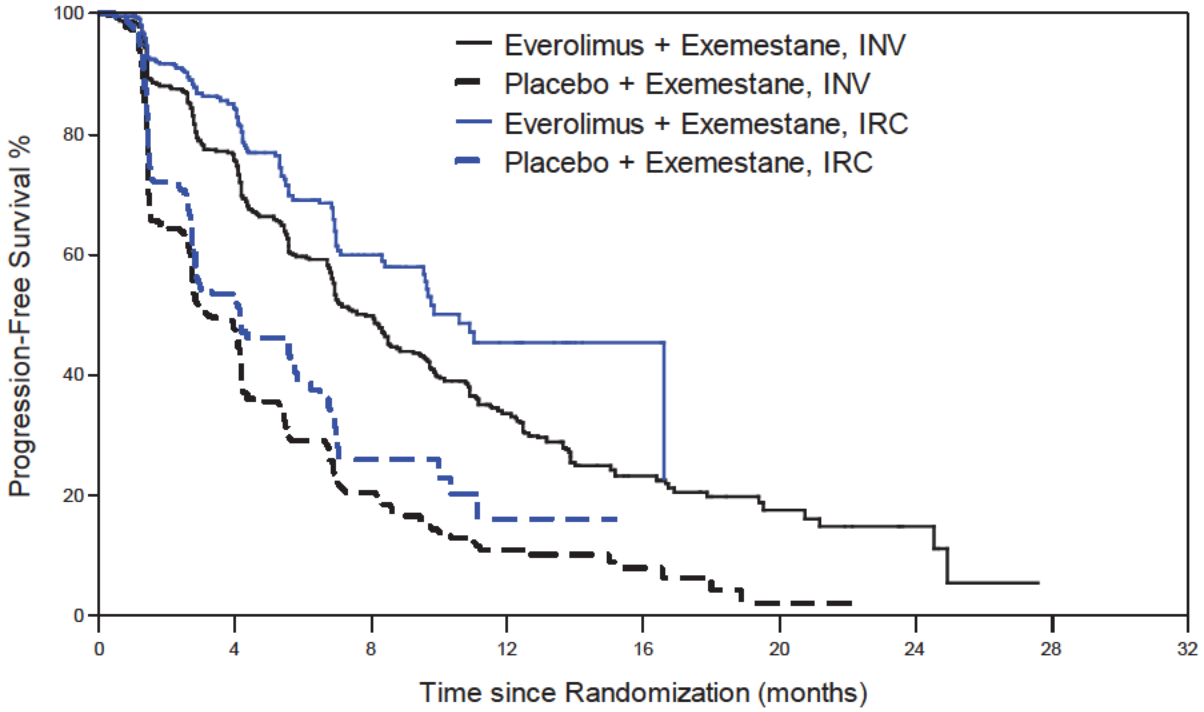
*Unadjusted for multiplicity

Figure 4: Kaplan-Meier Curve of PFS by IRC, Study Y2301, Final Analysis



Importantly, the PFS results by both investigator assessment and IRC are consistent. As seen in Figure 5, while the median PFS in both arms is greater by IRC than by investigator, the shape of the curves and the hazard ratios are quite similar.

Figure 5: Kaplan-Meier Curves of PFS by Investigator and IRC, Study Y2301, Final Analysis



6.1.5.2 Overall Survival

To control the overall type I error rate, OS was to be tested hierarchically after the analysis of PFS only if the primary endpoint had been met. Three interim analyses of OS, as well as a final analysis of OS, were planned.

The results of the first interim analysis of OS in Study Y2301 shown in Table 15 were included in the original sNDA submission. Fewer deaths occurred in the everolimus plus exemestane arm (11%) than in the control arm (13%). There was a non-statistically significant 21% reduction in the risk of death with wide confidence intervals. Note that this analysis was based upon only 83 deaths (21% of total).

Table 15: First Interim Analysis of Overall Survival, ITT Population, Study Y2301

	Everolimus + Exemestane	Placebo + Exemestane

	N=485	N=239
# of Deaths, n(%)	52 (11%)	31 (13%)
HR	0.79 (0.50, 1.24)	
P-value, one-sided*	0.15	

*Per the Lan-DeMets alpha spending function based on O'Brien-Fleming boundary, the nominal p-value for the first OS interim analysis was p < 0.000001 (one-sided).

A second interim analysis of OS was to be conducted when 173 events had occurred. This second interim analysis, using a data cutoff date of 10-31-2011, was submitted to the sNDA on 12-22-2011. As shown in Table 16, the second interim analysis included 182 events. Although the results remain immature with only 46% of planned total events observed at the time of the analysis and 11% power, again fewer deaths were observed in the everolimus plus exemestane arm (29%) than in the control arm (23%). There was a non-statistically significant 23% reduction in the risk of death. The 25th percentile of OS favored the combination arm by approximately 2 months.

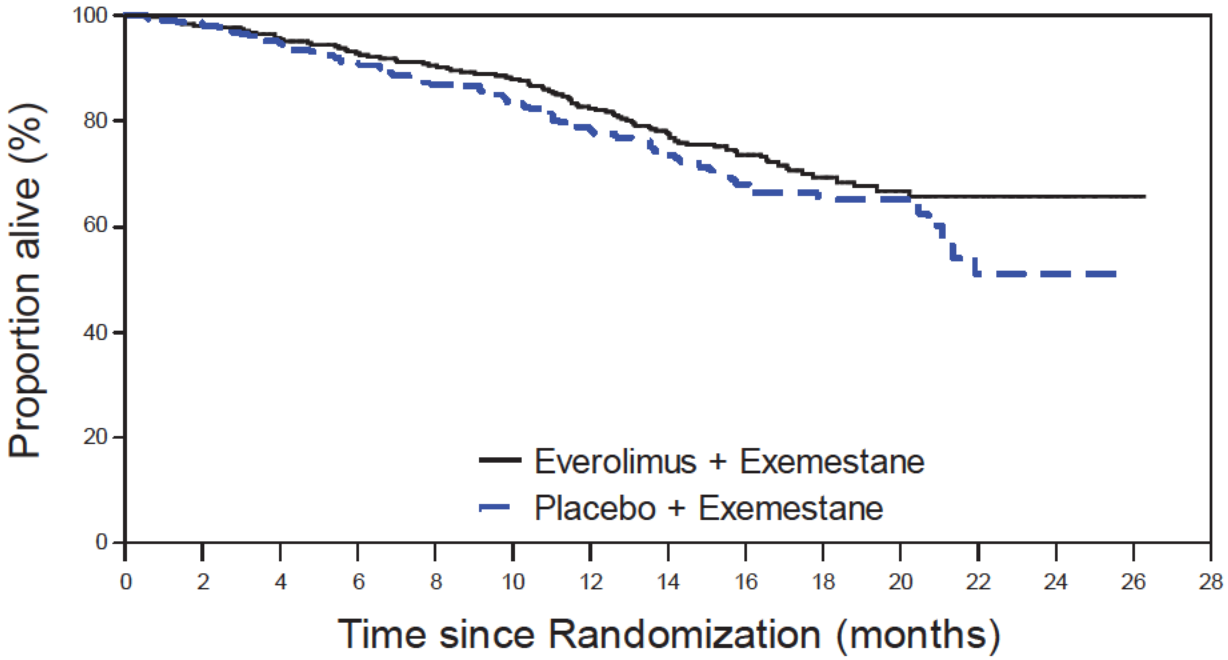
Table 16: Second Interim Analysis of Overall Survival, ITT Population, Study Y2301

	Everolimus + Exemestane N=485	Placebo + Exemestane N=239
# of Deaths, n(%)	112 (23%)	70 (29%)
Median (95% CI), mos	NR	NR (20.7, NR)
25th %ile (95% CI), mos	15.5 (13.1, 17.5)	13.6 (11.0, 15.7)
HR	0.77 (0.57, 1.04)	
P-value, one-sided*	0.046	

*Per the Lan-DeMets alpha spending function based on O'Brien-Fleming boundary, the nominal p-value for the second OS interim analysis was p < 0.001 (one-sided).

At the time of the second planned interim analysis, the Kaplan-Meier curve of OS, shown in Figure 6, shows a modest but consistent separation of the curves beginning approximately 5 months following randomization.

Figure 6: Kaplan-Meier Curve of Overall Survival, ITT Population, Study Y2301, Second Interim Analysis



A third interim analysis of OS is planned when 275 deaths have been observed, and the final analysis of OS will be performed when 398 deaths have occurred. The third interim analysis of OS is projected to occur in approximately September 2012, and the final analysis of OS is anticipated in June 2014. A final report on overall survival, including mature datasets, will be submitted to FDA by June 2015 per a postmarketing commitment.

At the time of the final analysis, Study Y2301 will have 80% power to demonstrate a statistically significant difference between arms in terms of OS. While the results of the second interim analysis of OS were not statistically significant, the study had only 11% power at the time of the second interim analysis to demonstrate a significant difference between arms. With 46% of expected events having occurred, there a trend for a 20-25% reduction in the risk of death with the addition of everolimus to exemestane. This finding was central to the regulatory decision-making process for the clinical reviewers. Despite an increased incidence of toxicity, and notably an increase in on-treatment mortality for those over age 65 years, in the everolimus arm, there remains a net favorable benefit-risk assessment for the general population of advanced breast cancer patients who receive everolimus in addition to exemestane, as well as the subset of patients over age 65. Efficacy and safety in the age > 65 subgroup are discussed in greater detail in Section 6.1.7 and Section 7.5.3.

6.1.5.3 Objective Response Rate and Clinical Benefit Rate

Other efficacy endpoints assessed included objective response rate (ORR), defined as the proportion of patients whose best overall response was either complete response (CR) or partial response (PR) according to RECIST. For patients lacking measurable disease at baseline, progression was classified as follows:

- In the absence of measurable disease at baseline, the following was classified as progression among patients with lytic or mixed (lytic + sclerotic) bone lesions:
    - Appearance of one or more new lytic lesions in bone
    - Appearance of one or more new lesions outside of bone
    - Unequivocal progression of existing bone lesions
    - Note: Pathologic fracture, new compression fracture, or complications of bone metastases will not be considered as evidence of disease progression, unless one of the above-mentioned criteria is fulfilled.
- Patients with symptoms of rapidly progressive disease without radiological evidence of progression were to be classified as progression only when clear evidence of clinical deterioration was documented and/or the patient discontinued due to 'disease progression' or death due to breast cancer.

The evaluation of overall lesion response was to be performed according to RECIST. For patients with only bone lesions, in absence of new lesions, the overall lesion response at each assessment was to be one of the following: CR, stable disease (SD), unknown, or progressive disease (PD) based on non-target lesion responses. Stable disease would include all assessments not qualifying as CR, PD, or unknown. If any new lesions were identified, the overall lesion response was to be categorized as PD.

Given that prolonged periods of stable disease may be observed in patients with hormone receptor positive advanced breast cancer, particularly in those with metastatic disease limited to bones, the clinical benefit rate (CBR), defined as the proportion of patients with a best overall response of CR, PR, or SD with a duration of 24 weeks or longer per RECIST, was also assessed by the local investigators.

As shown in Table 17, complete responses (CR) were rare, observed in only 3 patients in Study Y2301. All 3 patients were in the combination arm. Partial responses were observed in 58 patients (12%) on the everolimus plus exemestane arm compared with 4 patients (1.7%) on the exemestane alone arm. The overall clinical benefit rate was approximately doubled, from 26% to 51%, by the addition of everolimus to exemestane.

Table 17: Response Rate and Clinical Benefit Rate, ITT Population, Study Y2301 Final Analysis

	Everolimus + Exemestane N=485 N (%)	Placebo + Exemestane N=239 N (%)
Objective Response Rate (ORR)	61 (12.6)	4 (1.7)
Complete Response (CR)	3 (0.6)	0 (0)
Partial Response (PR)	58 (12)	4 (1.7)
Clinical Benefit Rate (CBR)	249 (51)	63 (26)

6.1.6 Other Endpoints

Other endpoints assessed in Study Y2301 included:

- Time to overall response (CR or PR), defined as the time from date of randomization until first documented response (CR or PR) per RECIST
- Duration of overall response (for patients whose best overall response was CR or PR), defined as the date of first documented response (CR or PR) to the date of event defined as first documented progression or death due to cancer.
- Quality of life, as assessed by the EORTC QLQ-C30 questionnaire along with the breast cancer specific module (BR23).

Duration of response and time to overall response were not formally reviewed in view of the low objective response rate.

For the quality of life assessment, the global health domain score of the EORTC QLQ-C30 questionnaire was pre-specified as the primary QoL domain of interest. For the first 12 weeks, when a high proportion of patients remained on treatment, $\geq$ 90% of patients on both arms completed the every 6 week questionnaires. At subsequent time points, there were greater percentages of missing data. Median times to deterioration (≥ 5%) of global health status/QoL domain score of QLQ-C30 were similar between treatment arms (HR 0.92, 97.5% CI 0.72, 1.17), although of note, the wide confidence interval could not exclude a detrimental effect on QoL for the addition of everolimus to exemestane. Likewise, physical, emotional, and social functioning scores, which were secondary QoL domains of interest, also did not differ significantly between treatment arms. All of these results should be interpreted with caution in view of the extent of missing data.

6.1.7 Subpopulations

A number of exploratory subgroup analyses were performed by the FDA clinical and biostatistical reviewers. These included a subgroup analysis of PFS by setting of disease-refractoriness to non-steroidal aromatase inhibitor (NSAI). While all patients appeared to benefit from the addition of everolimus to exemestane, patients who were NSAI refractory in the adjuvant setting appeared to have benefited to a somewhat greater extent more than patients who were refractory in the metastatic setting (HR 0.23 versus 0.41). There were very few patients defined as refractory in both the adjuvant and metastatic setting (N=20). In these patients, the HR again favored the combination arm (HR 0.62), but had a very wide confidence interval that could not exclude a detrimental effect of the addition of everolimus to exemestane.

Table 18: PFS by Setting for Refractoriness to Nonsteroidal Aromatase Inhibitor (NSAI), ITT Population, Study Y2301

	Everolimus + Exemestane N=485	Placebo + Exemestane N=239
Disease refractory to NSAI in adjuvant setting		
N	142	57
# of events (%)	55 (39)	38 (67)
Median, months	7.4	2.8
HR (95% CI)	0.23 (0.13, 0.41)	
Disease refractory to NSAI in metastatic setting		
N	333	172
# of events (%)	142 (43)	114 (66)
Median, monthss	6.8	3.3
HR (95% CI)	0.41 (0.30, 0.57)	
Disease refractory to NSAI in both settings		
N	10	10
# of events (%)	5	5
Median, months	5.4	2.9
HR (95% CI)	0.62 (0.14, 2.64)	

FDA also performed an exploratory subgroup analysis of PFS by time to first recurrence/metastasis. As shown in Table 19 below, the hazard ratio for PFS favored the everolimus plus exemestane arm in all subgroups, although patients with a relapse-free interval less than one year appeared to benefit to a lesser degree than patients with longer relapse-free intervals. For patients with relapse-free intervals of one to ten years or more, the benefit of adding everolimus to exemestane in terms of PFS was consistent across all subgroups.

Table 19: PFS by Relapse-Free Interval, ITT Population, Study Y2301

	Everolimus + Exemestane N=485	**Placebo + Exemestane N=239**
< 1 year		
N	121	58
# of events (%)	55 (45)	37 (64)
Median, months	6.4	3.0
HR (95% CI)	0.56 (0.32, 0.98)	
1-5 years		
N	168	86
# of events (%)	75 (45)	64 (74)
Median, months	5.5	2.8
HR (95% CI)	0.27 (0.17, 0.42)	
5-10 years		
N	110	51
# of events (%)	39 (35)	51 (59)
Median, months	10.9	5.3
HR (95% CI)	0.33 (0.18, 0.62)	
> 10 years		

	Everolimus + Exemestane N=485	Placebo + Exemestane N=239
N	82	43
# of events (%)	30 (37)	25 (58)
Median, months	7.0	3.3
HR (95% CI)	0.37 (0.17, 0.81)	

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The dose and schedule of exemestane used in Study Y2301 represents the standard dose and schedule used in the metastatic breast cancer setting and reflected in the approved product labeling. The dose and schedule of everolimus used in Study 2301 also represents the standard dose and schedule used in the other approved oncologic indications for everolimus and reflected in the approved product labeling.

Although there was a high incidence of treatment interruption and dose reduction of everolimus in Study Y2301, suggesting that the dose may be too high, there are no available efficacy data to support the use of an alternate dose or schedule of everolimus in advanced breast cancer. Investigators from a randomized phase 2 trial (NCIC IND.163) comparing two schedules of everolimus monotherapy—everolimus 10 po daily and 70 mg po weekly—in patients with advanced breast cancer reported a response rate of 12% for the 10 mg po daily regimen, which is identical to the response rate observed in the everolimus 10 mg po daily plus exemestane arm of Study Y2301, compared with 0% for the 70 mg weekly everolimus regimen.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

These issues are addressed throughout the efficacy review given that the primary endpoint of the trial is a time to event endpoint.

6.1.10 Additional Efficacy Issues/Analyses

A number of sensitivity analyses were conducted by the FDA clinical and biostatistical reviewers. Those most pertinent to the recommended regulatory action are presented below.

The first relied upon combined data from the investigator assessment and the independent radiographic review, but utilized the earlier date of progression provided by either source. This analysis, shown in Table 20 below, demonstrates results consistent with the primary PFS analysis with a hazard ratio of 0.42, corresponding to a median difference of 3.7 months in PFS, favoring the everolimus plus exemestane arm.

Table 20: Analysis of PFS Using Earliest Date of Progression or Death From Any Source, ITT Population, Study Y2301

	Everolimus + Exemestane N=485 N (%)	**Placebo + Exemestane N=239 N (%)**
PFS events	219 (45)	169 (71)
Disease Progression	208 (43)	168 (70)
Per IRC	48 (10)	41 (17)
Per investigator	117 (24)	73 (31)
Per both simultaneously	43 (9)	54 (23)
Death	11 (2)	1 (0.4)
Median PFS, mos [95% CI]	5.5 [5.3, 7.0]	2.8 [1.7, 2.8]
HR [95% CI]	0.42 [0.34, 0.52]	
p-value	<0.0001	

We also conducted an additional "worst case" analysis of PFS, in which patients who discontinued treatment without a documented PFS event were censored in the control arm but were classified as having had a PFS event in the everolimus plus exemestane arm. In this worst case analysis of PFS using the investigator data, the hazard ratio continues to favor the everolimus plus exemestane arm as shown in Table 21 below.

Table 21: FDA, Worst Case Analysis of PFS Using Investigator Assessment, ITT Population, Study Y2301

	Everolimus + Exemestane N=485	**Exemestane + Placebo N=239**
PFS event, n (%)	265 (55)	157 (66)
Median [95% CI], mos	5.42 [4.30, 6.70]	2.79 [2.69, 4.01]
HR [95% CI]	0.63 [0.52, 0.78]	

Finally, a sensitivity analysis was performed to address the introduction of bias due to informative censoring. In this analysis, for patients in the everolimus plus exemestane arm who were censored due to a new anti-cancer therapy per the independent review but assessed as having had a PFS event per the investigator review, PFS events were imputed and PFS duration extended by 6 weeks based upon the assumption that disease progression would have been documented at the subsequent tumor assessment. For patients in the control arm, patients who were censored due to a new anti-cancer therapy were not assumed to have had a progression event. The results of this analysis for PFS by independent review committee (IRC) are shown in Table 22 below and similarly demonstrate results favoring the everolimus plus exemestane arm.

Table 22: Sensitivity Analysis to Address Effect of Bias Related to Informative Censoring, ITT Population, Study Y2301

	Everolimus + Exemestane **N=485**	**Exemestane + Placebo** **N=239**
PFS event, n (%)	197 (41)	104 (44)
Median [95% CI], mos	6.89 [5.62, 7.66]	4.14 [2.83, 5.75]
HR [95% CI]	0.55 [0.43, 0.70]	

The results of these sensitivity analyses support the robustness of the primary efficacy analyses.

7 Review of Safety

Safety Summary

Major Findings:
1) Increased rate of on-treatment mortality seen on everolimus therapy in patients ≥ 65 years of age.
2) Potential safety signal in the ≥ 65 year old population in terms of serious adverse events, grade 3-4 events, and adverse events leading to treatment discontinuation.
3) High rate of treatment discontinuation, dose interruption, and dose reduction seen with the combination of everolimus plus exemestane compared to exemestane alone.
4) Toxicity rates, including fatal toxicities, are consistent with the known safety profile of everolimus in other advanced cancers in the adult population.
5) Overall, the safety profile is acceptable in the advanced hormone receptor positive breast cancer population given the robust and clinically meaningful improvement in progression free survival associated with the combination of everolimus plus exemestane.

7.1 Methods

Safety assessments in the pivotal phase 3 trial were performed at baseline, day 15, weeks 4, 6 and every 6 weeks thereafter. Safety assessments consisted of monitoring and recording all AEs, including SAEs, the regular monitoring of hematology, serum chemistry, coagulation, urinalysis, routine monitoring of vital signs (heart rate, blood pressure, and body temperature), weight, ECOG PS, chest CT scans, and physical condition. Toxicity was assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 3.0. In addition, monitoring of pneumonitis, a known AE associated with the use of rapamycin and its analogs, was performed in this study.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The pivotal trial used to evaluate safety is Study CRAD001Y2301. Studies C2240, C2324, and C2485, which were the pivotal trials used to support the approval of everolimus in renal cell carcinoma, pancreatic neuroendocrine tumor, and subependymal giant cell astrocytoma respectively, were used for cross-disease toxicitiy comparisons.

7.1.2 Categorization of Adverse Events

Adverse events were coded using the MedDRA terminology (Version 14.0) and were assessed according to the NCI-CTCAE, Version 3.0. A patient with multiple CTC grades for an AE was summarized under the maximum CTC grade recorded for the event. Additionally, as a result of signals observed during earlier studies, several AEs requiring close follow-up were identified. This list of clinically notable AEs was pre-specified in the analysis plan and included the following categories of events: stomatitis/oral mucositis/ulcers, infections and infestations, cytopenias, hemorrhages, non-infectious pneumonitis, hyperglycemia/new-onset diabetes mellitus, renal events, rash and similar events, thromboembolism, and hypersensitivity reactions (anaphylactic reactions).

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

On-treatment deaths, as defined by deaths occurring within 28 days of the last dose of study drug, were compared across studies C2240, C2324, C2485, and CRAD001Y2301 and are depicted in Table 23. Rates of stomatitis, pneumonitis, hemorrhages, and infections and infestations are depicted in Table 24.

Table 23: On Treatment Deaths Across Clinical Trials

Indication	Study	On-treatment deaths N (%)	Attributable to everolimus by FDA reviewer N (%)	Mean age of population In years
Breast cancer	Y2301	18 (3.7)	11 (2.3)	62
RCC	C2240	21 (7.7)	5 (1.9)	60
PNET	C2324	12 (5.9)	7 (3.4)	57
SEGA	C2485	0 (0)	0 (0)	13

Table 24: Rates of selected adverse events across clinical trials

Indication	Study	SAE	Stomatitis	Pneumonitis	Hemorrhages*	Infections and Infestations
Breast cancer	Y2301	27%	59%	19%	5%	50%
RCC[1]	C2240	50%	44%	14%	3%	37%
PNET[2]	C2324	41%	70%	17%	9%	56%
SEGA[3]	C2485	14%	86%	<1%	<1%	89%
TSC-AML	M2302	20%	79%	1%	22%	71%

*excludes epistaxis
[1]From the AFINITOR label, Study C2240 datasets, and the medical officer's review
[2]From the AFINITOR label, Study C2324 datasets, Final update of RAD001C2240 safety and overall survival CSR, and the medical officer's review
[3]From the AFINITOR label, Study C2485 datasets, and the medical officer's review

Reviewer's Comments

It is difficult to accurately perform cross-trial comparisons, especially when the trials are performed in different disease settings. What the above data suggest is that in the adult, advanced cancer population, treatment with everolimus is associated with a small, but real risk of treatment related mortality. The rate of both on-treatment mortality and treatment related mortality seen in Study Y2301 is similar to the rates seen in the pivotal studies conducted in the RCC and PNET population. There were no patients who died in the SEGA study and there is one death reported in the TSC-AML study which is clearly attributable to a co-morbid condition (status epillepticus). When performing a cross-disease comparison of the types and severity of adverse reactions that occur, it is quite apparent that there is an age-related association with the incidence and severity of certain toxicities. It is notable that in the SEGA study (median age 13) and the AML-TSC study (median age 32), there was a less than 1% incidence of pneumonitis seen in these populations as compared to a rate of 14-19% seen in the more older population enrolled in the RCC, PNET and HR+ Breast cancer studies (median ages 60, 57, and

62 respectively), whereas stomatitis occurred in 79-86% in the SEGA and TSC-AML studies as compared to 44-70% in the RCC, PNET, and HR+ Breast cancer studies. The rate of severe adverse events and the seriousness of the adverse events as measured by CTCAE grade were higher in the RCC, PNET, and HR+ Breast cancer studies as compared to the SEGA and TSC-AML studies. These data suggest that the toxicity profile of everolimus changes in its nature and severity in different age groups which reflects the mechanism of action of the drug and the physiology of aging.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure to everolimus and comparator therapy in Study Y2301 is summarized in Table 25 below.

Table 25: Exposure, Safety Population, Study Y2301

	Everolimus +Exemestane N=482		**Placebo+Exemestane N=238**	
	Everolimus	**Exemestane**	**Placebo**	**Exemestane**
Total Cumulative Dose (mg) Median	1292.50	4587.50	925.00	2462.50
Duration of Treatment Median (weeks)	23.93	26.64	13.36	14.07
Dose Intensity (mg/day) Median	8.66	25	10.00	25.00
Relative Dose Intensity (%) Median	87	100	100	100

Patients on the everolimus arm had a longer duration of treatment than did comparator arm patients. The relative dose intensity was 87% for everolimus as compared to 100% relative dose intensity for exemestane and placebo, reflecting the frequent need for dose delays, interruptions, and reductions.

Table 26 provides a summary of dose modifications, interruptions, and reductions.

Table 26: Dose Modifications, Safety Population, Study Y2301

	Everolimus +Exemestane N=482 N (%)	**Placebo+ Exemestane N=238 N (%)**
Patients with Any Dose Reduction/Interruption	307 (63.6)	49 (20.6)
1 delay/reduction	93 (19.3)	29 (12.2)
>1 delay/reduction	214 (44.4)	20 (8.4)
Patients with Dose Reductions	183 (38.0)	9 (3.8)
Patients with Dose Interruptions	278 (57.7)	43 (18.1)
Adverse Events Requiring Permanent Dose Discontinuation	115 (23.7)	11 (4.6)
Adverse Events Requiring Dose Reduction/Interruption	303 (62.9)	34 (14.3)

The majority of the patients on the everolimus arm required a dose reduction or interruption. Adverse events were the primary cause necessitating dose modifications. A total of 24% of the everolimus arm patients required a permanent dose discontinuation due to an adverse event. For further details regarding this matter please refer to section 7.3.3.

7.2.2 Explorations for Dose Response

Please see the Clinical Pharmacology Review

7.2.3 Special Animal and/or In Vitro Testing

Not Applicable

7.2.4 Routine Clinical Testing

Please reference the laboratory and vital sign analyses

7.2.5 Metabolic, Clearance, and Interaction Workup

Please see the Clinical Pharmacology review

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

See section 2.4

7.3 Major Safety Results

7.3.1 Deaths

As of the last OS analysis which had a cutoff date October 31, 2011, there were 182 deaths (25% of the enrolled population). Table 27 depicts the number and distribution of deaths across study arms.

Table 27: Total deaths, Study Y2301 (OS update)

	Everolimus +exemestane N=485 N (%)	**Placebo+ Exemestane N=239 N (%)**
Total	112 (23)	70 (29)
Age < 65 (N=449)	54 (19)	45 (28)
Age ≥ 65 (N=275)	58 (30)	25 (31)

Reviewer's comments: The analysis of overall survival as an efficacy endpoint has been addressed in section 6.1.5.2. The data from the above table suggest that the trend toward an improvement in overall survival is driven mainly by the < 65 year old population and that mortality is similar in the ≥ 65 year old population of both arms. In a prespecified subset analysis of the primary endpoint of PFS, the magnitude of PFS benefit is smaller for the ≥ 65 year old population as compared to the < 65 year old

population (median Δ = 5.4 mo for patients < 65 and 2.8 mo for patients ≥ 65), but still was associated with a 41% reduction of risk of progression (HR = 0.59 (0.43, 0.80)). These data are somewhat reassuring in that there does not appear to be a detriment in overall survival in the ≥ 65 year old population in spite of the increased on-treatment mortality and increased rate of adverse events that will be discussed in the sections that follow.

On-treatment mortality was defined by the protocol as all deaths that occurred within 28 days of the last treatment dose. The tables below depict the number of on-treatment deaths and attribution as per investigator.

Table 28: Deaths within 28 days of treatment, Safety Population, Study Y2301

	Everolimus +exemestane N=482 N (%)	**Placebo+ exemestane N=238 N (%)**
Total	18 (3.7)	4 (1.7)
Age < 65	6 (2.0)	3 (1.9)
Age ≥ 65	12 (6.2)	1 (1.3)
Listed Causes of Death		
Study Indication	9 (1.9)	3 (1.3)
AEs as primary cause	9 (1.9)	1 (0.4)

Below is the safety reviewer's assessment of each on-treatment death in Study Y2301.

Table 29: Analysis of On-treatment Deaths, Everolimus + Exemestane Arm, Study Y2301

Patient ID	**Progression Confirmed**	**Narrative and Comments**
Y2301-0100-00001 Age 55 **Prior AC, 5-FU therapy**	N	55 y/o f developed asthenia and decreased appetite (Grade 2) on day 19. On day 29, patient developed stomatitis (Grade 2) and was hospitalized on the same day with continued asthenia, decreased appetite, and stomatitis. Elevated liver enzymes were increased from baseline and clinical progression was called based on the laboratory values. No imaging was done to confirm progression. Study drug was

Patient ID	Progression Confirmed	Narrative and Comments
		stopped day 29. Patient died on day 39 due to disease progression. ***Reviewer's comment: Asthenia, decreased appetite, and stomatitis are known adverse events associated with everolimus therapy may have contributed to the patient's rapid clinical decline.***
Y2301-0177-0001 **Age 72** **Prior CMF therapy**	N	72 year old female developed lethargy and mouth ulceration on day 7. On day 8 the patient developed pain upon urination and was noted to have renal failure and pyelonephritis. Patient died on day 15 due to renal failure. ***Reviewer's comment: Renal failure and infections are known adverse events associated with everolimus therapy and may have contributed to the patient's death***
Y2301-0193-00002 **Age 60** **No prior chemotherapy**	N	60 year old female experienced hemoptysis on day 32 along with small spotting from an anterior chest wall mass. On day 34 the patient had hemorrhage from the anterior chest wall mass leading to hemodynamic instability and death. ***Reviewer's comment: Hemmorrhage is a known adverse event associated with everolimus therapy and may have contributed to the patient's death***
Y2301-0317-00014 **Age 76** **Prior Taxol therapy**	N	76 year old female experienced general physical health deterioration and decreased appetite leading to drug discontinuation on day 28 and requiring hospitalization on day 31. The patient experienced lung infection and septic shock on day 36. On day 40, the patient experienced a transient ischemic attack. On day 54 the patient died and the cause of death was listed as the TIA. ***Reviewer's Comments: Decreased appetite, fatigue, and infections (septic shock) are known adverse events associated with everolimus therapy and may have contributed to the patient's death.***
Y2301-0462-	N	70 year old female committed suicide on day 121 of therapy.

Patient ID	Progression Confirmed	Narrative and Comments
00001 Age 70 **Prior CMF, doxorubicin, therapy**		***Reviewer's comments: None***
Y2301-0465-00004 Age 78 **No prior chemotherapy**	Y	78 year old female experienced paraparesis on day 17 of therapy and was found to have medullary compression. Patient died on day 37 due to disease progression. ***Reviewer's comments: Agree with sponsor assessment of death.***
Y2301-0534-00008 Age 72 **Prior AC, 5-FU, Taxol**	N	72 y/o female experienced decreased weight (day 43) and general physical health deterioration (day 63). The patient died on day 72 due to clinical disease progression, but no imaging studies were performed to confirm progression and no autopsy was performed. The patient's baseline ECOG performance status was recorded at 1, but at the study day 1 visit, it was recorded as 0. The patient's ECOG score at the 6 week visit was 2 as it was on the end of study visit 20 days later. Patient's baseline scan demonstrated 2 3cm liver lesions and multiple non-measurable pulmonary nodules, a chest wall lesion, non-measurable liver lesions, and a bony lesion in the thoracic spine. Patients 6 week imaging assessment demonstrated stable disease. ***Reviewer's comments: While general physical health deterioration is not included in the everolimus label, associated symptoms such as fatigue, asthenia, decreased appetite, and weight loss are known adverse events associated with everolimus therapy and may have contributed to the patient's death. The patient's 6 week imaging assessment demonstrated stable disease.***

Patient ID	Progression Confirmed	Narrative and Comments
Y2301-0545-00001 Age 68 **Prior Gemcitibine, epirubicin, decetaxel, bevacizumab**	N	68 y/o female experienced pulmonary embolism on day 148 of treatment. The patient was treated with heparin but experienced muscle hemorrhage on day 154 which resolved. On day 165, the patient experienced respiratory failure and staphylococcal sepsis. Chest X-ray showed bilateral infiltrates. The patient died on day 165 due to staphylococcal sepsis. ***Reviewer's comment: Infections are known adverse events associated with everolimus therapy and may have contributed to the patient's death***
Y2301-0546-00014 **Age 76** **No prior chemotherapy**	Y	76 year old female experienced worsening of pleural effusion on day 16. The patient had thoracentesis but experienced dyspnea and hemoptysis and recurrence of effusion on day 18. The patient withdrew consent and was transferred to a hospice. The patient died on day 30. ***Reviewer's comment: None***
Y2301-0605-00001 Age 58 **No prior chemotherapy**	N	58 year old female experienced dyspnea on day 289. Lung infection was diagnosed on day 295 and a CT scan on day 296 demonstrated bilateral parenchymal opacities in the lung. The patient died on day 300 due to pneumonia. No further information regarding specific tests to distinguish pneumonia from interstitial lung disease. No autopsy was performed. ***Reviewer's comment: Infections are known adverse events associated with everolimus therapy and may have contributed to the patient's death. In addition, the patient may have had pneumonitis leading to respiratory failure and subsequent death.***
Y2301-0615-00003 Age 76	N	76 year old female experienced worsening depression on day 103 of study treatment. The patient also reported decreased oral intake and fatigue. Everolimus therapy was stopped on day 112. On day 122, the patient presented with sepsis and died on the

Patient ID	Progression Confirmed	Narrative and Comments
Prior AC		same day due to sepsis. ***Reviewer's comment: Infections are known adverse events associated with everolimus therapy and may have contributed to the patient's death. In addition, it is unclear from the narrative whether the increased depression the patient experienced may have been decreased appetite and increased fatigue which are known adverse events associated with everolimus therapy.***
Y2301-0746-00001 **Age 82** **No prior chemotherapy**	N	82 year old female experienced asthenia on day 31 and general physical health deterioration (grade 4) and worsening muscular weakness (grade 3) on day 33. The patient died on day 34. No autopsy was performed and no imaging was done to confirm disease progression. Patient's baseline scan showed 6cm hepatic lesion and small pleural effusion. Patient died before follow up imaging. Patient's baseline ECOG performance status was 0. No follow up ECOG scores were noted. ***Reviewer's comment: While general physical health deterioration is not included in the everolimus label, associated symptoms such as fatigue, asthenia, decreased appetite, and weight loss are known adverse events associated with everolimus therapy and may have contributed to the patient's death. The patient's ECOG performance status was 0 on study entry and the patient had one isolated liver metastasis (6cm) with no mention of non-target lesions except for non-measurable pleural effusion.***
Y2301-0200-00003 Age 59 Prior AC, docetaxel, paclitaxel	Y	59 year old female experienced abdominal distention on day 357. Everolimus was discontinued on day 376, and on day 384 the patient was diagnosed with duodenal obstruction. On day 391, the patient underwent esophagogastroduodenoscopy which demonstrated a duodenal mass consistent with metastatic breast cancer. The patient died on day 399 from cardiac arrest.

Patient ID	Progression Confirmed	Narrative and Comments
		Reviewer's comment: Agree with sponsor patient died from disease progression
Y2301-0217-00002 Age 49 Prior AC, docetaxel, paclitaxel	Y	49 year old female experienced change of mental status and convulsions on day 285. The patient underwent CT scan which revealed brain metastasis. The patient died on day 291 secondary to brain metastasis. ***Reviewer's comment: Agree with sponsor patient died from disease progression due to brain metastases.***
Y2301-0345-00009 Age 61 Prior paclitaxel, bevacizumab	Y	61 year old female was documented to have disease progression on day 378 and study treatment was discontinued. Patient was started on Navelbine therapy. On day 394 the patient died due to progressive disease. ***Reviewer's comment: Agree with sponsor patient died from disease progression.***
Y2301-0194-00001 Age 73 Prior AC, 5-FU	Y	73 year old female experienced non-infectious pneumonitits, atrial fibrillation, dyspnea, cough, and compensated cardiac failure on day 15. Everloimus was held and the symptoms resolved by day 25. On day 39, the patient experienced rectal hemorrhage and was admitted. The patient's performance status declined from ECOG 1 to ECOG 3 and CT scan on day 39 demonstrated disease progression. Due to a "reporting error", everolimus was re-initiated on day 51, after a temporary interruption of 8 days. Everolimus was stopped on day 61 and the patient died on day 78 due to "decompensated liver cell failure due to disease progression". ***Reviewer's comments: This is a very complicated case. Notable toxicities experienced by the patient that have been reported with the use of everolimus include pneumonitis, and hemorrhage. Elevated liver enzymes have been associated with the use of everolimus but no overt cases of fulminant hepatic failure leading to death have***

Patient ID	Progression Confirmed	Narrative and Comments
		been reported.
Y2301-0772-00001 Age 67 Prior epirubicin, docetaxel	Y	On Day 330, the patient experienced dyspnea, asthenia (both Grade 4); and was admitted to the hospital with a diagnosis of pleural effusion (Grade 4). The study treatment was temporarily interrupted for two days from Day 331. The patient underwent pleural puncture and port-implantation. On Day 332, a spiral CT scan revealed disease progression (new lesions in the liver and worsening of pleural effusion). The study treatment was not re-initiated and was permanently discontinued due to disease progression; the last dose of the study treatment was received on Day 330. On day 348, 18 days after the last dose of the study treatment, the patient died due to disease progression. The events (dyspnea, asthenia, pleural effusion) were ongoing at the time of patient's death. ***Reviewer's comments: Agree with sponsor patient died from disease progression.***
Y2301-0534-00004 Age 85 Prior arimidex, fulvestrant	N	85 year old discontinued study medication on day 131 for "symptomatic deterioration". Patient's AEs included: muscle weakness, weight loss, anorexia, bone pain, and fatigue. Patient had measureable disease in the lung and in the vertebrae and on the last imaging evaluation, the patient had stable disease. Patient's baseline ECOG performance status was recorded as 0 and remained at 0 through the 12 week assessment. The patient's recorded ECOG status even on the end of treatment visit 19 days after the 12 week assessment was 1. The patient withdrew consent on day 141 and died on day 158. The cause of death was listed as the study indication, but no objective radiologic tests were performed to confirm. Autopsy was not done. Baseline scan with lung lesions x 5 ~2-3cm each, bone lesions in thoracic and lumbar spine and pelvis. 6wk and 12 wk radiologic assessments showed stable disease. ***Reviewer's comments: While general physical health deterioration is not included in the everolimus label, associated symptoms such as fatigue, asthenia, decreased appetite, and weight loss are known adverse events associated with everolimus therapy and may have contributed to the patients death. The patient's last imaging***

Patient ID	Progression Confirmed	Narrative and Comments
		assessment demonstrated stable disease.

There were 4 cases of on-treatment deaths attributed to disease progression but associated with general physical health deterioration or asthenia. Three of these events occurred in patients over 70 years old. There were 3 cases of on-treatment deaths associated with sepsis. All these cases were in patients over the age of 65 and had prior chemotherapy.

Out of 18 (3.7%) on-treatment deaths that occurred on the everolimus arm, 12 (2.5% of total and 6.2% of the patients ≥ 65) occurred in patients ≥ 65 years of age. Of these 12, 9 patients had prior exposure to chemotherapy. Everolimus was considered to have a contributory role in the patient's death in 11 (2.3%) out of the 18 cases.

Cross disease comparison of on-treatment deaths
In the FDA review of everolimus for advanced renal cell cancer it was noted that in the pivotal study there were 21/274 on-treatment deaths (7.7%) compared to 7/131 (5.1%) on the placebo arm. The reviewer considered 5 cases (1.9%) to have been due to an adverse reaction related to everolimus therapy. In the pivotal study used to support the PNET application, there were 12 (5.9%) on-treatment deaths on the everolimus arm as compared to 4 (2.0%) on the placebo arm. The FDA reviewer considered 7 (3.4%) deaths to be related to everolimus therapy. There were no deaths reported on the pivotal trial used to support the SEGA indication.

Table 30: On-treatment Deaths in Other Studies of Everolimus

Indication	On-treatment deaths N (%)	Attributable to everolimus by FDA reviewer N (%)	Mean age of population in years
Breast cancer	18 (3.7)	11 (2.3)	62
RCC	21 (7.7)	5 (1.9)	60
PNET	12 (5.9)	7 (3.4)	57
SEGA	0 (0)	0 (0)	13

Reviewer's comment: On-treatment mortality is the objective number of deaths that occur within 28 days of study drug. The rate of on-treatment mortality in Study Y2301 is higher in the patients on the everolimus arm as compared to the placebo arm (3.7% vs.

1.7%), but when analyzing this data in terms of older (≥ 65) vs. younger (<65) patients, this difference becomes more striking (6.2% vs. 1.3%). Further discussion regarding the differences seen in the elderly vs. non elderly population is found in section 7.3.5.

7.3.2 Nonfatal Serious Adverse Events

Nonfatal serious adverse events occurred in 26.8% of patients on the everolimus arm and 13.9% on the placebo arm. SAEs that occurred in ≥1% of patients on either arm and SAEs by system organ class are summarized in the tables below.

Table 31: Serious Adverse Events Occurring in ≥ 1%, Safety Population, Study Y2301

Serious Adverse Events	Everolimus +exemestane N=482 N (%)	Placebo+ exemestane N=238 N (%)
All Serious AE	129 (26.8)	33 (13.9)
Asthenia	5 (1)	0
Dyspnea	9 (1.9)	2 (0.8)
Pleural Effusion	6 (1.2)	1 (0.4)
Pneumonia	8 (1.2)	2 (0.8)
Pneumonitis	12 (2.5)	0
Pulmonary Embolism	7 (1.5)	1 (0.4)
Pyrexia	6 (1.2)	4 (1.7)

Table 32: Serious Events by System Organ Class (SOC), Safety Population, Study Y2301

Serious Adverse Events	Everolimus +exemestane N=482 N (%)	Placebo+ Exemestane N=238 N (%)
Respiratory, thoracic and mediastinal disorders	35 (7.3)	6 (2.5)
Gastrointestinal disorders	31 (6.4)	4 (1.7)
Infections and infestations	28 (5.8)	5 (2.1)

Serious Adverse Events	**Everolimus +exemestane** **N=482** **N (%)**	**Placebo+ Exemestane** **N=238** **N (%)**
General disorders and administration site conditions	24 (5.0)	4 (1.7)
Metabolism and nutrition disorders	14 (2.9)	1 (0.4)
Nervous system disorders	13 (2.7)	1 (0.4)
Renal and urinary disorders	12 (2.5)	0
Musculoskeletal and connective tissue disorders	10 (2.1)	5 (2.1)
Cardiac disorders	9 (1.9)	1 (0.4)
Blood and lymphatic system disordersCardiac disorders	9 (1.9)	4 (1.7)
Investigations	8 (1.7)	1 (0.4)
Vascular disorders	8 (1.7)	1 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (1.5)	5 (2.1)
Injury, poisoning and procedural complications	6 (1.2)	3 (1.3)
Psychiatric disorders	4 (0.8)	2 (0.8)
Skin and subcutaneous tissue disorders	4 (0.8)	0
Hepatobiliary disorders	3 (0.6)	1 (0.4)

Reviewer's comments: SAEs were experienced at a higher rate on the everolimus arm as compared to the placebo arm in Study Y2301. The rate of SAEs is lower as compared with the rates seen in the RCC and PNET trial. See section 7.3.5 for a discussion of SAEs in the elderly vs. the non-elderly population.

7.3.3 Dropouts and/or Discontinuations

Specific adverse events leading to treatment discontinuation are summarized in Table 33 below. On the everolimus arm 23.7% of the patients permanently discontinued treatment due to adverse events as compared to 4.6% of patients on the placebo arm.

Table 33: Adverse Events Leading to Permanent Discontinuation (> 0.5%), Safety Population, Study Y2301

Adverse Events Leading to Discontinuation	**Everolimus +exemestane** **N=482** **N (%)**	**Placebo+ exemestane** **N=238** **N (%)**
Any AE leading to discontinuation	114 (23.7)	12 (5.0)
Pneumonitis	21 (4.4)	0
Stomatitis	12 (2.5)	0
Dyspnoea	9 (1.9)	0
Fatigue	9 (1.9)	0
Anaemia	8 (1.7)	1 (0.4)
Decreased appetite	8 (1.7)	1 (0.4)
Rash	7 (1.5)	
Aspartate aminotransferase increased	6 (1.2)	3 (1.2)
Gamma-glutamyltransferase increased	6 (1.2)	4 (1.7)
Interstitial lung disease	6 (1.2)	0
Alanine aminotransferase increased	5 (1.0)	2 (0.8)
Blood creatinine increased	5 (1.0)	0
Nausea	5 (1.0)	0
General physical health deterioration	4 (0.8)	0
Oedema peripheral	4 (0.8)	0
Asthenia	3 (0.6)	0
Diarrhoea	3 (0.6)	0

Adverse Events Leading to Discontinuation	Everolimus +exemestane N=482 N (%)	Placebo+ exemestane N=238 N (%)
Headache	3 (0.6)	0
Vomiting	3 (0.6)	0

Table 34 shows adverse events grouped by system organ class leading to permanent treatment discontinuation.

Table 34: Adverse Events Leading to Permanent Discontinuation by System Organ Class (SOC), Safety Population, Study Y2301

Adverse Events Leading to Discontinuation	Everolimus +exemestane N=482 N (%)	Placebo+ exemestane N=238 N (%)
Any AE leading to discontinuation	114 (23.7)	12 (5.0)
Respiratory, thoracic and mediastinal disorders	40 (8.3)	0
Gastrointestinal disorders	24 (5.0)	1 (0.4)
Infections and infestations	4 (0.8)	1 (0.4)
General disorders and administration site conditions	20 (4.1)	0
Metabolism and nutrition disorders	11 (2.3)	1 (0.4)
Nervous system disorders	6 (1.2)	0
Renal and urinary disorders	2 (0.4)	0
Musculoskeletal and connective tissue disorders	4 (0.8)	0
Cardiac disorders	3 (0.6)	0
Blood and lymphatic system disordersCardiac	10 (2.1)	1 (0.4)

Adverse Events Leading to Discontinuation	**Everolimus +exemestane N=482 N (%)**	**Placebo+ exemestane N=238 N (%)**
disorders		
Investigations	16 (3.3)	6 (2.5)
Vascular disorders	2 (0.4)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (0.8)	1 (0.4)
Injury, poisoning and procedural complications	0	0
Psychiatric disorders	0	0
Skin and subcutaneous tissue disorders	11 (2.3)	0

Reviewer's comments: There was no singular toxicity that led to permanent discontinuation in Study Y2301, yet 24% of the patients on the everolimus arm permanently discontinued treatment due to adverse event.

7.3.4 Significant Adverse Events

This list of clinically notable AEs was pre-specified in the analysis plan and included the following categories of events: stomatitis/oral mucositis/ulcers, infections and infestations, cytopenias, hemorrhages, non-infectious pneumonitis, hyperglycemia/new-onset diabetes mellitus, renal events, rash and similar events, thromboembolism, and hypersensitivity reactions (anaphylactic reactions).

Table 35: Notable Adverse Events, Safety Population, Study Y2301

Adverse Events	Everolimus + exemestane N=482 N (%)		Placebo+ exemestane N=238 N (%)	
Grade	**All Grades**	**Grade 3 & 4**	**All Grades**	**Grade 3 & 4**
Stomatitis[1]	321 (66.6)	39 (8.1)	27 (11.3)	2 (0.8)
Infections	243 (50.4)	28 (5.8)	60 (25.2)	4 (1.7)
Rash	212 (44.0)	9 (1.9)	20 (8.4)	1 (0.4)
Cytopenias	110 (22.8)	27 (5.6)	12 (5.0)	6 (2.5)
Hemorrhages	107 (22.2)	10 (2.1)	14 (5.9)	2 (0.8)
Pneumonitis[2]	90 (18.7)	18 (3.7)	1 (0.4	0
Hyperglycemia	74 (15.4)	26 (5.4)	6 (2.5)	2 (0.8)
Renal events	50 (10.4)	18 (3.7)	2 (0.8)	0
Thromboembolism	22 (4.6)	13 (2.7)	2 (0.8)	1 (0.4)
Hypersensitivity Reactions	5 (1.0)	1 (0.2)	2 (0.8)	0

1. Stomatitis as defined using the PT: Stomatitis, Mouth Ulceration, Apthous Stomatitis, Glossodynia, Gingival pain, Glossitis, Lip Ulceration.
2. Pneumonitis as defined using the PT: Pneumonitis, Interstitial lung disease, Lung infitltration, Pulmonary fibrosis.

Reviewer's comments: As discussed in section 7.1.2, the rates of these notable AEs are similar to the rates seen in the RCC and PNET trials. See section 7.3.5 for a more in depth discussion.

7.3.5 Submission Specific Primary Safety Concerns

During the course of the safety review, it became apparent that the toxicity profile of everolimus differed between age groups. As compared to the patients on the everolimus arm < 65 years of age, patients ≥ 65 on the everolimus arm experienced a higher rate of overall deaths (30% vs. 19%), higher rates of on-treatment mortality (6% vs 2%), higher rates of SAEs, grade 3-4 AEs, and AEs leading to permanent discontinuation (32% vs. 23%, 57% vs. 45%, and 33% vs. 17% respectively), and lower median progression free survival (6.8 vs. 8.3 months). This pattern was not apparent in the placebo arm as the rate of overall deaths and on-treatment mortality was similar between the age groups (31% vs. 28%, and 1.3% vs. 1.9% respectively). The rates of AEs were likewise similar and the ≥ 65 year old population had a longer median PFS as compared to the < 65 year old population (4.0 vs. 2.9 months). The table below summarizes the efficacy and safety parameters of Study Y2301 in terms of age grouping.

Table 36: Use in the elderly (≥ 65 years old) population, Study Y2301

Adverse Event:	**Everolimus + Exemestane** **N (%)** 482	**Placebo+ Exemestane** **N (%)** 238
Total Deaths	112 (23)	70 (29)
On Treatment Deaths	18 (3.7)	4 (1.7)
Median Progression Free Survival (mo)	7.8	3.2
Any grade 3 or 4 AE	239 (49.6)	65 (29.3)
Serious AE	129 (26.8)	33 (13.9)
Adverse Events Requiring Permanent Dose Discontinuation	115 (23.7)	11 (4.6)
Age <65 (N=438)	290	158
Total Deaths*	54 (18.6)	45 (28.3)
On Treatment Deaths	6 (2.0)	3 (1.9)
Median Progression Free Survival (mo)*	8.31	2.92
Any Serious AE	67 (23.1)	24 (15.2)
Any Grade 3 and 4	129 (44.5)	46 (27.7)
AE leading to permanent discontinuation	50 (17.2)	9 (5.7)
Age ≥ 65 (N=272)	192	80
Total Deaths*	58 (29.7)	25 (31.3)
On Treatment Deaths	12 (6.2)	1 (1.3)
Median Progression Free Survival (mo)*	6.83	4.01
Any Serious AE	62 (32.3)	9 (11.3)
Any Grade 3 and 4	110 (57.3)	19 (26.4)
AE leading to permanent discontinuation	64 (33.3)	3 (3.8)

*Full analysis datasets were used to generate these percentages

Grade 3 and 4 toxicities and SAEs were higher in the elderly population in similar proportions in both arms in the PNET and RCC trials as seen in the tables below.

Table 37: Use in the elderly (≥ 65 years old) population PNET C2324

Adverse Event:	**Everolimus 10mg** **N (%)**	**Placebo** **N (%)**
All Patients	204	203
Any grade 3 or 4 AE	**122 (60)**	**79 (39)**
Serious AE	**82 (40)**	**50 (25)**

Adverse Event:	**Everolimus 10mg N (%)**	**Placebo N (%)**
Age <65	**146**	**153**
Any Serious AE	57 (39)	33 (22)
Any Grade 3 and 4	78 (53)	54 (35)
Age ≥ 65	**61**	**50**
Any Serious AE	25 (41)	17 (34)
Any Grade 3 and 4	44 (72)	25 (50)

Table 38: Use in the Elderly (≥ 65 years old) population, RCC C2440C2440

Adverse Event:	**Everolimus 10mg N (%)**	**Placebo N (%)**
All Patients	274	137
Any grade 3 or 4 AE	**178 (65)**	**39 (29)**
Serious AE	**110 (40)**	**31 (23)**
Age <65	**163**	**98**
Any Serious AE	68 (42)	24 (24)
Any Grade 3 and 4	103 (63)	30 (31)
Age ≥ 65	**111[1]**	**39[2]**
Any Serious AE	42 (39)	7 (18)
Any Grade 3 and 4	75 (68)	9 (23)

Table 39: Notable Adverse Events by Age Group, Safety Population, Study Y2301

Adverse Events	**Everolimus +exemestane Age < 65, N=290 N (%)**		**Everolimus +exemestane Age ≥ 65 N=192 N (%)**	
Grade	**All Grades**	**Grade 3&4**	**All Grades**	**Grade 3&4**
Stomatitis[1]	203 (70)	21 (7)	118 (61)	18 (9)
Infections	148 (51)	16 (6)	95 (50)	12 (6)
Rash	138 (48)	6 (2)	74 (39)	3 (2)
Cytopenias	67 (23)	16 (6)	43 (22)	11 (6)
Hemorrhages	57 (20)	4 (1)	48 (25)	6 (3)
Pneumonitis[2]	53 (18)	6 (2)	37 (19)	12 (6)
Hyperglycemia	49 (17)	12 (4)	25 (13)	14 (7)
Renal events	20 (7)	8 (3)	29 (15)	10 (5)

Adverse Events	Everolimus +exemestane Age < 65, N=290 N (%)		Everolimus +exemestane Age ≥ 65 N=192 N (%)	
Grade	**All Grades**	**Grade 3&4**	**All Grades**	**Grade 3&4**
Thromboembolism	4 (1)	3 (1)	17 (9)	9 (5)
Hypersensitivity Reactions	5 (2)	1 (0.3)	0	0
General Physical Health Deterioration	4 (1)	3 (1)	6 (3)	4 (2)
Anorexia/Decreased Appetite	80 (28)	2 (1)	65 (34)	3 (2)
Asthenia/Fatigue	125 (43)	11 (4)	97 (51)	19 (10)
Muscular Weakness	4 (1)	0	3 (2)	2 (1)
Weight Decreased	71 (24)	3 (1)	48 (25)	3 (2)

1. Stomatits as defined using the PT: Stomatitis, Mouth Ulceration, Apthous Stomatitis, Glossodynia, Gingival pain, Glossitis, Lip Ulceration.
2. Pneumonitis as defined using the PT: Pneumonitis, Interstitial lung disease, Lung infitltration, Pulmonary fibrosis.

Table 40: Adverse Event: General Physical Health Deterioration, Safety Population, Study Y2301

Adverse Event: Where GPHD = PT: General Health Physical Deterioration, Anorexia, Decreased Appetite, Asthenia, Fatigue, Lethargy, Muscular Weakness, Weight Decreased	Everolimus + Exemestane N (%)	Placebo+ Exemestane N (%)
All Patients (N=720)	482	238
GPHD as a Serious AE	13 (3)	2 (0.8)
GPHD as Grade 3 and 4	41 (9)	4 (0.8)
Age <65 (N=455)	290	158
GPHD as a Serious AE	6 (2)	1 (1)
GPHD as Grade 3 and 4	17 (6)	2 (1)
Age ≥ 65 (N=265)	192	80
GPHD as a Serious AE	7 (4)	1 (1)
GPHD as Grade 3 and 4	24 (12)	2 (3)

Everolimus in Elderly HR+ Breast Cancer Patients:

In Study Y2301, there were 18 on-treatment deaths noted in the everolimus arm. In patients ≥ 65 years of age, 12 of these deaths occurred on the everolimus arm compared to 1 on the placebo arm. Three patients who died on the everolimus arm were over the age of 65 and experienced general physical health deterioration as manifested by anorexia, decreased appetite, asthenia, fatigue, lethargy, muscular weakness, and/or weight loss (Y2301-0534-00004, Y2301-0746-00001, Y2301-0534-00008). All 3 of these deaths were attributed to breast cancer; however, no objective radiologic findings were available to confirm this, and in 2 of the patients, their last imaging scans were noted to show stable disease. Grade 3-4 events related to general physical health deterioration occurred at a higher rate in the patients ≥ 65 years old who received everolimus compared to those ≥ 65 years old who received placebo (12% vs. 3%). These events also occurred at a higher rate in patients who received everolimus who were ≥ 65 years old compared to the patients < 65 years old who also received everolimus (12% vs. 6%) (table 3). In addition, 3 patients on the everolimus arm who were ≥ 65 years old were reported to have sepsis and had a fatal outcome in the treatment window. In 2 of these patients, sepsis was the listed cause of death (Y2301-0615-00003, Y2301-0545-00001). In the other patient, sepsis preceded an ischemic cerebrovascular event which was the listed cause of death (Y2301-0317-00014). All 3 of these patients had been exposed to prior chemotherapy. No cases of sepsis with fatal outcome were reported on the placebo arm, although we do note that there was a fatal pneumonia seen on the placebo arm. Cases of sepsis with fatal outcome were also reported in the RCC and PNET applications.

The mTOR pathway plays a critical role of regulating energy metabolism in normal cells and non-clinical studies demonstrate that the inhibition of the mTORC1 pathway leads to dysregulation of cellular metabolism and impaired protein synthesis and adipogenesis. The inhibition of protein synthesis has been linked to the immunosuppressive properties of everolimus and could also explain signs and symptoms such as fatigue, asthenia, weakness, general physical health deterioration, weight loss, and dysregulated glucose and triglyceride levels, which are all adverse reactions associated with the use of everolimus. Conceivably, dysregulation of synthesis of clotting factors such as Protein C and Protein S or Antithrombin may also explain why there appears to be associated toxicities of both bleeding and thrombosis that is unrelated to thrombocytopenia related to everolimus treatment. The question arises as to what is the contribution of exemestane to the toxicity profile of everolimus in the elderly population. As a whole, exemestane is well tolerated in the elderly population, but when combined with an mTOR inhibitor, do the decreased levels of estradiol, which itself play a role in the aging process, act to add to the toxicity profile of everolimus, especially in the areas of fatigue, asthenia, and muscle weakness? This will potentially be answered in the postmarketing study described in section 1.4. While there is no singular toxicity that appears to place elderly patients at risk for serious and potentially fatal outcomes, there were higher rates of on-treatment deaths, SAEs, grade 3 and 4 AEs, and AEs leading to permanent treatment discontinuation that prescribing physicians and patients should be aware of. Physicians and patients will be made aware of the higher incidence of on-treatment mortality and AEs leading to permanent

discontinuation seen in the elderly population in the HR+ Breast Cancer in the Warnings and Precautions and the Geriatric Use section of the label.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

More patients on the everolimus arm experienced grade 1-4 and grade 3-4 adverse events. The most common adverse events organized by SOC and by preferred term are included in Table 41 and Table 42. The most common grade 1-4 adverse events in everolimus treated patients were: stomatitis, rash, fatigue, diarrhoea, decreased appetite, nausea, cough, dysgeusia, headache, weight decreased, dyspnoea, arthralgia, anaemia, epistaxis, vomiting, oedema peripheral, and pyrexia.

Table 41: Adverse Events by System Organ Class (SOC), Safety Population, Study Y2301

System Organ Class	Everolimus +exemestane N=482 N (%)	Placebo+ Exemestane N=238 N (%)
Gastrointestinal disorders	437 (90.7)	135 (56.7)
Skin and subcutaneous tissue disorders	318 (66.0)	51 (21.4)
General disorders and administration site conditions	314 (65.1)	96 (40.3)
Respiratory, thoracic and mediastinal disorders	284 (58.9)	63 (26.5)
Nervous system disorders	249 (51.7)	71 (29.8)
Metabolism and nutrition disorders	236 (49.0)	42 (17.6)
Musculoskeletal and connective tissue disorders	251 (52.1)	117 (49.2)
Infections and infestations	243 (50.4)	60 (25.2)
Investigations	228 (47.3)	61 (25.6)

System Organ Class	Everolimus +exemestane N=482 N (%)	Placebo+ Exemestane N=238 N (%)
Blood and lymphatic system disorders	172 (35.7)	20 (8.4)
Psychiatric disorders	119 (24.7)	36 (15.1)
Vascular disorders	113 (23.4)	49 (20.6)
Eye Disorders	61 (12.7)	22 (9.2)
Injury, poisoning and procedural complications	51 (10.6)	19 (8.0)
Renal and urinary disorders	48 (10.0)	7 (2.9)
Cardiac disorders	36 (7.5)	8 (3.4)
Ear and labyrinth disorders	29 (6.0)	11 (4.6)
Reporoductive system and breast disorders	28 (5.8)	10 (4.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	20 (4.1)	13 (5.5)
Immune system disorders	13 (2.7)	6 (2.5)
Hepatobiliary disorders	15 (3.1)	8 (3.4)
Surgical and medical procedures	6 (1.2)	1 (0.4)
Social circumstances	2 (0.4)	0
Endocrine disorders	1 (0.2)	0

Table 42: Adverse Events by Preferred Term (>10% incidence), Safety Population, Study Y2301

Preferred Term	Everolimus +exemestane N=482 N (%)	Placebo+ Exemestane N=238 N (%)
Stomatitis	282 (58.5)	26 (10.9)
Rash	186 (38.6)	15 (6.3)

Preferred Term	Everolimus +exemestane N=482 N (%)	Placebo+ Exemestane N=238 N (%)
Fatigue	172 (35.7)	65 (27.3)
Diarrhoea	158 (32.8)	44 (18.5)
Decreased appetite	145 (30.1)	28 (11.8)
Nausea	139 (28.8)	66 (27.7)
Cough	118 (24.5)	28 (11.8)
Dysgeusia	104 (21.6)	14 (5.9)
Headache	103 (21.4)	34 (14.3)
Weight decreased	119 (24.7)	15 (6.3)
Dyspnoea	99 (20.5)	25 (10.5)
Arthralgia	94 (19.5)	40 (16.8)
Anaemia	96 (19.9)	10 (4.2)
Epistaxis	83 (17.2)	3 (1.3)
Vomiting	80 (16.6)	29 (12.2)
Oedema peripheral	92 (19.1)	15 (6.3)
Pyrexia	73 (15.1)	16 (6.7)
Hyperglycaemia	66 (13.7)	5 (2.1)
Aspartate aminotransferase increased	65 (13.5)	13 (5.5)
Constipation	67 (13.9)	32 (13.4)
Pneumonitis	72 (14.9)	0
Thrombocytopenia	61 (12.7)	1 (0.4)
Asthenia	65 (13.5)	9 (3.8)
Alanine aminotransferase increased	57 (11.8)	10 (4.2)
Pruritus	63 (13.1)	11 (4.6)
Insomnia	65 (13.5)	19 (8.0)
Back pain	66 (13.7)	23 (9.7)
Dry mouth	51 (10.6)	16 (6.7)
Alopecia	49 (10.2)	11 (4.6)
Pain in extremity	41 (8.5)	27 (11.3)
Hot flush	27 (5.6)	34 (14.3)

Table 43 describes the most common grade 3-4 adverse events. The most common grade 3-4 adverse events in everolimus-treated patients were: stomatitis, anemia,

increased GGT, hyperglycemia, dyspnea, fatigue, ALT increased, AST increased, pneumonitis, hypokalemia, thrombocytopenia, neutropenia, and diarrhea.

Table 43: Grade 3-4 Adverse Events by Preferred Term (>1% incidence), Safety Population, Study Y2301

Preferred Term	Everolimus +exemestane N=482 N (%)	Placebo+ Exemestane N=238 N (%)
Stomatitis	38 (7.9)	2 (0.8)
Anaemia	35 (7.3)	2 (0.8)
Gamma-glutamyltransferase increased	27 (5.6)	16 (6.7)
Hyperglycaemia	26 (5.4)	1 (0.4)
Dyspnoea	21 (4.4)	3 (1.3)
Fatigue	21 (4.4)	3 (1.3)
Alanine aminotransferase increased	16 (3.3)	5 (2.1)
Aspartate aminotransferase increased	16 (3.3)	3 (1.3)
Pneumonitis	16 (3.3)	0
Hypokalaemia	14 (2.9)	2 (0.8)
Thrombocytopenia	14 (2.9)	1 (0.4)
Neutropenia	11 (2.3)	3 (1.3)
Diarrhoea	10 (2.0)	2 (0.8)
Asthenia	9 (1.9)	0
General physical health deterioration	7 (1.5)	0
Pulmonary embolism	7 (1.5)	1 (0.4)
Renal failure	7 (1.5)	0
Blood creatinine increased	6 (1.2)	0
Bone pain	6 (1.2)	3 (1.3)
Pneumonia	6 (1.2)	2 (0.8)
Rash	6 (1.2)	1 (0.4)
Weight decreased	6 (1.2)	0
Alanine aminotransferase increased	5 (1.0)	5 (2.1)

Preferred Term	Everolimus +exemestane N=482 N (%)	Placebo+ Exemestane N=238 N (%)
Decreased appetite	5 (1.0)	1 (0.4)
International normalised ratio increased	5 (1.0)	0
Oedema peripheral	5 (1.0)	1 (0.4)
Vomiting	5 (1.0)	2 (0.8)
Blood alkaline phosphatase increased	1 (0.2)	4 (1.7)
Pain in extremity	2 (0.4)	4 (1.7)
Nausea	2 (0.4)	3 (1.3)
Hepatic enzyme increased	0	3 (1.3)

7.4.2 Laboratory Findings

Laboratory adverse events are summarized in Table 44 below.

Table 44: Laboratory Grade 1-4 Adverse Events in >10% in Either Arm, Safety Population, Study Y2301

Laboratory AE	Everolimus + exemestane N=482		Placebo+ Exemestane N=238	
	Grade 1-4 N (%)	Grade 3-4 N (%)	Grade 1-4 N (%)	Grade 3-4 N(%)
Hypercholesterolemia	201 (41.7)	4 (0.8)	25 (10.5)	4 (1.7)
Hyperglycemia	287 (59.5)	41 (8.5)	64 (26.9)	3 (1.3)
Increased Alkaline Phosphatase	93 (19.3)	4 (0.8)	64 (26.9)	8 (3.4)
Increased ALT	219 (45.4)	21 (4.4)	56 (23.5)	11 (4.6)
Increased GGT	214 (44.4)	48 (10.0)	100 (42.0)	35 (14.7)
Increased AST	270 (56.0)	20 (4.1)	81 (34.0)	9 (3.8)
Increased Bilirubin	17 (3.5)	4 (0.8)	22 (9.2)	2 (0.8)
Increased Creatinine	101 (21.0)	11 (2.3)	22 (9.2)	0
Hypokalemia	134 (27.8)	20 4.1)	12 (5.0)	3 (1.3)

Laboratory AE	Everolimus + exemestane N=482		Placebo+ Exemestane N=238	
	Grade 1-4 N (%)	Grade 3-4 N (%)	Grade 1-4 N (%)	Grade 3-4 N(%)
Hyperkalemia	29 (6.0)	3 (0.6)	24 (10.1)	1 (0.4)
Hypercalcemia	24 (5.0)	0	14 (5.9)	0
Decreased Hemoglobin	281 (58.3)	30 (6.2)	56 (23.5)	3 (1.3)
Decreased Lymphocytes	221 (45.9)	50 (10.4)	57 (23.9)	12 (5.0)
Hypoalbuminemia	135 (28.0)	4 (0.8)	33 (13.9)	2 (0.8)
Hypertriglyceridemia	182 (37.8)	4 (0.8)	26 (10.9)	0
Hypocalcemia	135 (28.0)	3 (0.6)	27 (11.3)	2 (0.8)
Decreased Neutrophils	143 (29.7)	11 (2.3)	22 (9.2)	4 (1.7)
Decreased WBCs	258 (53.5)	7 (1.5)	45 (18.9)	2 (0.8)
Decreased Platelets	246 (51.0)	15 (3.1)	7 (2.9)	1 (0.4)
Hyponatremia	68 (14.1)	14 (2.9)	34 (14.3)	5 (2.1)
Hypernatremia	50 (10.4)	0	11 (4.6)	0
Hyperbilirubinemia	17 (3.5)	4 (0.8)	22 (9.2)	2 (0.8)
Hypoglycemia	12 (2.5)	1 (0.2)	6 (2.5)	0

7.4.3 Vital Signs

Changes in vital signs, weight, and physical exam that were considered to be abnormal (by the investigator) were reported as AEs and graded as per NCI CTCAE v.3.0. Differences in vital signs between treatment groups were not considered to be clinically noteworthy. No appreciable changes in mean systolic and diastolic blood pressure were recorded at any time during the two pivotal studies for either treatment group. No significant changes in pulse, respiratory rate, or temperature were noted. More patients experienced weight loss of > 10% on the everolimus arm as compared to placebo.

Table 45: Weight Decreased > 10%, Safety Population, Study Y2301

Weight Decreased > 10%:	Everolimus + exemestane N=482 N (%)	Placebo+ Exemestane N=238 N (%)

All Patients	117 (24.3)	13 (5.5)
Age <65	70 (24.1)	8 (5.1)
Age ≥ 65	47 (24.5)	5 (6.3)

7.4.4 Electrocardiograms (ECGs)

Changes in ECG findings that were considered to be abnormal were reported as adverse events and graded as per NCI CTCAE, v.3.0. They were reported at baseline and subsequently at the investigator's discretion. No untoward ECG changes were recorded during the two pivotal studies.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable

7.4.6 Immunogenicity

See section 7.3.4 regarding data on hypersensitivity reactions.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See the Clinical Pharmacology Review

7.5.2 Time Dependency for Adverse Events

See the Clinical Pharmacology Review

7.5.3 Drug-Demographic Interactions

Table 46: Adverse Events by Race, Safety Population, Study Y2301

Adverse Events	Everolimus + exemestane N=482			
Race	**Caucasian N=358**	**Asian N=98**	**Black N=13**	**Other N=13**
	N (%)	**N (%)**	**N (%)**	**N (%)**
Stomatitis[1]	227 (63)	81 (83)	5 (38)	8 (62)
Infections	184 (51)	46 (47)	5 (38)	8 (62)
Rash	157 (44)	48 (49)	4 (31)	3 (23)
Cytopenias	74 (21)	30 (31)	3 (23)	3 (23)
Hemorrhages	80 (22)	19 (19)	3 (23)	5 38)
Pneumonitis[2]	55 (13)	30 (31)	2 (15)	3 (23)
Hyperglycemia	56 (16)	4 (4)	11 (85)	3 (23)
Renal events	37 (10)	1 (1)	10 (77)	2 (15)
Thromboembolism	19 (5)	1 (1)	1 (8)	1 (8)
Hypersensitivity Reactions	4 (1)	0 (0)	0 (0)	1 (8)

1. Stomatits as defined using the PT: Stomatitis, Mouth Ulceration, Apthous Stomatitis, Glossodynia, Gingival pain, Glossitis, Lip Ulceration.
2. Pneumonitis as defined using the PT: Pneumonitis, Interstitial lung disease, Lung infitltration, Pulmonary fibrosis.

See section 7.3.5 for a discussion on adverse events by age.

All the patients enrolled in Study Y2301 were women, so an analysis of AEs by gender was not done.

7.5.4 Drug-Disease Interactions

See the Clinical Pharmacology review, as well as section 7.3.5.

7.5.5 Drug-Drug Interactions

See the Clinical Pharmacology review. The co-administration of everolimus and exemestane increased the concentrations of exemestane. There are no apparent increases in the adverse events typically seen with aromatase inhibitors except for a small increase in the incidence of grade 1-4 arthralgia (19.5% vs. 16.8%) which is not clinically significant. It is unknown whether the increased concentrations of exemestane resulted in improvements in the efficacy parameters.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

See the Pharmacology/Toxicology review. No additional human carcinogenicity data were submitted with this sNDA. The current product labeling states the following:

"Administration of everolimus for up to 2 years did not indicate oncogenic potential in mice and rats up to the highest doses tested (0.9 mg/kg) corresponding respectively to 3.9 and 0.2 times the estimated clinical exposure (AUC_{0-24h}) at the 10 mg daily human dose .

Everolimus was not genotoxic in a battery of *in vitro* assays (Ames mutation test in *Salmonella,* mutation test in L5178Y mouse lymphoma cells, and chromosome aberration assay in V79 Chinese hamster cells). Everolimus was not genotoxic in an *in vivo* mouse bone marrow micronucleus test at doses up to 500 mg/kg/day (1500 mg/m^2/day, approximately 255-fold the 10 mg daily human dose and 103-fold the maximum dose administered to patients with SEGA, based on the body surface area), administered as two doses, 24 hours apart.

Based on non-clinical findings, male fertility may be compromised by treatment with AFINITOR. In a 13-week male fertility study in rats, testicular morphology was affected at 0.5 mg/kg and above. Sperm motility, sperm count, and plasma testosterone levels were diminished in rats treated with 5 mg/kg. These doses result in exposures which are 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 resulted in infertility in the rats at 5 mg/kg. Effects on male fertility occurred at the AUC_{0-24h} values below that of therapeutic exposure (approximately 10%-81% of the AUC_{0-24h} in patients receiving the 10 mg daily dose). After a 10-13 week non-treatment period, the fertility index increased from zero (infertility) to 60% (12/20 mated females were pregnant).

Oral doses of everolimus in female rats at ≥0.1 mg/kg (approximately 4% the AUC_{0-24h} in patients (b) (4) 10 mg daily) resulted in increases in pre-implantation loss, suggesting that the drug may reduce female fertility. Everolimus crossed the placenta and was toxic to the conceptus."

7.6.2 Human Reproduction and Pregnancy Data

No additional human reproduction or pregnancy data were submitted with this sNDA. Everolimus is classified as Pregnancy Category D. The current product labeling states the following:

"There are no adequate and well-controlled studies of AFINITOR in pregnant women. However, based on the mechanism of action, AFINITOR may cause fetal harm when administered to a pregnant woman. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to use an effective method of contraception while receiving AFINITOR and for up to 8 weeks after ending treatment.

In animal reproductive studies, oral administration of everolimus to female rats before mating and through organogenesis induced embryo-fetal toxicities, including increased resorption, pre-implantation and post-implantation loss, decreased numbers of live fetuses, malformation (e.g., sternal cleft), and retarded skeletal development. These effects occurred in the absence of maternal toxicities. Embryo-fetal toxicities occurred at (b) (4) in patients receiving the 10 mg daily dose. In rabbits, embryotoxicity evident as an increase in resorptions occurred at an oral dose approximately 1.6 times the 10 mg daily human dose, and 0.7 times the maximum dose administered to SEGA patients on a body surface area basis. The effect in rabbits occurred in the presence of maternal toxicities.

In a pre- and post-natal development study in rats, animals were dosed from implantation through lactation. (b) (4) approximately 10% (based on body surface area) of those achieved with the 10 mg daily human dose or 4% of the maximum dose administered to SEGA (b) (4) no adverse effects on delivery and lactation and there were no signs of maternal toxicity. However, there was reduced body weight (up to 9% reduction from the control) and slight reduction in survival in offspring (~5% died or missing). There were no drug-related effects on the developmental parameters (morphological development, motor activity, learning, or fertility assessment) in the offspring.

Doses that resulted in embryo-fetal toxicities in rats and rabbits were ≥0.1 mg/kg (0.6 mg/m^2) and 0.8 mg/kg (9.6 mg/m^2), respectively. The dose in the pre- and post-natal development study in rats that caused reduction in body weights and survival of offspring was 0.1 mg/kg (0.6 mg/m^2)."

7.6.3 Pediatrics and Assessment of Effects on Growth

No new pediatric or growth assessment data were provided with this sNDA There is clinical experience with everolimus in pediatric patients, including a labeled indication for pediatric patients age $\geq$ 3 years old with tuberous sclerosis and subependymal giant cell astrocytoma who are not candidates for surgical intervention.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No new data were submitted, and reported experience with human overdose is very limited. Per the existing label, the acute toxicity profile for single doses of up to 70 mg is similar to that of the 10 mg dose.

8 Postmarket Experience

The most recent periodic safety update report encompasses the period of 01 Jan 2012 – 31 Mar 2012. A total of 497 initial and follow-up reports were received from US and non-US sources that were submitted to the FDA as 15-day alerts during the reporting period. Of these, 260 were initial reports and 237 were follow-up reports.
During this reporting period, there were a total of 145 reports with a fatal outcome. Most cases were reported as death due to unknown or unreported causes. There are cases with noted infectious processes and renal failure; however, causality cannot be attributed given the information provided. There were 92 domestic and 168 foreign initial reports of serious but unlabeled events. There are no events noted in this report that alters the assessment of the safety profile of everolimus in combination with exemestane in HR+ advanced breast cancer.

9 Appendices

9.1 Literature Review/References

The following sources were used as background materials for the review of the sNDA:

Bachelot T, Bourgier C, Cropet C, et al. Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors: A GINECO study. J Clin Oncol 2012; epub ahead of print May 7, 2012.

Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone receptor-positive advanced breast cancer. N Engl J Med 2011; 366: 520-529.

Baselga J, Semiglazov V, van Dam P, et al. Phase II randomized study of neoadjuvant everolimus plus letrozole compared with placebo plus letrozole in patients with estrogen receptor-positive breast cancer. J Clin Oncol 2009; 27: 2630-2637.

Chia S, Gradishar W, Mauriac L, et al. Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT. J Clin Oncol 2008; 26: 1664-1670.

Ellard SL, Clemons M, Gelmon K, et al. Randomized phase II study comparing two schedules of everolimus in patients with recurrent/metastatic breast cancer. J Clin Oncol 2009; 27: 4536-4541.

Lonning P, Bajetta E, Murray R, et al. Activity of exemestane in metastatic breast cancer after failure of nonsteroidal aromatase inhibitors: a phase II trial. J Clin Oncol 2000; 18: 2234-2244.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: breast cancer (Version 1.2012).
http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

Laplante M, Sabatini D. mTOR Signaling in Growth Control and Disease. Cell 2012; 149: 274-293.

9.2 Labeling Recommendations

The following major labeling issues in clinical labeling were identified:

(b) (4)

(b) (4)

- New listings in the Warnings & Precautions and Geriatric Use were added to highlight the different safety profiles seen in the elderly advanced breast cancer population and to encourage closer monitoring of these patients.

9.3 Advisory Committee Meeting

An Oncologic Drugs Advisory Committee meeting was not convened. A Divisional Assignment was conducted using a special government employee, Dr. Deborah Armstrong, who had been cleared of any conflicts of interest. She was provided an overview of the efficacy and safety data from the FDA review of Study Y2301 and asked to comment on whether the benefit/risk ratio for the addition of everolimus to exemestane was favorable for a population of postmenopausal women with hormone receptor-positive advanced breast cancer after failure of (b) (4) She agreed with the review team that the available data supported regular approval of everolimus in the indication. She was also asked to comment on the proposed postmarketing commitment to conduct a three-arm randomized trial comparing everolimus plus exemestane versus everolimus monotherapy versus capecitabine monotherapy. She again concurred with the review team that this trial would be of value to determine the contribution of exemestane to the observed efficacy of the combination in view of the low response rate to exemestane monotherapy observed in Study Y2301. She also concurred with the review team that a trial comparing the combination to single-agent chemotherapy would be very beneficial to determine the appropriate placement of this combination in clinical practice in view of the toxicity of the combination, although she suggested that the trial may be of greater feasibility and relevance if the chemotherapy arm included a choice of either weekly paclitaxel or capecitabine.

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/s/

TANYA M PROWELL
07/16/2012

GEOFFREY S KIM
07/16/2012

PATRICIA CORTAZAR
07/16/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-334/S-016

CHEMISTRY REVIEW(S)

Chemistry Review: #1	**1. Division:** HFD-150	**2. NDA Number:** **22-334**
3. Name and Address of Applicant: Norvatis Pharmaceuticals Corporation One Health plaza East Hanover, NJ 07936-1080		**4. Supplement(s): PA** **Number:** 016 **Date(s): 03-NOV-2011**
5. Name of Drug: AFFINITOR®		**6. Nonproprietary name:** Everolimus
7. Supplement Provides for the treatment of postmenopausal women (b) (4) [redacted]		**8. Amendment(s):** N/A
9. Pharmacological Category: Postmenopausal (b) (4) [redacted]	**10. How Dispensed:** R_x	**11. Related Documents:** **N/A**
12. Dosage Form: Tablets	**13. Potency:** 2.5 mg, 5 mg, 7.5 mg and 10 mg	

14. Chemical Name and Structure:

(b) (4) [redacted]

Molecular Formula: $C_{53}H_{83}NO_{14}$ Molecular Weight: 958.22

(b) (4) [redacted]

16. Comments:

This PA supplement provides for the treatment of postmenopausal women (b) (4) [redacted] No change has been made or is planned to the CMC information of the proposed indication with the exception of batch information. The Clinical Trial Formulae (CTFO) document, which lists batch related information for all the batches used in the clinical studies, has been updated to include those batches that were used in clinical studies in support of the new indication. There is no CMC changes involved in the labeling. The sponsor claims a categorical exclusion from the requirement to prepare an environmental assessment in accordance with 21 CFR 25.31(b) as the concentration of the active moiety, everolimus, will be significantly less than 1 ppb as shown in the calculation provided in the EA assessment. Based on the sponsor's calculation and request of EA categorical exclusion, it appears to be acceptable.

17. Conclusion:

From the CMC stand point, approval is recommended based on the provided information

17. Name: **Signature:** **Date:**
Z. Jean Tang, Ph.D., Chemist

18. Concurrence: **Signature:** **Date:**
Hasmukh Patel, Ph.D., Acting Branch Chief, Div., VIII, ONDQA

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/s/

ZHE J TANG
04/12/2012

HASMUKH B PATEL
04/12/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-334/S-016

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Pharmacology and Toxicology Review and Evaluation

Labeling Review and Rationale for Changes

NDA Number	22334/Supplement-016
Supplement Number	016 (DARRTS supporting document #429; eCTD document #160, efficacy supplement; and DARRTS supporting document #445, eCTD document #169, labeling/package insert draft)
Date Received by Center	November 4, 2011
Product	AFINITOR® (everolimus) tablets for oral administration
New Clinical Indication	hormone-receptor positive breast cancer, in combination with exemestane after failure of treatment with letrozole or anastrozole
Sponsor:	Novartis Pharmaceuticals Corporation East Hanover, NJ 07936 USA
Review Division:	Division of Hematology and Oncology Toxicology
Pharm/Tox Reviewer:	Mary Jane M. Hinrichs, Ph.D.
Pharm/Tox Supervisor:	Anne M. Pilaro, Ph. D.
Division Director:	John Leighton, Ph.D., D.A.B.T.
Medical Division Director	Robert Justice, M.D.
Project Manager:	Christy Cottrell

Recommendations

***Comment**: This memorandum serves as both secondary review to document my concurrence with Dr. Mary Jane Masson-Hinrichs' final recommendation that this supplemental new drug application (sNDA) for Afinitor® (everolimus) can be approved for the new indication of treatment of hormone receptor-positive, advanced breast cancer, and to provide a labeling review to document the changes made by FDA to the Afinitor® labeling, based on the nonclinical data provided in this sNDA, Dr. Masson-Hinrichs' assessment of them, and her conclusions. There were no deficiencies identified by Dr. Masson-Hinrichs in her review of the submitted nonclinical data. A copy of Dr. Masson-Hinrichs' primary review, with supervisory sign-off, has been entered into the DARRTS database as of Feb 15, 2012 and is available for inclusion in the final action package.*

The label for Affinitor® can be approved, following incorporation of the requested revisions below. These changes have been communicated to the Applicant who has accepted the FDA's changes to Sections 8.1 and 13.1. Agreement to the changes proposed by the nonclinical discipline to Section 12.1 (Mechanism of Action) and incorporation of those revisions into the final version of the label are pending at the time of this memorandum. The changes in the nonclinical sections of the body of the product labeling are presented by Section, below; FDA changes or additions to the language are provided in blue text.

Section 8: USE IN SPECIFIC POPULATIONS
Section 8.1: Pregnancy

The Applicant proposes:

(b) (4)

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/s/

ANNE M PILARO
06/15/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	22334/S-016
Supporting document/s:	429
Applicant's letter date:	02-November-2011
CDER stamp date:	03-November-2011
Product:	Afinitor® (everolimus)
Indication:	Treatment of postmenopausal women (b) (4) [redacted]
Applicant:	Novartis Pharmaceuticals Corporation
Review Division:	DOP1 / DHOT
Reviewer:	Mary Jane Masson Hinrichs, PhD
Supervisor:	Anne M Pilaro, PhD
Division Director:	Robert Justice, MD / John Leighton, PhD, DABT
Project Manager:	Christy Cottrell

Disclaimer

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Any information or data necessary for approval of NDA 22334 that Novartis does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Novartis does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22334.

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1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

Supplement 16 to NDA 22334 is approvable from the nonclinical perspective.

1.1.2 Additional Non Clinical Recommendations

None.

1.1.3 Labeling

A separate labeling review will be conducted at a later date.

1.2 Brief Discussion of Nonclinical Findings

The sponsor submitted the results of several *in vitro / in vivo* primary pharmacology studies conducted with everolimus to demonstrate anti-tumor activity in the breast cancer setting. Specifically, initial *in vitro* experiments were conducted to demonstrate that estrogen-dependent and $HER2^+$ breast cancer cells are sensitive to the inhibitory effects of everolimus. Additional *in vitro* studies demonstrated that combination treatment with Akt inhibitors, HER2 inhibitors, and aromatase inhibitors enhances the anti-tumor activity of everolimus in a synergistic manner. Lastly, tumor xenograft studies were conducted to demonstrate that everolimus inhibits tumor growth of estrogen-dependent and estrogen receptor (ER^+)/$HER2^+$ breast cancer cell lines *in vivo*.

2 Drug Information

2.1 Drug

2.1.1 CAS Registry Number (Optional)

159351-69-6

2.1.2 Generic Name

Everolimus

2.1.3 Code Name

RAD001

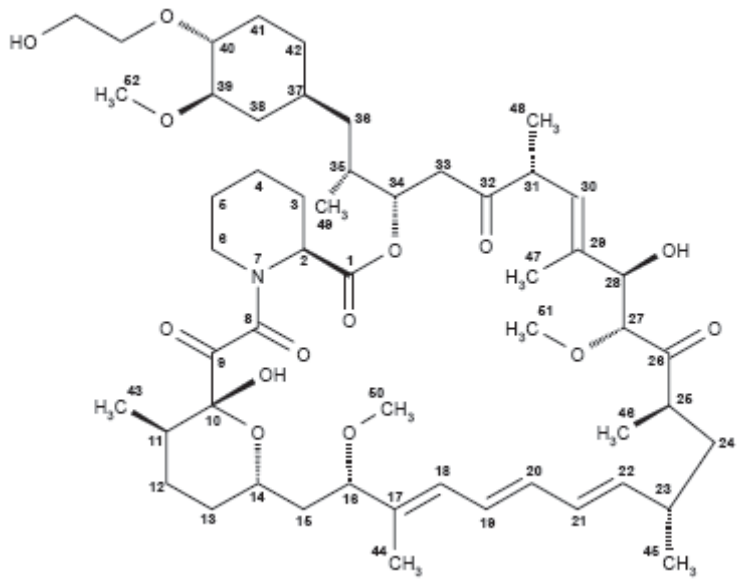
2.1.4 Chemical Name

1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-{(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.0$_{4,9}$]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone

2.1.5 Molecular Formula/Molecular Weight

$C_{53}H_{83}NO_{14}$

2.1.6 Structure



2.1.7 Pharmacologic class

Kinase inhibitor

2.2 Relevant IND/s, NDA/s, and DMF/s

IND 66279, NDA 21560

2.3 Clinical Formulation

2.3.1 Drug Formulation

Afinitor® is formulated as tablets for oral administration in strengths of 2.5, 5, and 10 mg everolimus. Each tablet contains 2.5 mg, 5 mg, or 10 mg of everolimus together with butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, crospovidone, and lactose anhydrous as inactive ingredients.

2.3.2 Comments on Novel Excipients

None.

2.3.3 Comments on Impurities/Degradants of Concern

None.

2.4 Proposed Clinical Population and Dosing Regimen

The proposed indication is for the treatment of postmenopausal (b) (4)

The proposed dosing regimen is 10 mg everolimus once daily.

2.5 Regulatory Background

Afinitor® (everolimus) was approved (NDA 22224) for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib in 2009.

Zortress® (everolimus) was approved (NDA 21560) for the prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant in 2010.

3 Studies Submitted

3.1 Studies Reviewed

Study Title	Study #	EDR Module
Pharmacology		
Effect of combinations of RAD001 and letrozole on the proliferation of the MCF7/Aro breast carcinoma cell line	RD-2003-02908	4.2.1.1.1.
Combinations of RAD001 and letrozole induce G1 accumulation and apoptosis in the MCF7/Aro breast carcinoma cell line	RD-2004-01714	4.2.1.1.1.
Effect of the combinations of RAD001 and NVP-BEZ235 in breast tumor cell lines	RD-2007-01540	4.2.1.1.1.
Effect of combinations of RAD001 and exemestane on the proliferation of the MCF7/Aro breast carcinoma cell line	RD-2011-50532	4.2.1.1.1.
Effect of the combination of RAD001 and trastuzumab on breast tumor models *in vitro* and *in vivo*	RD-2006-01111	4.2.1.1.1.
Everolimus (RAD001) is an effective agent against breast cancer xenografts established by direct transplantation of human tumor material to immunosuppressed mice	RD-2011-00537	4.2.1.1.1.
Evaluation of BKM120-AA, BEZ235-AN, RAD001, and BYL719-NX monotherapies for tumor growth inhibition in the MCF-7 human breast carcinoma nude mouse xenograft model	RD-2011-50270	4.2.1.1.1.
In vitro and *in vivo* assessment of everolimus in estrogen receptor positive (ER^+) human breast cancer cell lines	RD-2011-50447	4.2.1.1.1.
CXT-031: Evaluation of the anti-tumor activity of NVP-RAD001 as a single agent in comparison with standard of care in 6 human breast cancer xenograft models in nude mice	RD-2011-50492	4.2.1.1.1.

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

NDA 22334

4 Pharmacology

4.1 Primary Pharmacology

Afinitor® (everolimus) is a small molecule inhibitor of mammalian target of rapamycin (mTOR), a serine-threonine kinase, downstream of the PI3K/AKT pathway. The mTOR pathway is dysregulated in several human cancers and inhibition of mTOR by everolimus has been shown to reduce cell proliferation, angiogenesis, and glucose uptake in *in vitro* and *in vivo* studies.

The current submission contains data from several *in vitro/in vivo* pharmacology studies conducted to demonstrate activity in breast cancer cells, in support of the proposed indication.

***In vitro* anti-tumor activity of everolimus in breast cancer cell lines**
(Study report #RD-2003-02908; RD-2004-01714; RD-2007-01540; RD-2011-50532; RD-2006-01111; and RD-2011-50447)

Evaluation of the *in vitro* anti-aromatase activity of everolimus
A series of *in vitro* experiments was conducted to evaluate the anti-proliferative effects of combination treatment with everolimus and letrozole (Femara®), a potent non-steroidal aromatase inhibitor that blocks estrogen synthesis, in estrogen-dependent MCF7 breast cancer cells. All experiments were conducted using estrogen-dependent MCF7 cells transfected with aromatase (MCF7/Aro). These cells can proliferate in steroid-free medium by using aromatase to convert androstenedione (∇4A) into estrogen (E2). Briefly, MCF7/Aro cells were deprived of steroids or steroid analogs by culturing cells in steroid-free medium for 5 days at 37°C, prior to assessing inhibition of aromatase-driven proliferation by letrozole and/or everolimus in the presence of 10 nM ∇4A.

In study report RD-2003-02908, steroid-deprived MCF7/Aro cells were stimulated with 10 nM ∇4A in the presence of 0.2 or 2 nM everolimus with or without 10 or 100 nM letrozole for 6 days. Proliferation was assessed by measuring absorbance of YO-PRO® dye uptake at 485 nm. Both everolimus and letrozole inhibited ∇4A-driven proliferation as single agents in a concentration-dependent manner, with maximal inhibition rates of 43% and 41%, respectively. Combination treatment significantly increased the anti-proliferative effects of each agent. Maximal inhibition of ∇4A-driven MCF7/ARo proliferation of 93% was observed following combination treatment with 2 nM everolimus/ 100 nM letrozole. These results demonstrated that combination treatment with letrozole and everolimus can act additively and potentially synergistically in aromatase-expressing, estrogen-dependent breast cancer cells *in vitro*.

In a similar study (study report #RD-2004-01714), steroid-deprived MCF7/Aro cells were stimulated with 10 nM ∇4A in the presence of 0.2 or 2 nM everolimus with or without 100 or 500 nM letrozole for 6 days. Again, both everolimus and letrozole inhibited ∇4A-

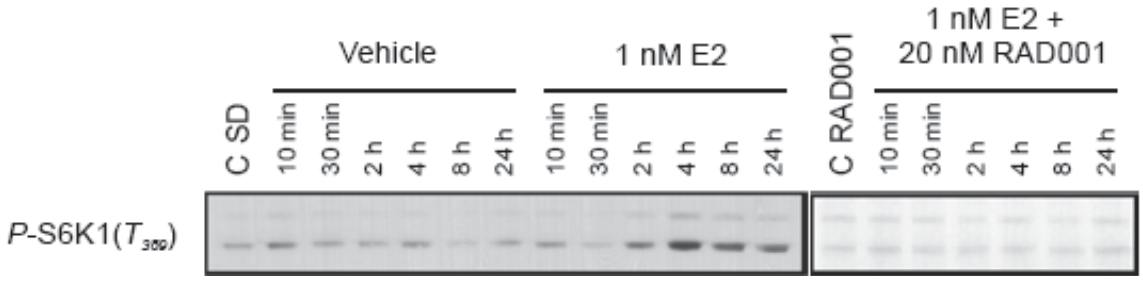
driven proliferation as single agents in a concentration-dependent manner, with maximal inhibition rates of 80% and 70%, respectively. Maximal inhibition of ∇4A-driven MCF7/Aro proliferation of 96% was observed following combination treatment with 2 nM everolimus / 500 nM letrozole, again demonstrating that combination treatment can act additively *in vitro*. A TUNEL assay was used to confirm that the anti-proliferative effects were related to apoptosis of cells.

The anti-aromatase effects of everolimus were further tested (study report #RD-2011-50532) in combination with exemestane, another aromatase inhibitor. Briefly, steroid-deprived MCF7/Aro cells were stimulated with 10 nM ∇4A in the presence of everolimus (1.2 to 100 nM), with or without exemestane (13.7 to 10,000 nM) for 3 days. Cell viability was assessed using Cell Titer Glo kit. Both everolimus and exemestane inhibited cell viability as single agents in a concentration-dependent manner, with maximal inhibition rates of 40% and 45%, respectively. Combination treatment with everolimus/exemestane significantly decreased cell viability compared to either agent alone, with maximal inhibition of 73% at a dose of 33 nM RAD001 / 1100 nM exemestane.

In study report RD-2004-01714, Western blotting was used to demonstrate involvement of the mTOR pathway in E2-dependent proliferation. Briefly, MCF7 cells were incubated with 1 nM E2 with or without 20 nM everolimus for up to 24 hours. Cell lysates were then probed for phosphorylated S6K1 (P-SK61), a downstream target of mTOR activation. Incubation of MCF7 cells with E2 resulted in upregulation of P-SK61 expression that was inhibited by co-treatment with everolimus (see Figure 1). These results provide evidence that mTOR is activated subsequent to E2-dependent proliferation, and support the rationale for use of everolimus in the treatment of HR^+ advanced BC.

Figure 1: Everolimus inhibits E2-driven upregulation of P-S6K1 expression

(Figure extracted from study report #RD-2004-01714, p14)



<u>*In vitro* evaluation of combination treatment with an Akt inhibitor</u>

A series of experiments (study report #RD-2007-01540) was conducted to evaluate the anti-tumor activity of everolimus in combination with an Akt inhibitor. Akt is a serine/threonine kinase that has downstream effector function in the mTOR/PI3K/Akt pathway. It has previously been reported that everolimus treatment is associated with

increased Akt phosphorylation through an insulin-like growth factor-1 (IGF-1) autocrine loop (Tamburini et al, 2007). The Applicant therefore hypothesized that simultaneous targeting of the both PI3K and mTOR pathway could increase the anti-tumor activity of everolimus *in vitro*. NVP-BEZ235, an investigational Akt inhibitor, was used to explore this hypothesis. Briefly, the *in vitro* anti-tumor activity of combination treatment with everolimus / NVP-BEZ235 was assessed in four, HER2- or HER3-expressing breast cancer cell lines (MCF7, T47D, sKBR3, and BT474). Cells were incubated with 20 nM everolimus and/or 6.25 nM NVP-BEZ235 for 3 days. The anti-proliferative effects were assessed using the YO-PRO® assay. Results are presented in Table 1, below. Combination treatment resulted in an increase in the anti-proliferative effects as compared to the effect of each agent alone in all four cell lines, irrespective of the level of HER2/3 expression.

Table 1: *In vitro* anti-proliferative effects of everolimus/NVP-BEZ235

	Everolimus (20 nM)	NVP-BEZ235 (6.25 nM)	Combination
MCF7 (low HER2 expression)	72 %	50 %	88 %
T47D cells (low HER2 expression	54 %	18 %	82 %
SKBR3 (high HER2/HER3 expression)	44 %	13 %	79 %
BT474 (high HER2/HER3 expression)	57 %	26 %	65 %

In vitro evaluation of combination treatment with a HER2 inhibitor

A further series of experiments was conducted to evaluate the anti-tumor activity of everolimus in combination with trastuzumab, an anti-HER2 antibody. Briefly, HER2-overexpressing breast cancer cell lines (SKBR3 and BT474) were incubated with 2 or 20 nM everolimus with and without 1, 10, or 100 nM trastuzumab for 6 days. Proliferation and cell cycle distribution were assessed by propidium iodide flow cytometry analysis. In both cell types, the combination of trastuzumab/everolimus induced slightly greater anti-proliferative activity than either drug alone, although the difference was not statistically significant (Table 2).

Table 2: *In vitro* anti-proliferative effects of everolimus/trastuzumab

	Everolimus (2 nM)	Trastuzumab (100 nM)	Combination
SKBR3 (high HER2/HER3 expression)	61 %	35 %	79 %
BT474 (high HER2/HER3 expression)	73 %	64 %	83 %

***In vivo* anti-tumor activity of everolimus in breast cancer xenograft models**
(Study reports # RD-2006-01111; RD-2011-00537; RD-2011-50270; and RD-2011-50492)

In vivo anti-tumor activity of everolimus as a single agent
Initial studies (study report #RD-2011-50270) were conducted to assess the anti-tumor activity of everolimus as a single agent in an estrogen-dependent MCF7 breast cancer xenograft model. Briefly, estradiol-implanted female nude mice (15/group) were inoculated subcutaneously with MCF7 cells. Mice were treated daily with 0 (vehicle control), 5, or 10 mg/kg everolimus by oral gavage once tumor size reached a mean volume of 111 mm^3. Inhibition of tumor growth was assessed by measuring the percentage of tumor volume change between study day 1 and termination at study day 22 in drug-treated (T), versus vehicle control-treated (C) groups (T/C). Daily treatment with everolimus inhibited tumor growth in a dose-dependent manner, with mean T/C values of 11 and 0% at doses of 5 and 10 mg/kg everolimus, respectively.

A further series of experiments (study report #RD-2011-00537) was conducted in which the anti-tumor activity of everolimus was assessed in tumor xenograft models derived from specialized patient-derived tumor fragments to minimize selective pressures of *in vitro* growth (Oncotest GmbH). In order to correlate *in vitro / in vivo* activity, the *in vitro* IC_{50} antitumor activity of everolimus was assessed in each tumor line prior to initiating *in vivo* xenograft studies. Briefly, a total of 6 breast cancer tumor fragments (MAXF401, MAXF574, MAXF583, MAXF857, MAXF132, and MXF1384) were implanted subcutaneously into the left and right flanks of female nude mice. Mice were treated with 0 (vehicle control) or 10 mg/kg everolimus by oral gavage on days 0-4, 7-11, and 14-18 once median tumor volume reached 70 to 130 mm^3. Results are presented in Table 3 below. Everolimus demonstrated significant *in vivo* anti-tumor activity in all breast cancer tumor lines, irrespective of *in vitro* sensitivity. These results clearly demonstrate that *in vitro* sensitivity is not a good indicator of *in vivo* anti-tumor activity of everolimus in these mouse xenograft models.

Table 3: Correlation of *in vitro* / *in vivo* anti-tumor activity of everolimus in breast cancer xenograft models

Cell line	*In vitro* IC_{50} (nM)	*In vivo* T/C (%)	p value
MAXF401	5	0.06	0.014
MAXF574	10000	0.09	0.002
MAXF583	4	0.17	0.026
MAXF857	1100	0.20	0.026
MAXF1322	37	0.12	0.002
MAXF1384	10000	-0.22	0.002

In vivo evaluation of combination treatment with a HER2 inhibitor

Initial experiments were conducted to determine whether $ER^+/HER2^+$ breast cancer cells are sensitive to everolimus *in vivo* (study report #RD-2011-50447). Briefly, female athymic nude mice (11/group) were inoculated with 4 different breast cancer cell lines with varying ER and HER2 expression [ZR751 (ER^+); UAC812 (ER^+HER2^+); MDA361 (ER^+HER2^+); and KPL1 (ER^+)]. Treatment was initiated once tumor size reached an average of 100 mm^3. Mice were treated daily with 0 (control) or 10 mg/kg everolimus by oral gavage for 30 days. Anti-tumor activity was assessed as percentage T/C, which denotes the mean increase in tumor volume of treated animals divided by the mean increase of tumor volumes of control animals x 100. Everolimus significantly inhibited tumor growth, with T/C values of 0.2%, 0.2%, 0.1%, and 0.2% for ZRT751, UACC812, MDA361, and KPL1 tumor xenografts, respectively. These results demonstrate that everolimus has significant anti-tumor activity in $ER^+/HER2^+$ breast cancer cells *in vivo*.

The anti-tumor activity of combination treatment with everolimus and trastuzumab, a HER2 (ErbB2) inhibitor, was assessed in an athymic nude mouse model (study report #RD-2006-01111) using an orthotopically implanted ErbB2-overexpressing breast carcinoma line, BT474. Briefly, tumor-bearing mice implanted with estrogen-pellets (10/group) were treated 3 times/week with 5 mg/kg everolimus (oral gavage), and/or 2 mg/kg trastuzumab (IP). Treatment was initiated once tumors reached ~100 mm^2 and the mice were sacrificed when the largest tumors reached ~1500 mm^2. Anti-tumor activity was assessed as percentage T/C. Both everolimus and trastuzumab demonstrated significant anti-tumor activity as single agents, with percentage T/C rates of 40% and 42%, respectively. Combination treatment with everolimus/ trastuzumab enhanced the anti-tumor activity (T/C, 14%) compared to either agent alone; however, the difference did not reach statistical significance.

11 References

Tamburini J, Chapuis N, Bardet V, Park S, Sujobert P, Willems L, Ifrah N, Dreyfus F, Mayeux P, Lacombe C, and Bouscary D. Mammalian target of rapamycin (mTOR) inhibition activates phosphatidylinositol 3-kinase/Akt by up-regulating insulin-like growth factor-1 receptor signaling in acute myeloid leukemia: rationale for therapeutic inhibition of both pathways. 2008. *Blood* 111(1) 379.

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/s/

ANNE M PILARO on behalf of MARY JANE M HINRICHS
02/15/2012

ANNE M PILARO
02/15/2012

I concur with the reviewer's conclusion that based on the nonclinical data submitted with this supplemental NDA, the supplement can be approved. A separate labeling review will be submitted when complete.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-334/S-016

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	NDA 22,334/ SE016
Drug Name:	EVEROLIMUS (AFINITOR)
Indication(s):	Locally Advanced or Metastatic ER-positive Breast Cancer
Applicant:	Novartis
Date(s):	Submission Date: 04 November 2011
	PDUFA Due Date: 04 September 2012
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 5 (HFD-711)
Statistical Reviewer:	Lijun Zhang, Ph.D.
Concurring Reviewers:	Shenghui Tang, Ph.D., Team Leader
	Thomas E. Gwise, Ph.D., Division Deputy Director
Medical Division:	Division of Oncology Products 1 (HFD-150)
Clinical Team:	Tatiana Prowell, M.D.
	Geoffrey Kim, MD
	Patricia Cortazar, M.D., Team Leader
Project Manager:	Christy Cottrell

Keywords: Progression-Free Survival, Overall Survival, Logrank Test, Randomization, Stratification

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1. EXECUTIVE SUMMARY

Everolimus (Afinitor®), a kinase inhibitor for mammalian target of rapamycin (mTOR), has been approved for the treatment of various cancers. In this supplemental New Drug Application (sNDA), the applicant seeks an approval of everolimus for the treatment of postmenopausal women with (b) (4)

The pivotal Phase 3 study CRAD001Y2301 was a multicenter, randomized, double-blind, placebo-controlled trial comparing everolimus plus exemestane to placebo plus exemestane in postmenopausal women with locally advanced or metastatic estrogen receptor (ER) positive breast cancer. The primary efficacy endpoint was progression-free survival (PFS) assessed by investigator.

A pre-specified interim analysis with 359 PFS events (68% of PFS events required for the planned final analysis) demonstrated a statistically significant PFS improvement with a hazard ratio (HR) of 0.43 (95% CI: 0.35, 0.54; $p<0.0001$) per investigator assessment in all randomized patients. The median PFS was 6.9 months in the everolimus plus exemestane arm versus 2.8 months in the placebo plus exemestane arm.

The protocol pre-specified final PFS analysis with 510 PFS events confirmed the interim PFS results. The median PFS at the final analysis was 7.8 months in the everolimus plus exemestane arm and 3.2 months in the placebo plus exemestane arm, with a HR of 0.45 (95% CI: 0.37, 0.54). The PFS analysis results based on an independent review committee (IRC) were consistent with those based on investigator assessment.

The overall survival (OS) results were not mature at this time. The first two pre-specified interim analyses showed no statistically significant OS difference between the two treatment arms. At the second interim analysis with 182 deaths (46% of deaths needed for the final OS analysis), OS medians were not reached in both arms. The HR was 0.77 (95 CI: 0.57, 1.04) with a one-sided p-value of 0.046, which did not cross the O'Brien-Fleming efficacy boundary of a one-sided alpha of 0.001. The third interim analysis and the final analysis will be performed when 275 and 398 deaths occur, respectively.

The judgment on the clinical meaningfulness of the improvement in PFS in light of the toxicities and pre-mature OS data is deferred to the clinical review team.

2. INTRODUCTION

2.1 Overview

Everolimus is a kinase inhibitor inhibiting mammalian target of rapamycin. It has been approved for the treatment of advanced kidney cancer (2009), organ rejection prophylaxis (2010), sybependymal giant cell astrocytomas (2010), and advanced neuroendocrine tumors of gastrointestinal, lung, or pancreatic origin (2011). The current sNDA submission is based on a Phase 3 pivotal study (CRAD001Y2301) (Table 1), entitled "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". The primary efficacy endpoint was PFS by

investigator assessment, and the secondary endpoints included overall survival, response rate, duration of response, time to ECOG deterioration, and quality of life.

Table 1: Overview of the Pivotal Study CRAD001Y2301

Study design	**Treatment period**	**Follow-Up period**	**Treatment arms (number of randomized subjects)**	**Enrollment period** **Geographic region: n**
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	Treated until PD or unacceptable toxicity	Follow-up for survival every 3 months until 398 deaths observed	Everolimus + Exemestane (n=485) Placebo + Exemestane (n=239)	July 2009 – January 2011 190 sites in: North America: 76 (Canada: 15; United States: 61) Europe: 68 Asia: 29 Other: 17

The original protocol of Study CRAD001Y2301 was implemented on 09 March 2009 and amended two times thereafter. Following the implementation of Amendment 1 (dated 17 February 2010), the primary endpoint was changed from PFS by independent central review to PFS by investigator assessment. Per the applicant, the change in the primary endpoint was made due to concerns for the high level of informative censoring that may be present in the independent radiographic review. In the Amendment 2 (dated 12 December 2011), a third interim analysis of overall survival at about 70% of the targeted total deaths was added.

In the pre-sNDA meeting (11 October 2011), results from a planned interim PFS analysis were discussed and the applicant proposed to submit an sNDA based on the interim results. FDA agreed that using the interim PFS analysis results for an sNDA submission with an efficacy update during the review cycle would not be a refuse-to-file issue.

In this review, patients who were randomized to receive everolimus and exemestane are referred as the "everolimus arm", whereas patients who were randomized to receive matching placebo and exemestane are referred as the "placebo arm".

2.2 Data Sources

Electronic submission including protocols, statistical analysis plan, study reports, and analysis datasets for this sNDA submission (clinical cutoff date: 11 February 2011) is located on network with network path: \\Cdsesub1\evsprod\NDA022334\0160\. Results and datasets of the second interim OS analysis are located at \\Cdsesub1\evsprod\NDA022334\0170. The report and datasets of the final PFS analysis can be found at: \\Cdsesub1\evsprod\NDA022334 \0179 .

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data and analysis quality was acceptable.

3.2 Evaluation of Efficacy

3.2.1 Overall Study Design

Study CRAD001Y2301 was a multicenter, randomized, double-blind, placebo-controlled Phase 3 study to evaluate efficacy and safety of everolimus plus exemestane compared to placebo plus exemestane in postmenopausal women with locally advanced or metastatic ER-positive breast cancer who are refractory to letrozole or anastrozole. Patients were also required to have documented recurrence or progression on or after the last therapy prior to randomization.

The study design is presented in Figure 1.

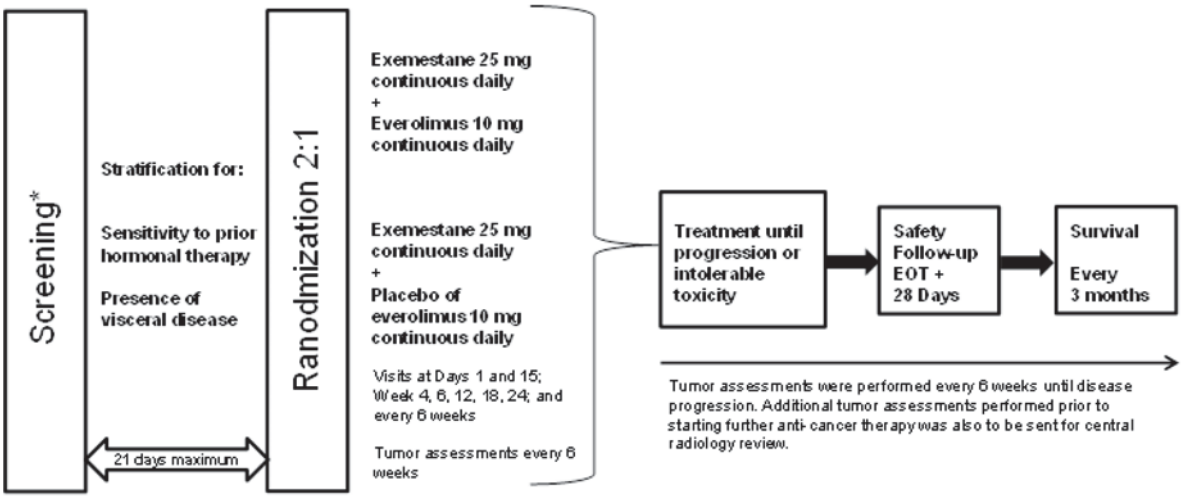

Figure 1. Study CRAD001Y2301 Design

[Source: CSR Figure 9-1]

The following stratification factors were used in randomization:

- Documented sensitivity to prior hormonal therapy (Yes vs. No)
- Presence of visceral disease (Yes vs. No)

Sensitivity to prior hormonal therapy was defined as either:

- Documented clinical benefit (complete response (CR), partial response (PR), stable disease (SD) ≥ 24 weeks) to at least one prior hormonal therapy in the advanced setting, or

- ≥ 24 months of adjuvant hormonal therapy prior to recurrence

The primary endpoint was PFS per investigator with OS as the key secondary endpoint. One interim PFS analysis and three interim OS analyses had been planned. The first interim analysis of OS was planned at the time of the interim PFS analysis. If PFS results crossed efficacy boundary at the interim analysis, the following OS interim analyses would be event-driven, otherwise, the second interim analysis of OS would be performed at the time of the final PFS analysis.

3.2.2 Schedule of Assessments

The primary PFS efficacy assessment was based on investigator tumor assessment. Tumor assessments were also reviewed by a blinded, independent central review committee, and the IRC-determined PFS data were used for a secondary supportive analysis. Based on the Response Evaluation Criteria In Solid Tumors (RECIST) version1.0, radiologic evaluation was performed every 6 weeks. Patients in the placebo arm were not allowed to crossover to receive study-supplied everolimus at the time of progression. No crossover was planned even if the study was to be stopped for positive results at the time of the interim analysis. Following progression or after study treatment discontinuation, patients continued to be followed for survival every 3 months until a total of 398 deaths are recorded.

3.2.3 Efficacy Endpoints

Primary endpoint:

- PFS as determined by investigator assessment

Secondary endpoint:

- OS
- Overall response rate (ORR)
- Duration of response
- Time to response
- Time to deterioration of ECOG Performance Status (PS)
- Quality-of-life (QoL) scores
- Clinical benefit rate (CBR)

PFS was defined as the time from the date of randomization to the date of the first documented disease progression or death due to any cause. Disease progression was based on the tumor assessment by investigator assessment using RECIST v1.0 criteria.

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

- No event (i.e., progression or death prior to progression) was observed up to the cut-off date
- The event occurred after a new anti-cancer therapy was given
- The event occurred after ≥ 2 missing tumor assessments

Note that discontinuation of study treatment (for any reason) was not considered as a reason for censoring.

OS was defined as the time from randomization to death due to any cause.

ORR was defined as the percentage of patients who achieved either a confirmed CR or PR as their best confirmed response, relative to all randomized patients.

Duration of response was defined for the subset of patients who achieved a confirmed CR or PR, and was calculated as the time from the date of the first documented evidence of CR or PR until the date of either the first documented sign of progressive disease or death due to any cause. Patients who have neither died nor progressed were censored at the date of the last adequate radiologic assessment. Same censoring rules have been applied as the primary PFS analysis.

Time to Response was the time between the date of randomization until first documented response (CR or PR) as determined by local investigator assessment.

CBR was defined as the proportion of patients with either a best overall response of CR, PR or SD lasting for 24 weeks or longer. A patient was considered to have a SD for 24 weeks or longer if a SD response has been recorded at 24 weeks or later from randomization.

ECOG PS scale was used to assess physical health of patients, ranging from 0 (most active) to 5 (least active). ECOG PS was assessed at screening, day 1 of treatment, and every 6 weeks thereafter as well as at the time of treatment discontinuation. An analysis of the time to definitive deterioration of the ECOG PS by one category of the score from baseline was performed. Deterioration was considered definitive if no improvement in the ECOG PS status was observed at a subsequent time of measurement during the treatment period following the time point where the deterioration was observed. Patients, who died after more than twice the planned period between two assessments, were censored at the date of their last assessment, otherwise, death was considered as worsening of ECOG PS. Patients receiving any further anti-cancer therapy prior to definitive worsening were censored at their date of last assessment prior to start of therapy. Patients who have not worsened at the data cut-off point were censored at the date of last assessment prior to the clinical cut-off date.

Patient reported outcomes (PRO) were collected by the EORTC QLQ-C30 questionnaire along with the breast module (BR23). The global health status/global QoL domain sub-scale score was indentified as the primary QoL variable of interest. Physical functioning, emotional functioning and social functioning sub-scale scores were identified as secondary QoL variables of interest. The PRO instruments (QLQ-C30 and BR23) were planned to be administered on first day the study drug was administered and then at every 6 weeks until progression.

Reviewer's Comments

- *To control the overall type I error rate, OS was tested in a hierarchical way after PFS analysis. However, the type I error rate was not adjusted for analyses of multiple secondary endpoints.* (b) (4)
- *Patient-reported outcome endpoints were evaluated by two instruments which were not validated for the patient population in this disease setting. Therefore, these endpoints in this study are considered as exploratory.*

3.2.4 Sample Size Determination

A total of 528 PFS events were needed to detect a HR of 0.74 (corresponding to an increase from 3.7 to 5 months in median PFS) with 90% power using a log-rank test and a 2-look Lan-Demets group sequential design with O'Brien-Fleming type boundary at one-sided cumulative 2.5% level of significance. Assuming an enrolment rate of 35 patients per month for approximately 18 months, a total of 633 patients was needed to be randomized in a 2:1 ratio to observe 528 events at about 4.9 months following the randomization of the last patient in this study. Assuming about 10% of the patients would be lost to follow-up or withdraw consent, a total of 705 patients were to be randomized.

Although this study was not specifically designed to detect an overall survival benefit, patients were followed for survival after disease progression. The distribution of OS was to be compared between the two treatment arms, provided that the primary endpoint PFS was statistically significant.

It was hypothesized that adding everolimus to exemestane would result in a 26% reduction in the hazard rate for overall survival (corresponding to an increase in median survival to 32.43 months), assuming a 24-month median survival for the placebo plus exemestane arm. To detect an OS HR of 0.74 with 80% power, a total of 398 deaths were needed to be observed (using a log-rank test and a 4-look Lan-Demets group sequential design with O'Brien-Fleming type boundary at one-sided 2.5% level of significance).

3.2.5 Interim Analyses

The interim PFS analysis was planned to occur after observing 317 PFS events (60% of the targeted total PFS events needed for the final analysis) as per local investigator assessment. Although the PFS analysis based on the independent central review of local radiology data was considered as supportive, 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 favor of everolimus, using a Lan-DeMets α-spending function with O'Brien-Fleming stopping boundaries that were driven by the number of local and central PFS events observed separately.

OS would be compared between the two treatment arms, provided the primary endpoint PFS was significant. A total of 3 interim analyses and one final analysis for OS were planned in this study. The first interim OS analysis was planned at the time of the interim PFS analysis. If PFS results crossed efficacy boundary at the interim analysis, the following OS interim analyses would be event-driven, otherwise, the secondary interim analysis of OS would be performed at the time of the final PFS analysis. The expected numbers of OS events at the projected time point of the interim analyses were 84, 173, and 275 respectively. The final OS analysis will be conducted when 398 deaths occur. An α-spending function due to Lan-DeMets with O'Brien-Fleming type stopping boundary was used to maintain the overall type I error rate. The trial allowed for the stopping of the study for a superior OS result, provided the primary endpoint PFS has already been shown to be significantly different.

To control the overall type I error rate when both PFS and OS had multiple looks, two separate alpha spending functions were used for PFS and OS respectively. These were two different alpha spending functions on two different information fraction scales, i.e., the observed number of PFS events and death events for PFS analysis and OS analysis, respectively.

Reviewer's Comments

- *The PFS interim analysis was planned to occur with 317 PFS events, and the actual analysis was conducted after observing 359 PFS events (68% information) as per investigator assessment (at which time 217 central PFS events were recorded as per IRC).*
    - *The nominal p-value for the PFS analysis as per investigator was $p \leq 0.0065$ (one-sided)*
    - *The nominal p-value for the PFS analysis as per IRC was $p \leq 0.0005$ (one-sided)*
- *The first two interim OS analyses were performed with 83 (21% information) and 182 (46% information) deaths.*
    - *The nominal p-value for the first OS interim analysis was $p \leq 0.000001$ (one-sided)*
    - *The nominal p-value for the second OS interim analysis was $p \leq 0.001$ (one-sided)*

3.2.6 Efficacy Analysis Population

The Full Analysis Set (FAS) population consisted of all randomized patients. Following the intent-to-treat (ITT) principle, patients were analyzed according to the treatment and stratum they were assigned to at randomization. Data from the FAS were the primary basis for all efficacy analyses.

3.2.7 Efficacy Analysis Methods

The primary efficacy analysis was to evaluate PFS based on investigator assessment within the FAS population. PFS was summarized using Kaplan-Meier survival curves, and compared between the two treatment arms using a stratified log-rank test (strata based on the two randomization stratification factors as obtained through central randomization system). The hazard ratio with a two-sided 95% confidence interval was derived from a stratified Cox proportional hazards model.

OS was the key secondary endpoint in this study, and was analyzed in the FAS population. OS was summarized using Kaplan-Meier survival curves, and compared between the two treatment arms using a stratified log-rank test. A stratified Cox proportional hazards model was used to estimate the hazard ratio of OS, along with a 95% confidence interval.

Overall response rate and clinical benefit rate were estimated in the FAS population based on investigator assessment. However, patients with only non-measurable disease at baseline were included in the numerator if they achieved a complete response. A Cochran-Mantel-Haenszel chi-square test was used to compare the two treatment arms with respect to ORR and CBR. As a secondary supportive analysis, ORR and CBR were also summarized using the independent central review of tumor data. However, no inferential statistics were provided.

Distribution of time to deterioration of ECOG PS was estimated by the Kaplan-Meier method. A stratified log-rank test was used to compare the distribution of time to definitive worsening between the two treatment arms.

In the analysis of PRO data, descriptive statistics were used to summarize the individual item and sub-scale scores at each scheduled assessment time point. A repeated measurements analysis model that included terms for treatment, baseline stratification factors, baseline value and time of visit by treatment group was used to compare the two treatment groups with respect to

changes in the sub-scale scores longitudinally over time. Time to definitive 5% deterioration in the global health status / quality of life scale were compared between the two treatment arms in the FAS using the stratified log-rank test.

3.2.8. Sponsor's Efficacy Results and FDA Statistical Reviewer's Findings/Comments

3.2.8.1 Patient Disposition, Demographic and Baseline Characteristics

Patients Disposition

A total of 724 patients from 190 clinical centers in 24 countries were randomized to either everolimus plus exemestane or placebo plus exemestane in a 2:1 randomization ratio. Three patients randomized to the everolimus arm and one patient randomized to the placebo arm did not receive their allocated treatment. As of the 11 February 2011 data cut-off date, 296 patients (41%) continued to receive at least one study drug (everolimus/placebo and/or exemestane) while 428 patients (59%) had discontinued study treatment. Treatment was ongoing for a greater proportion of patients in the everolimus arm (47% relative to 29% in the placebo arm). Disease progression was the primary reason for treatment discontinuation and was more frequent in the placebo arm, as shown in Table 2.

Table 2. Patient Disposition

	Number (%) of Patients	
	Everolimus + Exemestane (N=485)	**Placebo + Exemestane (N=239)**
Treated	482(>99)	238 (>99)
Treatment status		
Discontinued study treatment	255 (53)	169 (71)
On study treatment	227 (47)	69 (29)
Primary reason for discontinuation of study treatment		
Disease progression	181 (37)	157 (66)
Patient withdrew consent	33* (7)	5 (2)
Adverse event(s)	32 (7)	6 (3)
Death	7 (1)	1 (< 1)
Protocol deviation	3 (< 1)	0
New cancer therapy	2 (< 1)	0
Abnormal laboratory value(s)	0	1 (< 1)

*Verbatim reason for treatment discontinuation included potential adverse effects in 10 patients
[Source: CSR Table 10-1]

Reviewer's Comment

Reasons for never receiving the protocol assigned treatment included AE-worsening of liver enzyme, consent withdrawal, disease progression indicated by AEs, and exclusion criteria met.

Demographic and Baseline Characteristics

The demographic and baseline characteristics are presented in Tables 3 and 4. The median age of all randomized patients was 61 years old. Seventy-six percent were white, and 20% were Asian. Two hundred and twenty-three (31%) patients were enrolled in the United States; 275 (38%) patients were enrolled in Europe; 137 (19%) patients were enrolled in Asia. Seventy-six percent of patients had bone metastasis at baseline, and 21% patients had bone metastasis only. All patients were ER positive, and 72% patients were Progesterone receptor positive. Sixty percent of patients had baseline ECOG performance score of 0 compared to 36% with score of 1 and 2% with score of 2.

Table 3. Summary of Demographics Characteristics

	Everolimus + Exemestane N=485	**Placebo + Exemestane N=239**	**All patients N=724**
Age (years)			
n	485	239	724
Median	62	61	61
Range	34-93	28-90	28-93
Age category, n (%)			
<65	290 (60)	159 (66)	449 (62)
≥65	195 (40)	80 (34)	275 (38)
Race, n (%)			
Caucasian	361 (74)	186 (78)	547 (76)
Asian	98 (20)	45 (19)	143 (20)
Black	13 (3)	3 (1)	16 (2)
Pacific islander	2 (< 1)	1 (< 1)	3 (< 1)
Other	11 (2)	4 (2)	02 (2)
Region, n (%)			
Asia	94 (19)	43 (18)	137 (19)
Europe	192 (40)	83 (35)	275 (38)
North America	174 (36)	100 (42)	274 (38)
Other	25 (5)	13 (5)	38 (5)
Region, n (%)			
U.S.	146 (30)	77 (32)	223 (31)
Non – U.S.	339 (70)	162 (68)	501 (69)

[Source CSR Table 11-3]

Table 4. Summary of Baseline Disease Characteristics

	Everolimus + Exemestane (N=485) n (%)	Placebo + Exemestane (N=239) n (%)	All patients (N=724) n (%)
Current disease status			
Metastatic	482 (> 99)	239 (100)	721 (> 99)
Locally advanced	3 (< 1)	0	3 (< 1)
Metastatic site of cancer			
Bone	369 (76)	184 (77)	553 (76)
Bone only	105 (22)	50 (21)	155 (21)
Visceral (excluding CNS)	281 (58)	143 (60)	424 (59)
Liver	160 (33)	72 (30)	232 (32)
Lung	140 (29)	79 (33)	219 (30)
Liver and Lung	42 (9)	25 (11)	67 (9)
CNS	5 (1)	0	5 (< 1)
Other	243 (50)	132 (55)	375 (52)
Number of metastatic sites			
1	155 (32)	69 (29)	224 (31)
2	152 (31)	81 (34)	233 (32)
3	103 (21)	52 (22)	155 (21)
4	48 (10)	28 (12)	76 (11)
>4	24 (5)	9 (4)	33 (5)
Time since most recent recurrence/metastasis			
< 3 months	469 (97)	232 (97)	701 (97)
≥ 3 - < 6 months	11 (2)	5 (2)	16 (2)
≥ 6 months	3 (< 1)	1 (< 1)	4 (< 1)
Missing	2 (< 1)	1 (< 1)	3 (< 1)
ECOG PS			
0	293 (60)	142 (59)	435 (60)
1	174 (36)	84 (35)	258 (36)
2	9 (2)	7(3)	16 (2)
Missing	9 (2)	6 (3)	15 (2)
HER2-positive			
No	483 (> 99)	239 (100)	722 (> 99)
Missing	2 (< 1)	0	2 (< 1)
PgR* - positive			
No	122 (25)	62 (26)	184 (25)
Yes	351 (72)	173 (72)	524 (72)
Not assessable	12 (3)	4 (2)	16 (2)

*PgR: Progesterone receptor
[Source CSR Tables 11-4 and 11-5]

Reviewer's Comment

Demographics and baseline disease characteristics were balanced between the two treatment arms.

The numbers of patients in each of the four strata (presence of visceral metastasis (yes vs. no) and sensitivity to prior hormonal therapy (yes vs. no)) from centralized allocation (i.e., interactive web response system (IWRS)/interactive voice response system (IVRS); the combination of these two response systems is abbreviated to IXRS) and Case Report Form (CRF) are presented in Table 5. Overall, per IXRS, approximately 56% of patients enrolled in this study had visceral metastasis, and around 85% of patients were sensitive to prior hormonal therapy. Similar distribution of patients was observed per CRF-based strata.

Table 5. Stratification Data from IXRS and CRF

Stratum	Presence of visceral metastasis	Sensitivity to prior hormonal therapy	Everolimus + Exemestane N=485 n (%)	Placebo + Exemestane N=485 n (%)
		IXRS		
1	Yes	Yes	240 (50)	119 (50)
2	No	No	45 (9)	22 (9)
3	No	Yes	169 (35)	82 (34)
4	Yes	No	31 (6)	16 (7)
		CRF		
1	Yes	Yes	255 (53)	119 (50)
2	No	No	21 (4)	12 (5)
3	No	Yes	180 (37)	84 (35)
4	Yes	No	29 (6)	24 (10)

Reviewer's comments

- *There were 220 (30%) patients with inconsistent stratification data between IXRS and CRFs, as summarized in Table 6. However, the distribution of randomized patients was balanced between the two treatment arms by stratification factors from both sources, as shown in Table 5.*

- *Per the statistical analysis plan, IXRS-based stratification data was used in the primary efficacy analysis and this reviewer performed a sensitivity analysis based on stratification data from CRFs. Results from both analyses were consistent.*

Table 6. Discrepancies on Stratification Factors between IXRS and CRF

	Everolimus + Exemestane (N=485)	Placebo + Exemestane (N=239)
Total number of patients with discrepancies, n (%)	154 (32)	66 (28)
For each stratification factor		
Presence of visceral metastasis	93 (19)	38 (16)
Sensitivity to prior hormonal therapy	90 (19)	38 (16)
Patients with both mismatching	29 (6)	10 (4)

Prior Anti-Cancer Therapy

As required by the protocol, all patients had been treated with either letrozole or anastrozol. As shown in Table 7, 8% of patients had been treated by both. Around 70% of patients had also received prior chemotherapy, and a maximum of 1 line chemotherapy was allowed in the advanced setting as specified in the eligibility criteria.

Table 7. Summary of Prior Anti-Cancer Therapy

	Everolimus + Exemestane (N=485) n (%)	Placebo + Exemestane (N=239) n (%)	All patients (N=724) n (%)
Any prior anti-cancer therapy	485 (100)	239 (100)	724 (100)
Any prior surgery	451 (93)	220 (92)	671 (93)
Any prior radiotherapy	340 (70)	164 (69)	504 (70)
Any non-steroidal aromatase inhibitor (NSAI)			
Letrozole only	237 (49)	106 (44)	343 (47)
Anastrozole only	210 (43)	114 (48)	324 (45)
Both letrozole and anastrozole	38 (8)	19 (8)	57 (8)
NSAI setting			
Adjuvant/neoadjuvant only	142 (29)	57 (24)	199 (28)
Metastatic only	323 (67)	170 (71)	493 (68)
Both adjuvant/neoadjuvant and metastatic	20 (4)	12 (5)	32 (4)
Patients with NSAI as last treatment	361 (74)	178 (75)	539 (74)
Adjuvant/neoadjuvant	99 (20)	38 (16)	137 (19)
Metastatic	262 (54)	140 (59)	402 (56)
Chemotherapy			
Adjuvant/neoadjuvant only	211 (44)	95 (40)	306 (42)
Metastatic only	67 (14)	23 (10)	90 (12)
Both adjuvant/neoadjuvant and metastatic	58 (12)	38 (16)	96 (13)
Number of prior hormonal therapies			
1	182 (38)	84 (35)	266 (37)
2	210 (43)	108 (45)	318 (44)
3	65 (13)	25 (10)	90 (12)
> 3	28 (6)	22 (9)	50 (7)
Number of prior therapies in metastatic setting			
None	100 (21)	37 (16)	137 (19)
1	192 (40)	112 (47)	304 (42)
2	128 (26)	66 (28)	194 (27)
3	52 (11)	16 (7)	68 (9)
4-6	13 (3)	8 93)	21 (3)

[Source CSR Table 11-6]

Post-Study Treatment Anti-Cancer Therapy

As of the clinical cut-off date (11 February 2011) for this sNDA original submission, subsequent anti-cancer therapy was received by 195 (40%) patients in the everolimus arm and 145 (61%) in the placebo arm (Table 8). Patients in the placebo arm were not allowed to crossover to receive study-supplied everolimus at the time of progression.

Table 8. Summary of Subsequent Anti-Cancer Therapy

	Everolimus + Exemestane (N=485) n (%)	**Placebo + Exemestane (N=239) n (%)**
Any subsequent therapy	195 (40)	145 (61)
Type of Therapy		
Chemotherapy	118 (24)	100 (42)
Hormonal therapy	93 (19)	60 (25)
Immuotherapy	2 (<1)	0
Radiation therapy	17 (4)	8 (3)
Surgery	1 (< 1)	0
Targeted therapy	8 (2)	12 (5)
Other	4 (<1)	2 (< 1)

[Source: CSR Table 14.2-1.8]

3.2.2.3 Results and Conclusions

Primary Endpoint Results

Primary Efficacy Analysis

The primary analysis of PFS was based on local investigator assessment in the FAS population, using a stratified log-rank test. At the time of this sNDA original submission, the applicant submitted results of the pre-specified interim PFS analysis based on 359 PFS events (68% of 528 PFS events needed for the final analysis), as of data cut-off date 11 February 2011. A statistically significant improvement in PFS was observed in the everolimus arm compared with the placebo arm, which crossed the interim efficacy stopping boundary, one-sided alpha level of 0.0065, as determined by O'Brien-Fleming boundary. The median PFS was 2.83 months in the placebo arm and was 6.93 months in the everolimus arm, with a corresponding HR of 0.43 (95% CI: 0.35, 0.54) under adjustment of the two stratification factors, as presented in Table 9. The Kaplan-Meier curves are shown in Figure 2.

The protocol pre-specified final analysis of PFS was performed after 510 (97% of the targeted 528 PFS events) PFS events occurred as of 15 December 2011 and submitted on 21 March 2012 to the sNDA. The median PFS was 3.19 months in the placebo arm and was 7.82 months in the everolimus arm, with a corresponding HR of 0.45 (95% CI: 0.38, 0.54) under the adjustment of the two stratification factors, as presented in Table 10. The Kaplan-Meier curves are shown in Figure 3. PFS Results were consistent in the interim analysis and in the final analysis.

Table 9. Interim Analysis of Progression-Free Survival per Investigator

	Everolimus + Exemestane (N=485)	Placebo + Exemestane (N=239)
Patient Classification, n (%)		
PFS Events	202 (42)	157 (66)
Progressed	190 (40)	156 (65)
Died without progression	12 (2)	1 (<1)
Censored	283 (58)	82 (34)
Median (95% CI), in months	6.93 (6.44, 8.05)	2.83 (2.76, 4.14)
Hazard ratio (95% CI) [a]	0.43 (0.35, 0.54)	
Stratified log rank p-value (one-sided) [b]	<0.0001	

[a] Hazard ratio was obtained from a Cox proportional hazards model stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis

[b] P-value was obtained from a one-sided log rank test model stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis per IXRS

[Source CSR Table 11-7]

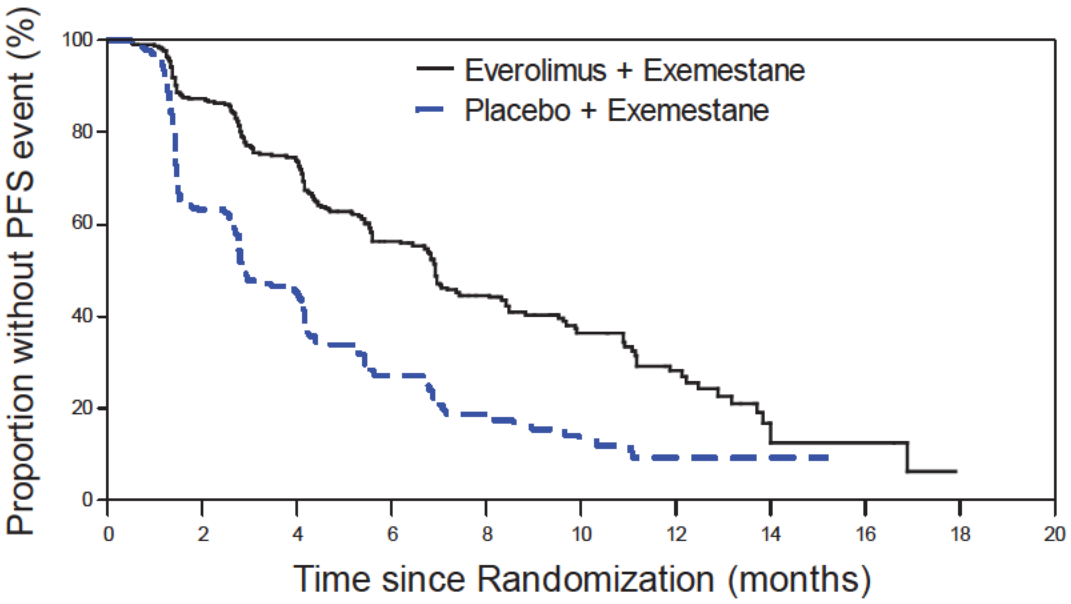

Figure 2. Kaplan-Meier Curves of Interim Progression-Free Survival per Investigator

[Source CSR Figure 11-1]

Table 10. Final Analysis of Progression-Free Survival per Investigator

	Everolimus + Exemestane (N=485)	Placebo + Exemestane (N=239)
Patient Classification, n (%)		
PFS Events	310 (64)	200 (84)
Progressed	294 (61)	198 (83)
Died without progression	16 (3)	2 (1)
Censored	175 (56)	39 (16)
Median (95% CI), in months	7.82 (6.93, 8.48)	3.19 (2.76, 4.14)
Hazard ratio (95% CI) [a]	0.45 (0.38, 0.54)	
Stratified log rank p-value (one-sided) [b]	<0.0001	

[a] Hazard ratio was obtained from a Cox proportional hazards model stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis

[b] P-value was obtained from a one-sided log-rank test model stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis per IXRS

[Source Addendum to 2.7.3 Summary of Clinical Efficacy Table 2-1]

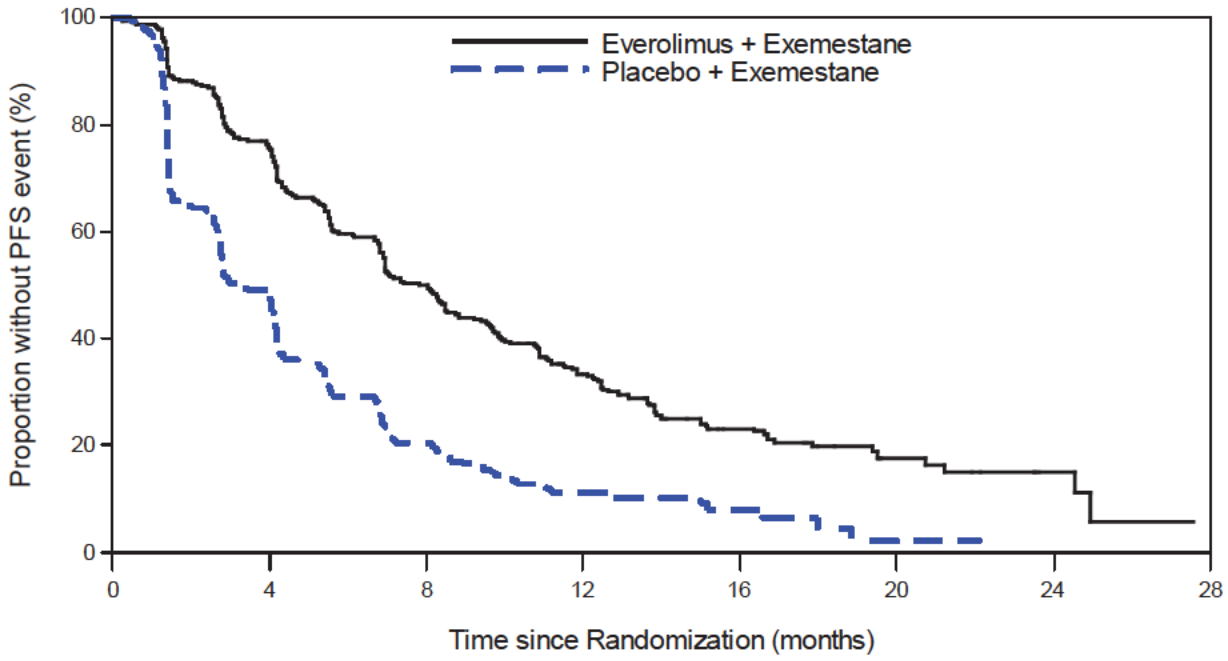

Figure 3. Kaplan-Meier Curves of Final Progression-Free Survival per Investigator

[Source Addendum to 2.7.3 Summary of Clinical Efficacy Figure 2-1]

Reviewer's Comments

- *The interim PFS data were submitted to support this sNDA efficacy. Due to issues related to PFS interim analyses in general, FDA requested that the applicant provide the final PFS analysis during the review cycle to confirm the interim findings. As shown in Tables 9 and 10, a similar PFS improvement was observed in the everolimus arm in the final PFS analysis as compared to the interim analysis.*
- *For the interim analysis, the FDA clinical and statistical review teams have re-evaluated each patient's progression status based on investigator raw lesion data following RECIST 1.0 criteria and identified 29 patients with different PFS event type and/or time. Based on FDA's evaluation, the median PFS was 2.79 months in the placebo arm and was 6.93 months in the everolimus arm, with a HR of 0.44 (95% CI: 0.35, 0.54). The results from FDA's PFS analysis are similar to the primary findings based on investigator assessment.*
- *At the time of the final PFS analysis, using the inverse Kaplan-Meier method, the median follow-up time of the FAS population was 14 months, based on investigator assessment.*

PFS Supportive Analysis -- per Independent Central Radiology Review

A supportive analysis of PFS based on the IRC review was conducted to evaluate the robustness of the primary findings based on investigator assessment. At the time of the interim PFS analysis (cutoff date of 11 February 2011), there were 208 (41% information) PFS events documented per IRC review. The estimated medians of IRC-based PFS was 10.58 months in the everolimus arm and 4.14 months in the placebo arm, with a HR of 0.36 (95% CI: 0.27, 0.47) and a p-value < 0.0001 (Table 11). Interim PFS results per IRC crossed the efficacy boundary, one-sided alpha level of 0.0005, as determined by O'Brien-Fleming boundary. Kaplan-Meier curves of PFS per IRC are illustrated in Figure 4.

At the time of the final PFS analysis (data cutoff date of 15 December 2011), per IRC review, 320 PFS events occurred. The estimated medians of IRC-based PFS in the everolimus arm and the placebo arm were 11.01 and 4.14 months, respectively, with a HR of 0.38 (95% CI: 0.31, 0.48). Final PFS results per IRC are presented in the Table 12. Kaplan-Meier curves per IRC are illustrated in Figure 5.

Table 11. Interim Analysis of Progression-Free Survival per IRC

	Everolimus + Exemestane (N=485)	Placebo + Exemestane (N=239)
Patient Classification, n (%)		
PFS Events	114 (24)	104 (44)
Progressed	101 (21)	100 (42)
Died without progression	13 (3)	4 (2)
Censored	371 (77)	135 (57)
Median (95% CI), in months	10.58 (9.53, NA)	4.14 (2.83, 5.75)
Hazard ratio (95% CI) [a]	0.36 (0.27, 0.47)	
Stratified log rank p-value (one-sided) [b]	<0.0001	

[a] Hazard ratio was obtained from a Cox proportional hazards model stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis per IXRS

[b] P-value was obtained from a one-sided log-rank test model stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis.

[Source CSR Table 11-8]

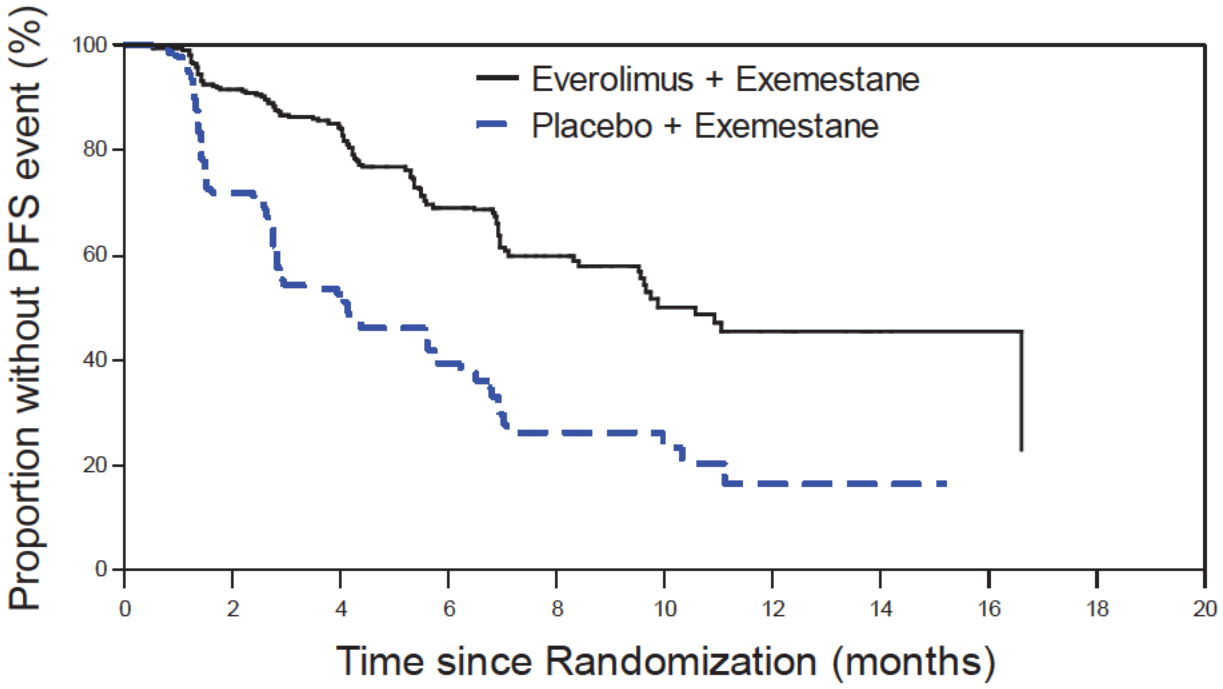

Figure 4. Kaplan-Meier Curves for Interim Progression-Free Survival per IRC

[Source: CSR Figure 11-2]

Table 12. Final Analysis of Progression-Free Survival per IRC

	Everolimus + Exemestane (N=485)	Placebo + Exemestane (N=239)
Patient Classification, n (%)		
PFS Event	188 (39)	132 (55)
Progressed	167 (34)	128 (54)
Died without progression	21 (4)	4 (2)
Censor	297 (61)	107 (45)
Median (95% CI), in months	11.01 (9.66, 15.01)	4.14 (2.89, 5.55)
Hazard ratio (95% CI) [a]	0.38 (0.31, 0.48)	

[a] Hazard ratio was obtained from a Cox proportional hazards model stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis per IXRS

[Source Addendum to 2.7.3 Summary of Clinical Efficacy Table 2-2]

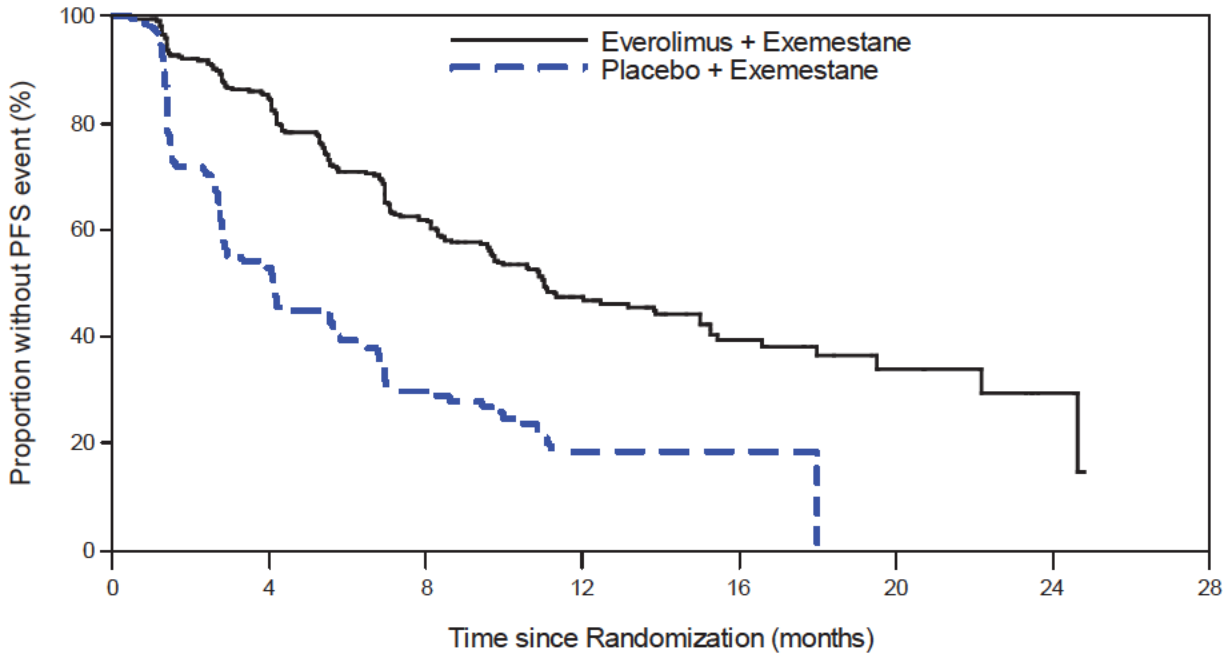

Figure 5. Kaplan-Meier Curves for Final Progression-Free Survival per IRC

[Source Addendum to 2.7.3 Summary of Clinical Efficacy Figure 2-2]

Reviewer's Comment:

In the protocol Amendment 1, the primary endpoint was changed from PFS by IRC to PFS by investigator assessment. The independent central review of the radiological data was retained

and the results served as supportive analyses for the primary efficacy analysis. The PFS analysis results per IRC were consistent with those per investigator assessment.

Censoring Reasons for PFS

The censoring reasons for PFS based on investigator and IRC review are summarized in Table 13. Among patients with follow-up ended, the major censoring reasons based on investigator assessment included 'adequate assessment no longer available' and 'new anti-cancer therapy added'. In IRC-based PFS analysis, more patients were censored due to "new anti-cancer therapy added" in both arms. The notable increase in "new anti-cancer therapy added" in IRC-based PFS analysis (relative to investigator assessment) was mainly caused by patients receiving further anti-cancer therapy following documented progression by the local investigator, which was subsequently not confirmed through central radiology review. In IRC-based PFS analysis, there were a total of 172 patients (110 in the everolimus arm and 62 in the placebo arm) censored due to new therapy added, of whom, 138 patients had documented disease progression by investigator.

Table 13. Summary of Censoring Reasons for PFS (Interim) based on Investigator and IRC

	Investigator assessment		IRC review	
	Everolimus + Exemestane N=485 n (%)	**Placebo + Exemestane N=239 n (%)**	**Everolimus + Exemestane N=485 n (%)**	**Placebo + Exemestane N=239 n (%)**
Censored patients	283 (58.4)	82 (34.3)	371 (76.5)	135 (56.5)
Censored, follow-up ongoing	220 (45.4)	63(26.4)	212 (43.7)	58 (24.3)
Censored, follow-up ended	63 (13.0)	19 (7.9)	159 (32.8)	77 (32.2)
Adequate assessment no longer available	33 (6.8)	7 (2.9)	47 (9.7)	15 (6.3)
New anti-cancer therapy added	29 (6.0)	9 (3.8)	110 (22.7)	62 (25.9)
Events after ≥ 2 missing tumor assessments	1 (<1)	3 (1.3)	2 (<1)	0

[Source: CSR Table 11-15]

Reviewer's Comment

Of patients censored due to "new anti-cancer therapy added" in the IRC-based PFS analysis, a large proportion was expected to be close to disease progression per IRC, which might contribute to informative censoring. To address this potential informative censoring, a conservative sensitivity analysis was performed and the results are summarized in the section of "Sensitivity Analyses of PFS".

Comparison of Independent and Investigator Assessment of Progression

The discordance rate between IRC and investigator in terms of PFS event type (event vs. censored) was 32% in the placebo arm and 25% in the everolimus arm, based on interim PFS data, as presented in Table 14.

Table 14. Comparison of Progression (Interim) based on Investigator and IRC

	Everolimus plus Exemetane (N=485)	Placebo plus Exemestane (N=239)
Overall discordance rate, n (%)	122 (25)	77 (32)
PFS event by IRC, n (%)	114 (24)	104
PFS event by Investigator, n (%)	97	92
Censored by Investigator, n (%)	17	12
Censored by IRC, n	371	135
Censored by Investigator, n (%)	266	70
PFS event by Investigator, n (%)	105 (22)	65 (27)

[Source: CSR Table 11-9]

Reviewer's Comments

- *If considering the time of censoring/event as well, the discordance rate was 50% in the placebo arm and 42% in the everolimus arm (Table 15). The median of difference on time between IRC and investigator was 42 days among patients with different PFS times but same event type. Despite the high discordance rate, the analysis results were consistent based on IRC review and investigator assessment.*

Table 15. Discordance between Investigator and IRC, including PFS Event Type and Time

Everolimus plus Exemestane			Placebo plus Exemestane		
Type	**Timing**	**Total**	**Type**	**Timing**	**Total**
25%	17%	42%	32%	18%	50%

- *To evaluate assessment bias of the investigators, this reviewer calculated Early Discrepancy Rate (EDR) and Late Discrepancy Rate (LDR) between IRC and investigator for each arm as described by Amit et al [1]. The differential discordance was calculated as the difference of EDR or LDR between the everolimus arm and placebo arm. A negative differential discordance on EDR and/or a positive differential discordance on LDR are suggestive of a bias in the investigator assessment favoring the everolimus arm.*

  Based on the interim PFS data, the everolimus arm had an EDR of 0.53 and a LDR of 0.29, while the placebo arm had an EDR of 0.46 and a LDR of 0.36. The differential discordance was positive on EDR and negative on LDR, which suggested that no investigator assessment bias favoring the everolimus arm was detected.

- *Based on the final PFS data, similar discordance results were observed compared to the interim data.*

Sensitivity Analyses of PFS

The applicant has conducted sensitivity analyses on the interim PFS based on investigator assessment, as summarized in Table 16.

Table 16. Overview of Applicant's Sensitivity Analyses of PFS (Interim) per Investigator Assessment

Sensitivity Analysis	Everolimus + Exemestane	Placebo + Exemestane	Hazard Ratio (95% CI)
	Median PFS (months)		
Unstratified Cox model	6.93	2.83	0.44 (0.36, 0.54)
Stratified Cox model, adjusting for baseline covariates [a]	6.93	2.83	0.40 (0.32, 0.50)
'Actual event' [b]	6.93	2.92	0.43 (0.35, 0.54)
'Backdating' [c]	6.93	2.83	0.43 (0.35, 0.53)
No censoring for anti-cancer therapy [d]	6.93	2.83	0.44 (0.36, 0.54)

[a] Baseline covariates included in the Cox proportional hazard model are prior chemotherapy (Yes vs. No), performance status (0 vs. 1 or 2), bone only lesions at baseline (Yes vs. No), time since first diagnosis of metastasis/recurrence to randomization (≤ 6 months vs. > 6 months), non-steroidal aromatase inhibitor usage (adjuvant vs. metastatic), number of organs involved (1 vs. 2 vs. ≥ 3), and progesterone receptor status (positive vs. 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 anti-cancer therapy

[Source CRS Table 11-11]

In addition, to address potential bias by informative censoring in the PFS analysis based on IRC review, the applicant performed a conservative sensitivity analysis.

- For patients in the everolimus arm, who were censored due to 'new anti-cancer therapy added' as per IRC and assessed as PFS event as per investigator, PFS events were imputed and the corresponding PFS time was extended by 6 weeks, assuming they would have progressed at the next tumor assessment.
- For patients in the placebo arm, there was no imputation rule applied and patients who were censored for new anti-cancer therapy were not imputed to have an event.

PFS data based on IRC review were used in this analysis if not imputed. Treatment HR was 0.55 (95% CI: 0.43, 0.70), with a median PFS of 6.89 months in the everolimus arm and 4.14 months in the placebo arm.

This reviewer also conducted sensitivity analyses to evaluate the robustness of the primary analysis results based on the interim PFS data per investigator assessment. The results are summarized in Table 17.

FDA Sensitivity Analysis 1: PFS analysis was stratified by randomization stratification factor data collected from CRFs.

FDA Sensitivity Analysis 2: Patients whose treatments were discontinued due to toxicity before progression were censored at the last tumor assessment.

FDA Sensitivity Analysis 3: In this "worst case" analysis of PFS based on investigator assessment, patients whose treatments were discontinued without a documented PFS event were censored at the date of discontinuation in the placebo arm but were classified as having had a PFS event in the everolimus arm.

FDA Sensitivity Analysis 4: If PFS event types (event vs. censoring) were same between IRC and investigator assessment, the shortest PFS time was used. For discrepant cases (i.e. cases that have been deemed failure according to one source and censored observation according to the other source), patients were considered as failures and failure time was used.

Table 17. Overview of FDA's Sensitivity Analyses of PFS (Interim) per Investigator Assessment

Sensitivity Analysis	Everolimus + Exemestane	Placebo + Exemestane	Hazard Ratio (95% CI)
	Median PFS (months)		
FDA Sensitivity Analysis 1	6.93	2.83	0.44 (0.36, 0.54)
FDA Sensitivity Analysis 2	6.97	2.92	0.43 (0.34, 0.53)
FDA Sensitivity Analysis 3	5.42	2.79	0.63 (0.52, 0.78)
FDA Sensitivity Analysis 4	5.55	2.76	0.42 (0.35, 0.52)

The same sensitivity analyses were conducted based on the final PFS data, and consistent PFS benefit from the everolimus arm was observed. The results of sensitivity analyses support the robustness of the primary efficacy findings.

FDA Exploratory Analysis: Evaluation of Time to Tumor Assessment

To evaluate whether the assessment time influenced PFS outcome, an exploratory analysis comparing time to tumor assessment between the two treatment arms was performed. Time from randomization to each assessment (including unscheduled visits) was calculated. When a patient missed a scheduled visit, his/her next visit time was used to calculate the time to the current assessment. Log-rank test was used to test if cumulative percentages (survival curves) were equal in the two treatment arms. Medians and test results are presented in Table 18. The log-rank test showed that there was no significant difference between the two treatment arms on time to assessment, except for the first assessment. Although the p value in the first assessment was less than 0.05, the median in the first assessment was the same for both arms. There were eight patients in the everolimus arm and one patient in the placebo arm with the first post-baseline tumor assessment performed after week 8. Among these nine patients, only one patient developed disease progression at the first assessment. Therefore, the significant difference in time to the first assessment should unlikely bias the overall PFS analysis. Assessment visits appeared to be equally divided amongst early and late visits (Figure 4). The actual assessment date occurred at a mean of 0.5 days prior to the scheduled date for patients on the placebo arm versus a mean of 0.4 days later for patients on the everolimus arm.

Table 18. Median (in weeks) of Time to Tumor Assessment and Log-rank Test

Time from randomization to the	Median (n), in weeks		Log-rank Test P-value
	Everolimus + Exemestane (N=485)	Placebo + Exemestane (N=239)	
1st assessment	6 (457)	6 (228)	0.027
2nd assessment	12 (343)	12 (136)	0.199
3rd assessment	18.14 (248)	18 (93)	0.806
4th assessment	24 (179)	23.86 (59)	0.567
5th assessment	30.14 (130)	30.14 (37)	0.632
6th assessment	36.07 (86)	36 (20)	0.334
7th assessment	42.14 (62)	42 (15)	0.501
8th assessment	48.14 (41)	48.14 (10)	0.631

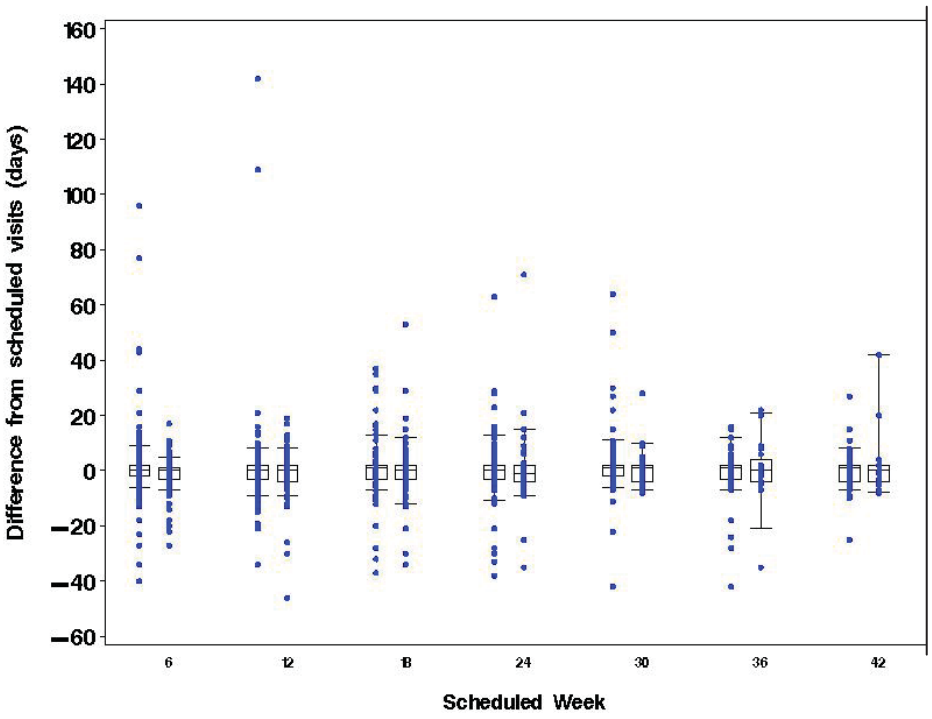

Figure 6. Compliance with Scheduled Tumor Assessment Times Based on Investigator Assessment

Secondary Endpoint Results

Overall Survival

Overall survival was the key secondary efficacy endpoint. The first interim OS analysis was conducted at the time of the interim PFS analysis, when 83 (21%) of 398 required death events for the final OS analysis occurred. The second interim OS analysis was conducted when 182 (46%) deaths events occurred. The results of the 1st and 2nd OS interim analyses in the FAS population are presented in Table 19. The corresponding Kaplan-Meier plots are given in Figure 5 and Figure 6, respectively. There was no statistically significant difference between the two treatment arms with respect to OS at both interim analyses (one-sided p-value of 0.15 at the first interim analysis and 0.046 at the second interim analysis). The hazard ratio for OS was 0.79 (95% CI: 0.50, 1.24) at the first interim analysis and 0.77 (95% CI: 0.57, 1.04) at the second interim analysis.

Table 19. Summary of Overall Survival Interim Analyses

	Everolimus + Exemestane (N=485)	**Placebo + Exemestane (N=239)**
First interim analysis		
Number of deaths, n (%)	52 (11)	31 (13)
Median (95% CI), in months	17.1 (17.1, NR)	15.1 (15.1, NR)
25th percentile (95% CI), in months		
Hazard ratio (95% CI) [a]	0.79 (0.50, 1.24)	
Stratified log rank p-value (one-sided) [b]	0.15	
Second interim analysis		
Number of deaths, n (%)	112 (23)	70 (29)
Median (95% CI), in months	NR (NR, NR)	NR (20.7, NR)
25th percentile (95% CI), in months	15.5 (13.1, 17.5)	13.6 (11.0, 15.7)
Hazard ratio (95% CI) [a]	0.77 (0.57, 1.04)	
Stratified log rank p-value (one-sided) [b]	0.046	

NR= not reached

[a] Hazard ratio was obtained from a Cox proportional hazards model stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis

[b] P-value was obtained from a one-sided log-rank test model stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis.

[Source Module 1.11 "bolero-2-efficacy-report-20110622" Table 8 and "crad001y2301-second-interim-os-analysis" Table 1]

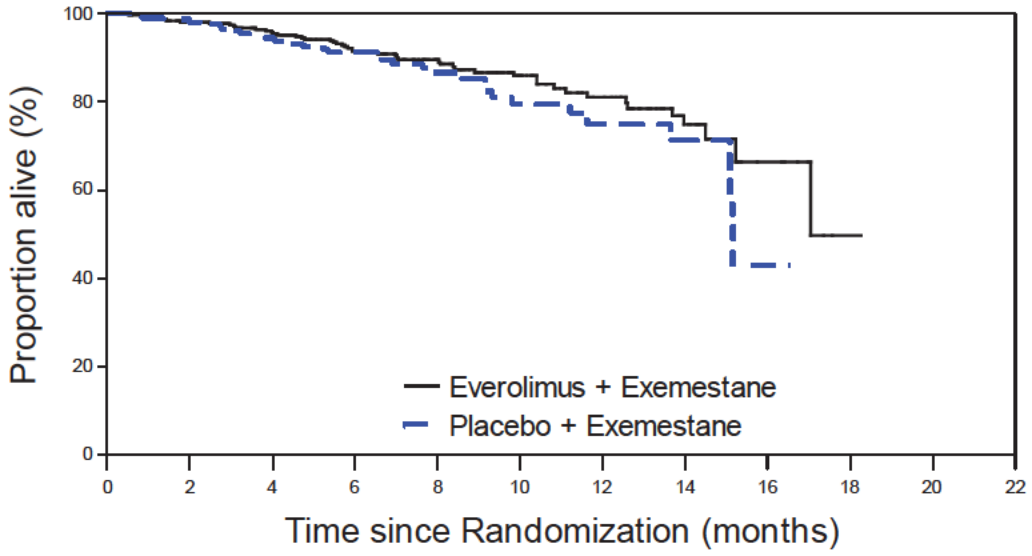

Figure 7. Kaplan-Meier Curves of the 1st Interim Overall Survival Analysis

[Source Module 1.11 "bolero-2-efficacy-report-20110622" Figure 3]

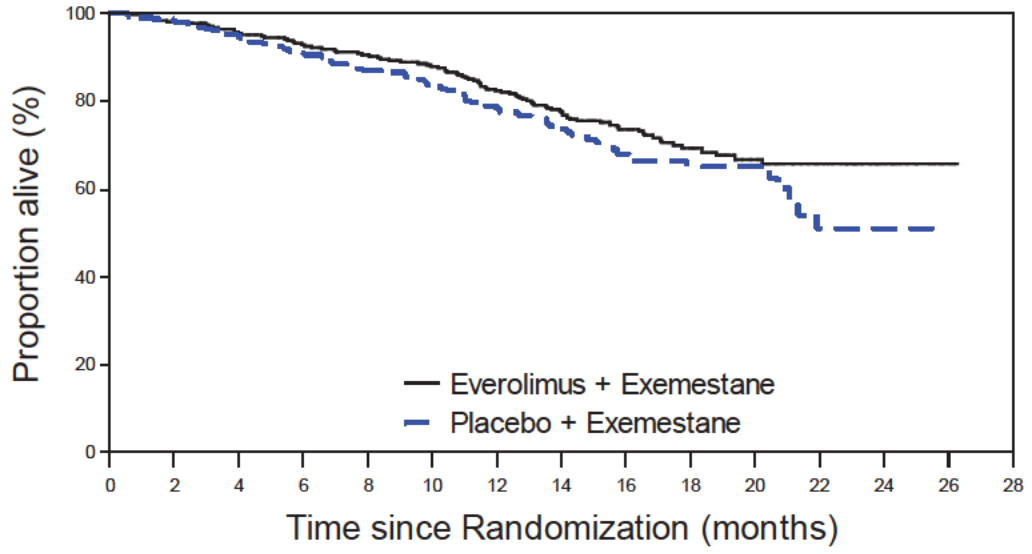

Figure 8. Kaplan-Meier Curves of the 2nd Interim Overall Survival Analysis

[Source Module 1.11 "crad001y2301-second-interim-os-analysis" Figure 1]

Reviewer's Comments

- *Based on the actual number of deaths at each interim analysis, the significance level was 0.000001 at the first interim analysis and 0.001 at the second interim analysis using O'Brien-Fleming boundary. Both interim analyses did not cross the pre-specified efficacy boundary.*
- *As specified in the study protocol, patients enrolled in the placebo arm were not allowed to crossover to receive study-supplied everolimus after disease progression. Therefore, no confounding effect due to crossover was expected.*

Overall Response Rate

At the time of the final PFS analysis, objective response rate per investigator was 12.6% in the everolimus arm vs. 1.7% in the placebo arm. Three complete responses (0.6%) were observed among patients in the everolimus arm. Similarly, objective response rate per central radiology review was 12.6% in the everolimus arm vs. 2.1% in the placebo arm. Due to the small values of the response rate, duration of response and time to response were not calculated.

ECOG performance status

Time to deterioration of ECOG performance status by ≥1 point was similar between the two treatment arms with a HR of 1.05 ((95% CI: 0.76, 1.44). The estimated medians of time to deterioration were 13.8 and 8.7 months for the everolimus arm and the placebo arm, respectively.

Patient Report Outcomes

The primary QoL variable of interest was the global health domain score of the QLQ-C30 questionnaire. Completion rates within on-study patients for the QLQ-C30 in each treatment group across each assessment time point were shown in Table 20. Per protocol, QoL data were collected up to disease progression. A lot of missing data were observed due to patients progressing at different time points.

Table 20. Completion Rate of EORTC QLQ-C30

Visit	Everolimus + Exemestane	Placebo + Exemestane
	Patients with valid questionnaire/Patients on study (%)	Patients with valid questionnaire/Patients on study (%)
Baseline	452/485 (93)	224/239 (94)
Wk 6	415/454 (91)	198/216 (92)
Wk 12	309/341 (91)	121/134 (90)
Wk 18	217/251 (87)	84/91 (92)
Wk 24	155/180 (86)	47/58 (81)
Wk 30	112/126 (89)	31/39 (80)
Wk 36	77/88 (88)	16/22 (73)
Wk 42	54/59 (92)	14/15 (93)
Wk 48	32/38 (84)	9/11 (82)

[Source: CSR Table 14.2-3.7]

Median times to deterioration (≥ 5%) of global health domain score were similar for the two treatment arms; no significant difference was observed with a HR of 0.92 (95% CI: 0.72, 1.17).

A mixed effect longitudinal model was fit on the change from baseline in the global health domain score, and showed a 5-point reduction in the everolimus arm relative to the placebo arm. However, the results should be interpreted with caution due to a large amount of missing data.

Reviewer's Comment
All QoL analyses are considered as exploratory due to large portion of missing data and un-validated instruments.

Conclusions for Efficacy

The pivotal study CRAD001Y2301 met the study primary objective by showing a hazard ratio of 0.45 (95% CI: 0.38 – 0.54; p-value < 0.0001) for the everolimus arm versus the placebo arm in PFS as per local investigator assessment. The median PFS time was 7.82 months in the everolimus arm compared to 3.19 months in the placebo arm. Subgroup and sensitivity analyses for PFS were consistent with the overall results of the primary analysis. The overall survival results were not yet mature and no statistically significant difference in OS was noted in the first two pre-specified interim analyses. At the second interim analysis, the overall survival curves numerically favored the everolimus arm. In addition, the everolimus arm did not show improvement in quality of life compared to the placebo arm.

3.3 Evaluation of Safety

There was a higher rate of on-treatment mortality (6.2% vs. 1.3%) in patients 65 years of age or older who received everolimus compared to those that received placebo. Please refer to the clinical evaluations of this application for safety results and conclusions for safety.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Table 21 summarizes PFS results by gender, age, race and geographic region. PFS results across all subgroups were consistent, with point estimates for HR ranging from 0.38 to 0.62. All PFS analyses in this section were based on the final PFS data per investigator assessment.

Table 21. PFS Subgroup Analysis by Age, Race, and Region

	N	Everolimus + Exemestane		Placebo + Exemestane		Hazard Ratio[a] (95% CI)
		# event/n (%)	Median (months)	# event/n (%)	Median (months)	
Age						
< 65 years	449	192/290 (66)	8.31	138/159 (87)	2.92	0.38 (0.30, 0.47)
≥ 65 years	275	118/195 (61)	6.83	62/80 (77)	4.01	0.59 (0.43, 0.80)
Race						
Asian	143	67/98 (68)	8.48	35/45 (78)	4.14	0.62 (0.41, 0.94)
Caucasian	547	229/361 (63)	7.36	158/186 (85)	2.96	0.42 (0.34, 0.51)
Other	34	14/26 (54)	6.93	7/8 (87)	1.41	0.42 (0.34, 0.51)
Region						
Asia	137	64/94 (68)	8.48	34/43 (79)	4.14	0.60 (0.40, 0.92)
Europe	275	128/192 (67)	7.16	72/83 (87)	2.83	0.46 (0.34, 0.61)
North America	274	100/174 (57)	8.41	81/100 (81)	2.96	0.38 (0.28, 0.52)
Other	38	18/25 (72)	4.53	13/13 (100)	1.48	0.40 (0.19, 0.87)
Region						
U.S.	223	81/146 (55)	6.97	62/77 (81)	3.19	0.41 (0.29, 0.57)
Non – U.S.	501	229/339 (68)	8.08	138/162 (85)	3.32	0.47 (0.38, 0.58)

[a] Hazard ratios were estimated from unstratified Cox proportional hazards models. A hazard ratio <1 indicates a lower risk with everolimus compared placebo

4.2 Other Special/Subgroup Populations

Exploratory analyses of PFS by sensitivity to prior hormonal therapy, presence of visceral metastasis, extent of prior therapy, and bone only disease at baseline are presented in Table 22. All PFS analyses were based on the final PFS data per investigator assessment.

Table 22. Additional PFS Subgroup Analyses

	N	Everolimus + Exemestane		Placebo + Exemestane		Hazard Ratio [a] (95% CI)
		# event/n (%)	Median (months)	# event/n (%)	Median (months)	
Sensitivity to prior hormonal therapies						
No	114	54/76 (71)	6.83	33/38 (87)	2.83	0.55 (0.35, 0.84)
Yes	610	256/409 (63)	8.05	167/201 (83)	3.94	0.43 (0.35, 0.53)
Visceral metastasis						
No	318	122/214 (57)	9.86	84/104 (81)	4.21	0.41 (0.31, 0.55)
Yes	406	188/271 (69)	6.83	116/135 (86)	2.76	0.47 (0.37, 0.60)
Bone only lesions at baseline						
No	569	262/380 (69)	6.90	164/189 (87)	2.79	0.46 (0.38, 0.56)
Yes	155	48/105 (43)	12.88	36/50 (72)	5.49	0.36 (0.23, 0.55)
Prior chemotherapy						
No	232	94/149 (63)	6.97	69/83 (83)	3.45	0.52 (0.38, 0.72)
Yes	492	216/336 (64)	8.18	131/156 (84)	3.19	0.42 (0.33, 0.52)
Disease-refractoriness to NSAI						
In adjuvant only	199	83/142 (58)	8.74	48/57 (84)	2.83	0.32 (0.22, 0.46)
In metastatic only	505	217/333 (65)	6.97	146/172 (85)	4.01	0.49 (0.40, 0.61)
In both settings	20	10/10 (100)	6.08	6/10 (60)	2.92	0.93 (0.33, 2.63)
Time since Diagnosis to 1st recurrence/metastasis						
< 1 year	179	87/121 (72)	6.70	49/58 (84)	2.96	0.58 (0.41, 0.83)
1-5 years	254	108/168 (64)	7.03	77/86 (90)	2.76	0.32 (0.24, 0.44)
5-10 years	161	59/110 (54)	12.35	40/51 (78)	5.29	0.40 (0.27, 0.60)
> 10 years	125	53/82 (65)	8.41	33/43 (77)	4.17	0.58 (0.38, 0.91)
Number of prior hormonal therapies						
1	266	114/182 (63)	7.43	73/84 (87)	4.07	0.49 (0.37, 0.66)
2	318	133/210 (63)	8.08	88/108 (81)	2.86	0.45 (0.34, 0.59)
3	90	38/65 (58)	9.66	19/25 (76)	2.96	0.33 (0.18, 0.59)
> 3	40	25/28 (89)	6.97	20/22 (91)	1.74	0.43 (0.23, 0.79)

[a] Hazard ratios obtained using unstratified Cox proportional hazards models. A hazard ratio <1 indicates a lower risk with everolimus compared to placebo

Reviewer's Comments

- *All the subgroup analyses presented in this section are considered exploratory or hypothesis generating and no formal inference may be drawn.*

- *The PFS improvement in the everolimus arm was held across various subgroups except in the small subgroup of Disease-refractoriness to NSAI in both adjuvant and metastatic settings which had only 20 patients.*

5. SUMMARY AND CONCLUSIONS

This efficacy supplemental NDA submission was for a regular approval of everolimus in (b) (4) Results from one pivotal Phase 3 study (CRAD001Y2301) were submitted to support the efficacy and safety evaluation. The pivotal study enrolled a total of 724 patients with 485 patients randomized to the everolimus arm and 239 patients to the placebo arm. The primary efficacy endpoint of this study was progression-free survival per local investigator assessment. At the final PFS analysis, per investigator assessment, the everolimus arm showed a statistically significant PFS improvement over the placebo arm in the FAS population, with a hazard ratio of 0.45 (95% CI: 0.38, 0.54; p-value<0.0001) and a 4.6-month improvement in the median (3.2 vs. 7.8 months for placebo arm and everolimus arm, respectively). The overall survival results were not yet mature and no statistically significant difference in OS was noted in the first two pre-specified interim analyses. At the second interim analysis (46% information), the overall survival curves numerically favored the everolimus arm with a hazard ratio of 0.77 (95% CI: 0.57, 1.04) and median were not reached in both treatment arms. The 3rd interim analysis and the final analysis of OS will be conducted when 275 and 398 deaths occur, respectively. The overall response rate was 12.6% in the everolimus arm and 1.7% in the placebo arm based on the responses assessed by investigator. No quality of life benefit from everolimus treatment was observed.

5.1 Statistical Issues and Collective Evidence

Statistical issues included (1) the change of data source for the primary endpoint and (2) the use of results from the interim PFS analysis to support efficacy. However, this review concluded that these issues do not have impact on the efficacy conclusions.

In the protocol Amendment 1, the primary endpoint was changed from PFS by IRC to PFS by investigator assessment. The independent central review of the radiological data was retained and the results served as supportive analyses for the primary efficacy analysis. The discordance between investigator and IRC assessment was seen in 42% of the everolimus patients and 50% of the placebo patients. This review concluded that consistent hazard ratios were produced despite various assessments of PFS.

In addition, to evaluate potential assessment bias from investigator assessment, Early Discrepancy Rate (EDR) and Late Discrepancy Rate (LDR) between IRC and investigator for each arm were calculated according to the method proposed by Amit et al [1]. The differential discordance was calculated as the difference of EDR or LDR between the everolimus arm and placebo arm. A negative differential discordance on EDR and/or a positive differential discordance on LDR suggest a bias in the investigator assessment favoring the everolimus arm. In this study, the everolimus arm had an EDR of 0.53 and a LDR of 0.29, while the placebo arm had an EDR of 0.46 and a LDR of 0.36. This review concluded that no investigator bias favoring the everolimus arm was detected as the differential discordance was positive on EDR and negative on LDR.

In the initial submission of this sNDA, results from a planned interim PFS analysis (68% information) were used to support efficacy. Due to issues related to interim PFS analyses in general, FDA requested that the applicant provide results from the final PFS analysis during the review cycle to confirm the interim findings. This review concluded that the PFS improvement in the everolimus arm was consistent in the interim analysis and in the final analysis. The efficacy results from the final PFS analysis will be used for labeling.

5.2 Conclusions and Recommendations

The applicant submitted results from a multicenter, phase 3, randomized, double-blind, placebo-controlled clinical study (Study CRAD001Y2301) comparing everolimus plus exemestane to placebo plus exemestane in the treatment of postmenopausal women with ER- positive locally advanced or metastatic breast cancer who are refractory to letrozole or anastrozole. The everolimus arm showed a statistically significant improvement over placebo in PFS as assessed by local investigator in all randomized patients, which was supported by consistent PFS results as per independent central review.

The overall survival results were not mature at this time and no statistically significant difference in OS was noted in the first two interim analyses. The third interim analysis and the final analysis of OS will be performed when 275 and 398 deaths occur, respectively. No quality of life benefit was observed in everolimus compared with placebo. As PFS has not been proven to be a surrogate for OS in this disease setting, the clinical benefit of everolimus plus exemestane in treating patients with ER-positive metastatic breast cancer is not clear. The judgment on the meaningfulness of the improvement in PFS (in light of the toxicities and pre-mature OS) is deferred to the clinical review team.

REFERENCE

1. O. Amit, F. Mannino, A.M. Stone, W. Bushnell, J. Denne, J. Helterbrand, and H.U. Burger, Blinded independent central review of progression in cancer clinical trials: Results from a meta-analysis. European Journal of Cancer, 2011 Aug; 47(12):1772-8

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Lijun Zhang, Ph.D.
Date: May 18th, 2012

Concurring Reviewer(s)

Statistical Team Leader: Shenghui Tang, Ph.D.

Biometrics Division Deputy Director: Thomas E Gwise, Ph.D.

cc:
Project Manager: Christy Cottrell
Medical Officer: Tatiana Prowell, M.D., Geoffrey Kim, M.D.
Medical Team Leader: Patricia Cortazar, M.D.
Primary Statistical Reviewer: Lijun Zhang, Ph.D.
Statistical Team Leader: Shenghui Tang, Ph.D.
Biometrics Division Deputy Director: Thomas E Gwise, Ph.D.
Lillian Patrician

CHECK LIST

Number of Pivotal Studies: 1

Trial Specification
Specify for each trial:

Protocol Number (s): CRAD001Y2301
Protocol Title (optional): 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
Phase: 3
Control: placebo
Blinding: double-blind
Number of Centers: 190
Region(s): North America, Europe, Asia, and other
Treatment Arms: Everolimus plus Exemestane vs. placebo plus Exemestane
Treatment Schedule: everolimus (10 mg daily) + exemestane (25 mg daily)
Placebo + exemestane (25 mg daily)

Randomization: Yes
Ratio: 2:1
Method of Randomization: stratified
Stratification Factor: Documented sensitivity to prior hormonal therapy (yes vs. no)
Presence of visceral metastasis (yes vs. no)

Primary Endpoint: PFS per investigator
Primary Efficacy Analysis Population: intent-to-treat population
Statistical Design: Superiority
Adaptive Design: No
Primary Statistical Methodology: stratified log-rank test
Interim Analysis: Yes for both PFS and OS
If yes:
PFS
No. of Times: 1
Method:
α Adjustment: Yes
α Spending Function: O'Brien-Fleming Boundary
OS
No. of Times: 3
Method:

α Adjustment: Yes

α Spending Function: O'Brien-Fleming Boundary

DSMB: Yes

Sample Size: 705

Sample Size Determination:

Statistic = log rank

Power= 90% for PFS

HR= 0.74 (corresponding medians: 3.7 vs. 5 months)

α = 0.025 (one-sided)

Was there an **Alternative Analysis** in case of violation of assumption? No.

- Were there any major changes, such as changing the statistical analysis methodology or changing the primary endpoint variable? Yes. In protocol Amendment #1, the primary endpoint was changed from PFS by independent review or PFS by investigator
- Were the **Covariates** pre-specified in the protocol? No.
- Did the Applicant perform **Sensitivity Analyses**? Yes
- How were the **Missing Data** handled? In time-to-event analyses, patients without events were censored.
- Was there a **Multiplicity** involved? Yes. PFS and OS were tested in a hierarchical way
- **Multiple Secondary Endpoints**: Yes. However, only OS will be included in label.

Were Subgroup Analyses Performed? Yes

- Were there any **Discrepancies** between the protocol/statistical analysis plan vs. the study report? No.
- Overall, was the study positive (Yes/No)? Yes for primary endpoint

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/s/

LIJUN ZHANG
05/18/2012

SHENGHUI TANG
05/18/2012

THOMAS E GWISE
05/18/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-334/S-016

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA	22-334
Submission Date:	3 Nov, 2011
Brand Name:	Afinitor™
Generic Name:	Everolimus
Formulation:	Everolimus: 2.5, 5 and 10 mg tablets Exemestane: 25 mg tablet
Pharmacometrics (PM) Reviewer (Primary Reviewer):	Jingyu Yu, PhD
PM Team Leader:	Christine Garnett, PharmD
OCP Reviewer:	Elimika Pfuma, PharmD, PhD
OCP Team Leader:	Qi Liu, PhD
OCP Division:	Division of Clinical Pharmacology V
ORM Division:	Division of Drug Oncology Products
Sponsor:	Novartis
Submission Type; Code:	Supplement 016; SDN # 429; Serial # 168
Proposed Dosing regimen:	10 mg daily
Proposed Indication:	(b) (4)

1 EXECUTIVE SUMMARY

Everolimus (Afinitor®) is an inhibitor of the human kinase mammalian target of rapamycin (mTOR). Afinitor® is currently indicated for the treatment of patients with advanced renal cell carcinoma (RCC), progressive neuroendocrine tumors of pancreatic origin (PNET) and in subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS). The approved dose in RCC and PNET is a fixed dose of 10 mg once daily. Therapeutic drug monitoring is used in SEGA with a starting dose (b) (4) with the dose titrated to C_{trough} of 5 to 10 ng/mL.

The current submission is an efficacy supplement (NDA 22-334, SN 16) for everolimus in combination with (b) (4). This recommendation is in agreement with the FDA clinical reviewers' proposed revisions to the label.

In the pivotal trial (Study Y2301), patients were randomized to receive everolimus (10 mg/day) plus exemestane (25 mg/day) or placebo plus exemestane (25 mg/day). There was a 45 – 64% mean increase in exemestane exposure when given in combination with everolimus. It is unclear if this mean increase in exemestane exposure has an effect on efficacy or safety in the combination arm. The exemestane exposure-response relationship for efficacy and safety could not be established due to limited PK data (10% of patients). The estradiol levels at steady state (4 weeks) were similar between the two treatment arms; however, estradiol levels may not be directly related to PFS.

The sponsor proposed labeling language stating that no increase in adverse events related to exemestane were observed in patients receiving the combination. The clinical safety reviewer agreed that the sponsor's statement was acceptable.

In the combination arm, on-treatment deaths in elderly patients (≥65 y) were higher than younger patients (< 65 y). Based on the original NDA review of everolimus, age, weight, gender and renal function have no effect on PK. It is known that hepatic impairment and coadministration of CYP3A4 inhibitors increase everolimus exposure; however, the elderly patients who died on-treatment in pivotal trial had normal baseline bilirubin and serum albumin levels and only one of these patients had a strong CYP3A4 inhibitor as concomitant medication. Therefore, we can not conclude that the higher on-treatment deaths in elderly patients were due to higher exposures.

Pharmacometrics Reviewer: Jingyu (Jerry) Yu, PhD	Team Leader: Christine Garnett, PharmD
Reviewer: Elimika Pfuma, PharmD, PhD	Team Leader: Qi Liu, PhD
Division of Clinical Pharmacology 5	Division of Clinical Pharmacology 5

Cc: DDOP: CSO - C Cottrell; MTL - E Maher MO - T Prowell and G Kim

DCP-5: Reviewers - E Pfuma and J Yu; DDD - B Booth; PM TL - C Garnett; DCP5 TL - Q Liu; DD - A Rahman

1.1 RECOMMENDATION

The Office of Clinical Pharmacology finds this supplemental NDA acceptable, provided the Applicant and the Agency come to a mutually satisfactory agreement regarding the labeling language.

For detailed labeling recommendations please see Section 3 – Detailed Labeling Recommendations.

1.2 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

Everolimus (Afinitor) has previously been reviewed under NDA 22334 (original submission 06/27/08). For brevity only QBR questions regarding this current sNDA

submission will be addressed below.

2 QUESTION BASED REVIEW

2.1 What is the proposed indication?

The sponsor is seeking approval of Afinitor in (b) (4) a combination with exemestane and are in agreement with the FDA clinical reviewers labeling language recommendation: "AFINITOR is a kinase inhibitor indicated for the treatment of patients with postmenopausal hormone receptor-positive advanced breast cancer (HR+ advanced BC) in combination with exemestane, (b) (4) (b) (4)

2.2 What are the design features of the clinical studies used to support dosing or claims?

The pivotal trial Y2301 was a randomized, double-blind, placebo-controlled phase 3 study of everolimus in combination with exemestane in the treatment of postmenopausal women (N=724) with estrogen receptor positive locally advanced or metastatic breast cancer who are refractory to letrozole or anastrozole. At a pre-specified interim analysis (cut-off 02/11/11), a reduction in PFS as per investigator assessment of 57% was observed (HR 0.43; 95% CI (0.35, 0.54); p-value of $1.4x10^{-15}$). This corresponded to a 4.10 month prolongation in median PFS, from 2.83 months for patients receiving placebo plus exemestane to 6.93 months for everolimus plus exemestane-treated patients.

2.3 Is there an exposure-response relationship for exemestane?

Co-administration of everolimus and exemestane increased exemestane exposure by 45% and 64% in C_{min} (trough concentration) and C_{2h} (concentration at 2 h post-dose), respectively. This result was based on PK data from the 88 patients in original submission and additional PK data from 43 patients submitted later. Therefore, the 64% increase in C_{2h} was updated from the 71% initially proposed in sponsor's label based on the 88 patients. The between-subject variability in C_{min} and C_{2h} in both arms was high, with CV% ranged from 98.8% to 146 % (Table 1).

To evaluate whether the mean increase in exemestane exposure has impact on efficacy and safety in the combination arm, the reviewer attempted to conduct an exposure-response analysis (e.g., PFS or adverse events) for exemestane. The total number of subjects included in the everolimus + exemestane arm and placebo + exemestane arm were 485 and 239, respectively. However, either C_{min} (N=42) or C_{2h} (N=47) data for exemestane are only available in approximately 10% of all patients in the pivotal study (Table 1). Due to the insufficient exposure data collected in this trial, we could not evaluate the exposure-response relationships for exemestane.

No significant difference in estradiol levels at steady state (4 weeks) was observed between the two treatment arms; however, it should be noted that estradiol levels may not be directly related to PFS.

To summarize, we can not make a conclusion regarding whether or not the increased exemestane exposure has impact on efficacy or safety.

Table 1. Exemestane plasma concentrations [ng/mL] at week 4 – Safety Set

	Everolimus plus exemestane	Placebo plus exemestane
Pre-dose (C_{min})		
N	42	25
Mean ± sd (CV%)	1.42 ± 4.64 (327%)	0.65 ± 0.91 (140%)
Geometric mean (Geometric CV%)	0.65 (101%)	0.45 (98.8%)
Median (Range)	0.53 (0.2 – 30.6)	0.40 (0.0 – 4.6)
Geometric mean ratio [90% CI] [a]	1.45 [1.01, 2.06]	
2 hours post administration (C_{2h})		
N	47	25
Mean ± sd (CV%)	22.8 ± 19.0 (83.4%)	12.6 ± 11.3 (89.4%)
Geometric mean (Geometric CV%)	15.6 (146%)	9.49 (114%)
Median (Range)	16.4 (0.4 - 96.8)	10.1 (0.0 - 50.8)
Geometric mean ratio [90% CI] [a]	1.64 [1.07, 2.51]	

[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.

Sources: CTD 2.7.2 Addendum to Summary of Clinical Pharmacology - Breast Cancer, Page 8

2.4 Can the disproportional number of deaths within 28 days of treatment between elderly patients (≥65 y) and younger patients (<65 y) (Table 2) be explained by possible higher everolimus exposures in elderly patients?

The exposure data were collected at or after 28 days of treatment (at steady state). Therefore, the exposure data in elderly patients who died within 28 days of treatment is not available for direct comparison with younger patients. Absence of exposure data in patients that died within 28 days of treatment also precludes assessment of exposure-safety (death) relationship of everolimus.

Based on a population PK analysis of everolimus for the treatment of advanced renal cell carcinoma (RCC) in the original NDA review, the oral clearance of everolimus does not depend on age, weight, gender and renal function within the range evaluated (age: 27-85 years, weight: 38-147 kg, creatine clearance: 25–178 ml/min) [*See* Pharmacometrics Review in clinical Pharmacology Review at 27 June 2008 by Dr. Nitin Mehrotra).

Based on the current everolimus label, increases in everolimus exposures are observed in patients with moderate hepatic impairment and with the concomitant use of strong CYP3A4 inhibitors. However, in this pivotal trial, elderly patients who died on-treatment had normal baseline bilirubin and serum albumin level and only one of them took strong CYP3A4 inhibitor as concomitant medication.

To summarize, the exposures in the elderly patients are not expected to be significantly higher than those in the younger patients. Therefore we can not conclude that higher on-treatment deaths in elderly patients were due to higher exposures.

Table 2. Everolimus plasma concentrations [ng/mL] at week 4 – Safety Set in pivotal trial (Y2301)

	Deaths within 28 days of treatment	
	Everolimus 10mg+exemestane	Placebo+exemestane
Total	12 (2.5%)	4 (1.7%)
Age < 65	3 (0.6%; 1.0%)	3 (1.3%; 1.9%)
Age ≥ 65	**9 (1.9%; 4.6%)**	1 (0.4%; 1.3%)

3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included. The single underlined words are the proposed changes added by the applicant and the double underlined words are proposed by the clinical pharmacology reviewer. The language rejected by the clinical pharmacology reviewer has a double strikethrough.

(b) (4)

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/s/

JINGYU YU
06/05/2012

ELIMIKA PFUMA
06/05/2012

CHRISTINE E GARNETT
06/05/2012

QI LIU
06/05/2012

BIOPHARMACEUTICS REVIEW
Office of New Drug Quality Assessment

Application No.:	NDA 22-334/ES-016 (SDN 429) Efficacy Supplement	**Reviewer:** Elsbeth Chikhale, PhD	
Submission Date:	November 4, 2011		
Division:	Division of Oncology Drug Products	**Team Leader:** Angelica Dorantes, PhD	
Applicant:	Novartis Pharmaceuticals Corporation	**Acting Supervisor:** Angelica Dorantes, PhD	
Trade Name:	Afinitor	**Date Assigned:**	December 5, 2011
Established Name:	Everolimus	**Date of Review:**	April 25, 2012
Indication:	Treatment of postmenopausal wome (b) (4)	**Type of Submission:** Priority Efficacy Supplement	
Formulation/ strengths	Tablets/ 2.5 mg/tablet, 5 mg/tablet, 7.5 mg/tablet, 10 mg/tablet		
Route of Administration	Oral		
Type of Review	Review of Biopharmaceutics information.		

SUBMISSION:

This submission is a Priority Efficacy Supplements for NDA 22-334. This supplement provides for an additional indication of treatment of postmenopausal women (b) (4) The new indication is supported by one pivotal phase 3 clinical study (Y2301).

BIOPHARMACEUTIC INFORMATION:

The dosage strength and formulation used in clinical study Y2301 has been previously approved under NDA 22-334 for the same route of administration (oral) for a different indication.

According to the information submitted in the P.2 section (Pharmaceutical Development), study Y2301 uses 5 mg tablets that have the marketing formulation: round tablets with curvature, no imprint, manufactured at (b) (4) (NDA approved site). The Applicant states that this sNDA does not propose any changes to the CMC information.

Reference is made to the pre-sNDA meeting held on October 11, 2011, between Norvartis and the

FDA, during which the Applicant requested a waiver to submit section 2.7.1 (Summary of Biopharmaceutics Information) as part of the sNDA. The FDA confirmed during the meeting that it was acceptable for the Applicant to leave this section out of the sNDA, because the Biopharmaceutics information to support the 5- and 10-mg dosage strengths were previously submitted in the original NDA (Seq. 000) and the information for the 2.5-mg dosage strength was submitted as part of a CMC supplement (PAS-5, SN 0061) submitted on 22-Dec-2009 and approved on 9-Jul-2010. Information for the 7.5-mg dosage strength was submitted to NDA 22-334 as a CMC supplement on 29-Mar-2011 (PAS-11, SN 0132), and was subsequently approved on 29-Jul-2011. In addition, the PK everolimus samples from the pivotal phase 3 clinical study (Y2301) that supports this sNDA were analyzed using the same LC/MS validated method that was described in the Biopharmaceutical Information submitted in the original NDA.

EVALUATION:

During the pre-sNDA meeting it was agreed that Norvartis did not have to resubmit any Biopharmaceutics information for the proposed dosage strengths, (2.5 mg, 5 mg, 7.5 mg, and 10 mg), since this information was previously submitted and reviewed by FDA. The Applicant states that no new Biopharmaceutics data have been generated for the approved dosage strengths of their product and therefore the current sNDA ES-016 submission only refers to the Biopharmaceutics information that was previously reviewed and approved by FDA under the Original NDA and Supplements.

RECOMMENDATION:

From the Biopharmaceutics viewpoint, NDA 22-334/S-016 is recommended for approval. Additional CMC issues associated with this sNDA should be evaluated by the CMC Reviewer.

Signature	**Signature**
Elsbeth Chikhale, Ph.D.	Angelica Dorantes, Ph.D.
Biopharmaceutics Reviewer	Acting Biopharmaceutics Supervisory Lead
Office of New Drug Quality Assessment	Office of New Drug Quality Assessment

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/s/

ELSBETH G CHIKHALE
04/25/2012

ANGELICA DORANTES
04/25/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-334/S-016

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
Division of Prescription Drug Promotion (DPDP)
Division of Consumer Drug Promotion (DCDP)

******Pre-decisional Agency Information******

Memorandum

Date: June 20, 2012

To: Christy Cottrell, Regulatory Project Manager
Division of Oncology Products 1 (DOP1)
Office of Hematology Oncology Products (OHOP)

From: Marybeth Toscano, PharmD, Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
OPDP

Michelle Safarik, MSPAS, PA-C, Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)
OPDP

Subject: OPDP comments on draft product labeling for Afinitor (everolimus) tablets (Afinitor)
NDA 022334/SE1-016

In response to your consult request dated January 31, 2012, we have reviewed the draft version of the Package Insert for Afinitor tablets, SE1-016. We offer the following comments based on the substantially complete label sent to us on June 11, 2012.

(b) (4)

[redacted]

39 Pages Immediately Following Withheld - b(4) Draft Labeling

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/s/

MARYBETH TOSCANO
06/20/2012

MICHELLE L SAFARIK
06/20/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	June 25, 2012
To:	Robert Justice, MD Director **Division of Oncology Products 1 (DOP 1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	AFINITOR (everolimus)
Dosage Form and Route:	tablets
Application Type/Number:	NDA 22-334
Supplement Number:	S-016
Applicant:	Novartis Pharmaceuticals Corporation

1 INTRODUCTION

On November 3, 2011, Novartis submitted for the Agency's review an Efficacy Supplement to their New Drug Application (NDA) 22-334/S-016, for AFINITOR (everolimus) tablets. The Applicant proposes a new indication for the treatment of postmenopausal women with advanced hormone receptor-positive breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole. On January 31, 2012, the Division of Oncology Products 1 (DOP 1) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for AFINITOR (everolimus).

This review is written in response to a request by DOP 1 for DMPP to review the Applicant's proposed Patient Package Insert (PPI) for AFINITOR (everolimus).

2 MATERIAL REVIEWED

- Draft AFINITOR (everolimus) Patient Package Insert (PPI) received on November 3, 2011, revised by the Applicant on June 11, 2012 , and received by DMPP on June 11, 2012.
- Draft AFINITOR (everolimus) Prescribing Information (PI) received on November 3, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on June 11, 2012.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. The proposed PPI was provided in Verdana font, size 11; therefore, we did not need to reformat the document.

In our review of the PPI we have:

- performed a focused review of the proposed revisions to the PI and PPI
- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
06/25/2012

BARBARA A FULLER
06/25/2012

LASHAWN M GRIFFITHS
06/25/2012

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: May 25, 2012

TO: Geoffrey Kim, Reviewing Medical Officer
Tatiana Prowell, Reviewing Medical Officer
Patricia Cortazar, Medical Team Leader
Christy Cottrell, Regulatory Project Manager
Division of Oncology Products 1

FROM: Robert Young
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Lauren Iacono-Connors, Ph.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 022334/S-016

APPLICANT: Novartis Pharmaceuticals Corporation
East Hanover, NJ

DRUG: Afinitor (everolimus) Tablets
NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: Treatment of post-menopausal women (b) (4)

CONSULTATION REQUEST DATE: 3 Feb 2012
INSPECTION SUMMARY GOAL DATE: 28 May 2012
DIVISION ACTION GOAL DATE: 15 June 2012
PDUFA DATE: 3 Sept 2012

I. BACKGROUND: Protocol CRAD001Y2301 was a 2:1 randomized, double blind, placebo controlled trial of everolimus 10 mg daily vs. placebo, both in combination with exemestane 25 mg daily in postmenopausal women with estrogen receptor positive locally advanced or metastatic breast cancer refractory to non-steroidal aromatase inhibitors (NSAIs) letrozole or anastozole, and with documented recurrence or progression on last therapy for breast cancer. There was no fixed treatment duration. Dosing continued until objective tumor progression was determined locally using Response Evaluation Criteria in Solid Tumors (RECIST 1.0) or unacceptable toxicity, death or discontinuation for any other reason. The primary response variable was progression free survival with progression being based exclusively on radiological findings interpreted by the local investigator. Secondary response variables included overall survival. A central radiology review was also conducted. The study was conducted in 24 countries with a total of 196 sites enrolling 724 subjects. The US sites enrolled 223 subjects, the largest number of subjects by country.

II. RESULTS (by Site):

Name of CI	Site # and # of Subjects	Inspection Date	Final Classification
Denise Yardley Sarah Cannon Research Institute 250 25th Avenue North, Suite 110 Nashville, TN 37203	Site #545 12 subjects	3/27-29/2012	Pending - VAI
Mikhail Shtivelband Ironwood Cancer and Research Centers 695 South Dobson Road Chandler, AZ 85224	Site #540 11 subjects	4/09-10/2012	Pending – NAI
J. Thaddeus Beck Highlands Oncology Group 3232 N. North Hills Blvd. Fayetteville, AR 72703	Site #534 14 subjects	4/17-19/2012	Pending - VAI

Key to Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; the Establishment Inspection Report (EIR) has not been received from the field, and complete review of EIR is pending.

1. Denise Yardley
   Nashville, TN

a. What was inspected: The case histories for all twelve enrolled subjects were examined.

b. General observations/commentary: There were no unreported protocol deviations or SAEs. There was documentation of all early terminations based primarily on clinical investigator assessment of clinical progression and no indication that the clinical investigator attempted to influence the study outcome. There were two consent issues raised, discussed with the clinical investigator and noted on a Form FDA 483 which was issued to the clinical investigator. Subjects 006 and 007 did not timely execute an updated amended version of the consent document as instructed by the IRB and subjects 001, 005, and 010 did not clearly indicate on the consent document whether they agreed or disagreed to storage of their samples for future research. The clinical investigator replied in writing to the issued Form FDA 483 and has taken appropriate steps to ensure that the observed regulatory violations will not be repeated in the future.

c. Assessment of data integrity: No data integrity issues were raised. The data from this site may be used in support of the pending application.

Note: Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

2. Mikhail Shtivelband
   Chandler, AZ

a. What was inspected: Seventeen subjects were screened, 11 subjects were enrolled in the study, and 9 subjects completed the study. The records of 100% of enrolled subjects (11) were reviewed for adverse events, concomitant medications, and inclusion/exclusion eligibility criteria. The case histories for five subjects were examined in depth.

b. General observations/commentary: The records appeared to be in good order. There was no under-reporting of AEs. No serious violations of the regulations were found and a Form FDA 483 was not issued.

c. Assessment of data integrity: The study appears to have been properly executed and the data generated by this site may be used in support of the pending application.

Note: Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon full review of the EIR.

3. J. Thaddeus Beck
Fayetteville, AR

a. What was inspected: The case histories of participating subjects were reviewed.

b. General observations/commentary: A number of different issues were identified which were discussed with the investigator and noted on the Form FDA 483 issued to the investigator. For example, the site failed to modify subject 00008's medication dose in accordance with the protocol sliding scale; failed to consistently obtain a five parameter hematology analysis as required by the protocol and instead on several occasions performed a three parameter hematology analysis; incorrectly transcribed subject 00015's platelet count from source document to eCRF on 12/15/10; and reported on the case report form for subject 00015 on 11/18/10 only one of four subject-reported adverse events. The clinical investigator responded to the issued Form FDA 483 on 23 April 2012 and took appropriate actions including the purchase of new laboratory equipment and correction of incomplete or incorrectly transcribed reports.

c. Assessment of data integrity: The data provided by this site appears to be reasonably reliable and may be used in the assessment of this application. The performance issues raised by this inspection were limited in number, varied in nature and were not related to the main study parameters. Most probably the overall validity of the study results will not be seriously affected.

Note: Observations noted above are based on the Form FDA 483 and communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical data from the inspected sites appear reliable based on available information and may be used in assessment of the pending application.

Note: Observations noted above are based on Form FDA 483 and/or communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and/or full review of the EIRs.

{See appended electronic signature page}

Robert Young
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

ROBERT S K YOUNG
05/25/2012

JANICE K POHLMAN
05/25/2012

LAUREN C IACONO-CONNORS
05/30/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-334/S-016

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name: 022334 s016/ Everolimus

PMC Description: Submit a final report, including datasets, for the final overall survival results from trial CRAD001Y2301 (BOLERO-2).

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	December 2011
	Trial Completion:	June 2014
	Final Report Submission:	June 2015
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☐ Unmet need
   ☒ Life-threatening condition
   ☒ Long-term data needed
   ☒ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☐ Theoretical concern
   ☐ Other

   Overall survival is a key secondary endpoint of the applicant's pivotal study. At the time of approval, the overall survival data were not mature and longer follow-up is needed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   Overall survival is a key secondary endpoint of the applicant's pivotal study. At the time of approval, the overall survival data were not mature and longer follow-up is needed to determine whether there is a survival advantage of the use of everolimus in conjunction with exemestane as compared to placebo plus exemestane in advanced hormone receptor positive breast cancer.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized double-blind, placebo-controlled trial 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

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other
A final determination of the overall survival of all subjects in the pivotal phase 3 trial.

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name: 022334 s016/ Everolimus

PMC Description: Conduct a 3-arm randomized trial 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 anastrazole

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	November 2012
	Study/Trial Completion:	August 2016
	Final Report Submission:	August 2017
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

The pivotal trial that led to the approval of everolimus in combination with exemestane for postmenopausal women with advanced hormone receptor positive breast cancer, did not address the contribution of exemestane to the treatment regimen. The everolimus monotherapy arm will address the contribution of exemestane to the treatment combination. The third treatment arm will compare the efficacy and safety of capecitabine monotherapy, a treatment regimen frequently used after progression on hormonal therapies, to the everolimus plus exemestane combination.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

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, biomarker evaluation, and safety. The trial will also evaluate capecitabine monotherapy relative to the combination of everolimus and exemestane, with respect to the same endpoints.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A 3-arm randomized trial 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 anastrazole

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☒ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

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/s/

CHRISTY L COTTRELL
07/13/2012

ROBERT L JUSTICE
07/20/2012

EXCLUSIVITY SUMMARY

NDA # 022334 SUPPL # 016 HFD # 150

Trade Name Afinitor

Generic Name everolimus

Applicant Name Novartis Pharmaceuticals Corporation

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1); SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 22334 Afinitor (everolimus) Tablets

NDA# 21560 Zortress (everolimus) Tablets

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study CRAD001Y2301

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

CRAD001Y2301

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 066279	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Christy Cottrell
Title: Regulatory Project Manager
Date: July 11, 2012

Name of Office/Division Director signing form: Robert L. Justice, MD, MS
Title: Director, DOP1

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALICE KACUBA
07/19/2012

ROBERT L JUSTICE
07/20/2012

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 022334 BLA #	NDA Supplement # 016 BLA Supplement #	If NDA, Efficacy Supplement Type: SE1
Proprietary Name: Afinitor Established/Proper Name: everolimus Dosage Form: Tablets		Applicant: Novartis Pharmaceuticals Corporation Agent for Applicant (if applicable):
RPM: Christy Cottrell		Division: DOP1

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is September 3, 2012 but Target Date=July 20, 2012	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

swer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA plement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

Copy of this Action Package Checklist[4]	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☐ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Ap July 20, 2012
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Included 7-19-12
• Original applicant-proposed labeling	Included
• Example of class labeling, if applicable	N/A

[4] Fill in blanks with dates of reviews, letters, etc.

Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Included 7-19-12
• Original applicant-proposed labeling	Included
• Example of class labeling, if applicable	N/A
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	N/A
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	N/A
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☐ DMEPA ☒ DMPP/PLT (DRISK) 6-25-12 ☒ ODPD (DDMAC) 6-20-12 ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)*	Included; 7-11-12
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☐ Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC June 13, 2012 If PeRC review not necessary, explain: ____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	Included
❖ Internal memoranda, telecons, etc.	N/A
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 10-11-11
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 4-8-09
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	N/A
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 7-20-12
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 7-19-12
PMR/PMC Development Templates *(indicate total number)*	☐ None Included - 2 PMCs
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	Concurred with 7-16-12 MOR
• Clinical review(s) *(indicate date for each review)*	7-16-12
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	N/A ☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested 5-30-12

[6] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology ☒ None	
Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None See concurrence with primary stat review
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None See concurrence with primary stat review
Statistical Review(s) *(indicate date for each review)*	☐ None 5-18-12
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None See concurrence with primary clin pharm review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 6-5-12
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None See concurrence with primary P/T review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 6-15-12 (2); 2-15-12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None See concurrence with primary CMC review
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 4-12-12
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None 4-25-12

Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	4-12-12
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☒ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

pendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's RA.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALICE KACUBA
07/20/2012

Kacuba, Alice

From: Thomas, Lincy [lincy.thomas@novartis.com]
Sent: Thursday, July 19, 2012 7:14 PM
To: Kacuba, Alice
Cc: Wang, Jessica-1
Subject: Final clean and track change: RE: question PPI- RE: URGENT----------Afinitor S-016
Importance: High
Sensitivity: Confidential
Attachments: Afinitor PI S-016_HER2negative.doc.zip; Afinitor PI S-016_FINAL clean.doc.zip

Alice

Attached is the final clean and track changes (HER2-) version of the PI.

We added 'HER2-negative' in Section 7.3, 8.5 and in the Patient PI (indication and common side effects list).

Also noticed that there is a comma before HER2-negative (Advanced Hormone Receptor-Positive, HER2-Negative...) – so we have made this consistent throughout.

Please let us know if there is anything else needed – please copy Jessica as I am driving home now.

The labels will be sent through the gateway tomorrow AM.

We would greatly appreciate approval tomorrow – so please keep us informed and we will have our colleagues on standby all day.

Thank you
Lincy

From: Kacuba, Alice [mailto:Alice.Kacuba@fda.hhs.gov]
Sent: Thursday, July 19, 2012 5:49 PM
To: Thomas, Lincy
Cc: Wang, Jessica-1
Subject: RE: question PPI- RE: URGENT----------Afinitor S-016
Importance: High
Sensitivity: Confidential

Sorry was at fax machine. I checked with DD and yes, it needs to be changed there too.

Thank you.
Alice
Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Oncology Products 1 (new name for DDOP)
Office of Hematology and Oncology Products
OND/CDER/FDA

301-796-1381
(f) 301-796-9845
alice.kacuba@fda.hhs.gov
*Consider setting your email font setting to at least 12 font.

From: Thomas, Lincy [mailto:lincy.thomas@novartis.com]
Sent: Thursday, July 19, 2012 5:40 PM
To: Kacuba, Alice
Cc: Wang, Jessica-1
Subject: question PPI- RE: URGENT----------Afinitor S-016
Importance: High
Sensitivity: Confidential

Alice

Just left you a voicemail – it appears that the indication in the Patient PI has not been modified. Just want to confirm Agency wants to keep as is for consumers.

AFINITOR is a prescription medicine used to treat:

- advanced hormone receptor-positive breast cancer, along with the medicine exemestane, in postmenopausal women who have already received certain other medicines for their cancer.

Thanks
Lincy

From: Kacuba, Alice [mailto:Alice.Kacuba@fda.hhs.gov]
Sent: Thursday, July 19, 2012 5:21 PM
To: Thomas, Lincy
Cc: Wang, Jessica-1
Subject: RE: URGENT----------Afinitor S-016
Importance: High
Sensitivity: Confidential

I will be leaving work about 6 PM today so if there are any questions after that, please call me on BB (b) (6) or email as I will be reading BB. Same thing in AM if I do not answer office phone,email or call me on BB.

Thank you.
Alice

From: Thomas, Lincy [mailto:lincy.thomas@novartis.com]
Sent: Thursday, July 19, 2012 5:12 PM
To: Kacuba, Alice
Cc: Wang, Jessica-1

Subject: RE: URGENT----------Afinitor S-016
Sensitivity: Confidential

Will check with team and get back to you asap so we can move along.

Thanks
Lincy

From: Kacuba, Alice [mailto:Alice.Kacuba@fda.hhs.gov]
Sent: Thursday, July 19, 2012 5:09 PM
To: Thomas, Lincy
Subject: URGENT----------Afinitor S-016
Importance: High
Sensitivity: Confidential

Hi,

At the last minute, we noticed that the indication should be "HER2 negative" and not "HER2 positive". Please see track changes and let us know if there are other places that it need to be changed. If you can turn this around by 11 am Friday (or earlier), we might still be able to take an action tomorrow, Friday. We apologize for this oversight.

Please submit a clean WORD version of "agreed to " labeling by 1) by email to me and 2) official submission.

Thank you.
Alice
Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Oncology Products 1 (new name for DDOP)
Office of Hematology and Oncology Products
OND/CDER/FDA
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(f) 301-796-9845
alice.kacuba@fda.hhs.gov
*Consider setting your email font setting to at least 12 font.

34 Pages Immediately Following Withheld - b(4) Draft Labeling

Kacuba, Alice

From: Kacuba, Alice
Sent: Thursday, July 19, 2012 5:09 PM
To: Thomas, Lincy
Subject: URGENT----------Afinitor S-016

Importance: High

Attachments: Afinitor PI S-016.doc

Hi,

At the last minute, we noticed that the indication should be "HER2 negative" and not "HER2 positive". Please see track changes and let us know if there are other places that it need to be changed. If you can turn this around by 11 am Friday (or earlier), we might still be able to take an action tomorrow, Friday. We apologize for this oversight.

Please submit a clean WORD version of "agreed to " labeling by 1) by email to me and 2) official submission.

Afinitor PI
l6.doc (1,014

Thank you.
Alice
Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Oncology Products 1 (new name for DDOP)
Office of Hematology and Oncology Products
OND/CDER/FDA
301-796-1381
(f) 301-796-9845
alice.kacuba@fda.hhs.gov
*Consider setting your email font setting to at least 12 font.

36 Pages Immediately Following Withheld - b(4) Draft Labeling

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALICE KACUBA
07/19/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 022334 BLA#	NDA Supplement #:S- 016 BLA Supplement #	Efficacy Supplement Type SE- 1
Proprietary Name: Afinitor Established/Proper Name: everolimus Dosage Form: Tablets Strengths: 2.5 mg, 5 mg, 7.5 mg, 10 mg		
Applicant: Novartis Pharmaceuticals Corporation Agent for Applicant (if applicable):		
Date of Application: November 2, 2011 Date of Receipt: November 3, 2011 Date clock started after UN:		
PDUFA Goal Date: September 3, 2011	Action Goal Date (if different): July 20, 2012	
Filing Date: January 1, 2012	Date of Filing Meeting: December 1, 2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): New indication: treatment of postmenopausal women with advanced hormone receptor-positive breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☐ 505(b)(2) ☒ 505(b)(1) ☐ 505(b)(2)	
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)	

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 066279	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** *http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm* **If yes**, please list below:				

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*		X		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**X**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Applications in "the Program" (PDUFA V) (NME NDAs/Original BLAs)	**YES**	**NO**	**NA**	**Comment**
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			**X**	
• If yes, were all of them submitted on time?				
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			**X**	
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			**X**	
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			

Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)]. ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*				
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***		X		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			**X**	

Pediatrics	**YES**	**NO**	**NA**	**Comment**

PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			Full waiver
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			X	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***		X		Name already approved
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels			

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829 htm
[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837 htm

	☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X			
Is the PI submitted in PLR format?[4]	X			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?			X	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	X			OSI; ONDQA biopharm
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 5/6/09 ***If yes, distribute minutes before filing meeting***	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 10/11/11 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 1, 2011

BLA/NDA/Supp #: NDA 022334/S-016

PROPRIETARY NAME: Afinitor

ESTABLISHED/PROPER NAME: everolimus

DOSAGE FORM/STRENGTH: Tablets, 2.5 mg, 5 mg, 7.5 mg, 10 mg

APPLICANT: Novartis Pharmaceuticals Corporation

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Proposed new indication: Treatment of postmenopausal women with advanced hormone receptor-positive breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole.

BACKGROUND: NDA 022334 received initial approval on March 30, 2009. Afinitor is currently approved for the following indications:

- AFINITOR® is indicated for the treatment of adult patients with progressive neuroendocrine tumors of pancreatic origin (PNET) with unresectable, locally advanced or metastatic disease.

  The safety and effectiveness of AFINITOR® in the treatment of patients with carcinoid tumors have not been established.

- AFINITOR® is indicated for the treatment of adult patients with advanced RCC after failure of treatment with sunitinib or sorafenib.

- AFINITOR® is indicated for the treatment of adult patients with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery.

  The effectiveness of AFINITOR in treatment of renal angiomyolipoma is based on an analysis of durable objective responses in patients treated for a median of 8.3 months. Further follow-up of patients is required to determine long-term outcomes.

- AFINITOR® is indicated for the treatment of adult and pediatric patients, 3 years of age or older, with SEGA associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not candidates for curative surgical resection.

  The effectiveness of AFINITOR is based on an analysis of change in SEGA volume *[see Clinical Studies (14.5)]*. Clinical benefit such as improvement in disease-related symptoms or increase in overall survival has not been demonstrated.

This supplement was submitted on November 2, 2011, received November 3, 2011, and provides for a new indication for the treatment of postmenopausal women with advanced hormone receptor-positive breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Christy Cottrell	Y
	CPMS/TL:	Alice Kacuba	N
Cross-Discipline Team Leader (CDTL)	Patricia Cortazar		Y
Clinical	Reviewer:	Geoff Kim/Tatiana Prowell	Y
	TL:	Patricia Cortazar	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Elimika Pfuma	Y
	TL:	Qi Liu	Y
Biostatistics	Reviewer:	Lijun Zhang	Y
	TL:	Shenghui Tang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Mary Jane Masson-Hinrichs	Y
	TL:	Anne Pilaro	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Jean Tang	Y
	TL:	Hari Sarker	Y
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Robert Young	N
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees	Amna Ibrahim, Robert Justice, Dawn Arrington, Raji Sridhara		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: None	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

or efficacy issues o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT
Signatory Authority: Robert Justice **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): April 12, 2012 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:

	REGULATORY CONCLUSIONS/DEFICIENCIES
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

	ACTIONS ITEMS
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review:

	• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in "the Program")
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

CHRISTY L COTTRELL
07/11/2012

From: Cottrell, Christy L.
Sent: Tuesday, July 03, 2012 2:26 PM
To: 'Thomas, Lincy'; Wang, Jessica-1
Subject: NDA 022334/S-016 for Afinitor: Labeling and PMCs

Attachments: 7-3-12 fda edited labeling.doc

Lincy-

Please refer to your pending NDA 022334/S-016 for Afinitor. Attached is the FDA-revised labeling. Please review and track your counterproposals. Response requested by COB on Tuesday, July 10th.

7-3-12 fda
lited labeling.doc

In addition, please see the following slightly revised PMC's with your proposed milestone dates:

Submit a final report, including datasets, for the final overall survival results from trial CRAD001Y2301 (BOLERO-2).

Final Protocol Submission:	December 2011
Trial Completion:	June 2014
Final Report Submission:	June 2015

Conduct a 3-arm randomized trial 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 anastrazole.

Final Protocol Submission:	November 2012
Trial Completion:	August 2016
Final Report Submission:	August 2017

In response to your question from yesterday, the OS PMC will just have OS results as written. Please submit these PMCs as a general correspondence to the supplement ASAP.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
☎301.796.4256 (phone) ● 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov


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/s/

CHRISTY L COTTRELL
07/03/2012

From: Cottrell, Christy L.
Sent: Thursday, June 14, 2012 3:10 PM
To: 'Thomas, Lincy'
Cc: Wang, Jessica-1
Subject: NDA 022334/S-016 for Afinitor: Proposed PMC's

Lincy,

Attached are the proposed PMC's for NDA 022334/S-016 for Afinitor. Please provide dates for PMC #1 and confirm agreement with the proposed dates in PMC #2.

PMC #1:

PMC Description: Submit the final overall survival results from study CRAD001Y2301 (BOLERO-2).

Schedule Milestones:	Final Protocol Submission:	PROVIDE DATE
	Study/Trial Completion:	PROVIDE DATE
	Final Report Submission:	PROVIDE DATE
	Other - Dataset Submission:	PROVIDE DATE

PMC #2

PMC Description: Conduct a 3 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 anastrazole.

Schedule Milestones:	Final Protocol Submission:	08/15/2012
	Study/Trial Completion:	12/15/2015
	Final Report Submission:	06/15/2016

Feel free to contact me with any questions.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
☎301.796.4256 (phone) ● 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

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/s/

CHRISTY L COTTRELL
06/14/2012

From: Cottrell, Christy L.
Sent: Wednesday, April 25, 2012 3:23 PM
To: 'Thomas, Lincy'
Cc: Wang, Jessica-1
Subject: NDA 022334/S-016 for Afinitor: Rationale for (b) (4)

Importance: High

Attachments: Afinitor (b) (4) .doc

Lincy,

Attached is (b) (4)

(b) (4)

Let me know if your team has any questions.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
301.796.4256 (phone) • 301.796.9845 (fax) | christy.cottrell@fda.hhs.gov

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/s/

CHRISTY L COTTRELL
04/25/2012

From: Cottrell, Christy L.
Sent: Wednesday, March 07, 2012 11:52 AM
To: 'Thomas, Lincy'
Cc: Wang, Jessica-1
Subject: NDA 022334/S-016 for Afinitor: Review comments

Importance: High

Lincy,

See below for comments from the review team and management regarding Afinitor S-016.

1. We are no longer planning to take this application to ODAC.

2. Please submit as soon as possible, the final PFS analysis and dataset with the cutoff of December 15th, 2011. Please state the date of submission.

3. We are no longer requesting any unplanned analysis of OS. We are requesting that you send the datasets and OS analysis for the 3rd interim analysis after 275 deaths and the final OS analysis when these data become available.

4. We received your concept proposal for a randomized phase II trial investigating the combination of everolimus with exemestane versus everolimus alone. We request that you amend this proposal with the following considerations and would like to discuss the rationale for the proposed changes to the trial in a teleconference prior to the development of the full protocol.
    - Conduct a 3 arm randomized trial investigating the combination of everolimus with exemestane versus everolimus alone versus single-agent chemotherapy (to be specified).
    - Prospectively evaluate potential biomarkers that may predict sensitivity to everolimus therapy. Such biomarkers may include mutation analyses of pathways involving PIK3CA/PI3K, AKT, PTEN, TSC1 and 2, RAS, RAF and any other potential biomarkers of efficacy identified in the BOLERO-2 trial.
    - Conduct correlative science analysis to identify predictors of SAEs leading to death in particular those cases that you addressed as "general health deterioration". We believe this is an important question because it appears there is no warning sign that anticipates the deadly outcome and perhaps finding a marker that will predict this toxicity could be very useful.

Feel free to contact me with any questions.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
☎301.796.4256 (phone) ● 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

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/s/

CHRISTY L COTTRELL
03/07/2012

From: Cottrell, Christy L.
Sent: Wednesday, February 22, 2012 10:39 AM
To: 'Thomas, Lincy'
Subject: NDA 022334/S-016 for Afinitor: Biometrics information request

Importance: High

Lincy,

Refer to your NDA 022334/S-016 for Afinitor. See below for an information request from the biometrics reviewer regarding pivotal study CRAD001Y2301. (I thought I had already sent this information request to you, but I can't find any documentation of having sent it. If it is duplicate, please disregard.)

- Please submit an updated survival dataset in the first week of April. Please use a cutoff date as late as possible. The survival dataset should at least contain the following information: subject ID, randomized treatment arm, randomization date, survival status, date of death, cause of death, and date of last contact.

Feel free to contact me with any questions.

Regards,
Christy Cottrell

Christy Cottrell | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
301.796.4256 (phone) ● 301.796.9845 (fax) | christy.cottrell@fda.hhs.gov


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/s/

CHRISTY L COTTRELL
02/22/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO:

CDER-DMPP-PatientLabelingTeam

FROM: (Name/Title, Office/Division/Phone number of requestor)

Christy Cottrell, RPM
Division of Oncology Products 1, OHOP

REQUEST DATE:	NDA/BLA NO.:	TYPE OF DOCUMENTS: (PLEASE CHECK OFF BELOW)
January 31, 2012	NDA 022334/SE1-016	New efficacy supplement with updated patient labeling

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE
Afinitor (everolimus) Tablets			July 19, 2012

SPONSOR:
Novartis Pharmaceuticals Corporation

PDUFA Date: September 3, 2012
Action goal date: August 3, 2012

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☒ PATIENT PACKAGE INSERT (PPI)
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☒ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ MANUFACTURING (CMC) SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☒ LABELING REVISION

EDR link to submission:

EDR Location: \\CDSESUB1\EVSPROD\NDA022334\022334.enx

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS:

Filing/Planning Meeting: Already held

Mid-Cycle Meeting: April 12, 2012

Labeling Meetings: June 25, June 26, June 28, July 12, July 19, 2012

Wrap-Up Meeting: July 23, 2012

SIGNATURE OF REQUESTER
Christy Cottrell

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)
☐ eMAIL (BLAs Only) X DARRTS

Version: 12/9/2011

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/s/

CHRISTY L COTTRELL
01/31/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-DDMAC-RPM	Christy Cottrell, RPM Division of Oncology Products 1, OHOP

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
January 31, 2012		NDA 022334/ SE1-016	New efficacy supplement

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Afinitor (everolimus) Tablets			July 19, 2012

NAME OF FIRM:	
Novartis Pharmaceuticals Corporation	PDUFA Date: September 3, 2012 Action goal date: August 3, 2012

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☒ PACKAGE INSERT (PI)
- ☒ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☒ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☒ LABELING REVISION

EDR link to submission:

EDR Location: \\CDSESUB1\EVSPROD\NDA022334\022334.enx

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: April 12, 2012
Labeling Meetings: June 25, June 26, June 28, July 12, July 19, 2012
Wrap-Up Meeting: July 23, 2012

SIGNATURE OF REQUESTER
Christy Cottrell

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one)
	☐ eMAIL ☐ HAND

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/s/

CHRISTY L COTTRELL
01/31/2012

DSI CONSULT: Request for Clinical Inspections

Date: January 31, 2012

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Geoffrey Kim, MD, Clinical Reviewer
Tatiana Prowell, MD, Clinical Reviewer
Patricia Cortazar, MD, Clinical Team Leader
Division of Oncology Products 1, OHOP

From: Christy Cottrell, Regulatory Project Manager
Division of Oncology Products 1, OHOP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 022334/S-016
Applicant/ Applicant contact information (to include phone/email):

Novartis Pharmaceuticals Corporation
Lincy Thomas, PharmD
Lincy.thomas@novartis.com
Phone: 862 778 2605
Fax: 973 781 5217

Drug Proprietary Name: Afinitor (everolimus) Tablets
NME or Original BLA (Yes/No): No
Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s):
Treatment of post-menopausal wome (b) (4)

PDUFA: September 3, 2012
Action Goal Date: August 3, 2012
Inspection Summary Goal Date: July 6, 2012

II. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site 545 PI: Dr. Denise Yardley Sarah Cannon Research Institute 250 25th Avenue North, Suite 110 Nashville, TN 37203 P: 615-329-7274	RAD001Y2301	12	HR+ breast cancer
Site 540 PI: Dr. Mikhail Shtivelband Ironwood Cancer and Research Centers 695 South Dobson Road Chandler, AZ 85224	RAD001Y2301	11	HR+ breast cancer
Site 534 PI: Dr. Thaddeus Beck Highlands Oncology Group 3232 N. North Hills Blvd. Fayetteville, AR 72703 P: 479-587-1700	RAD001Y2301	14	HR+ breast cancer

III. Site Selection/Rationale

DOP1 is requesting audit of these sites based on the numbers of patients they enrolled on the trial.

Domestic Inspections:

Reasons for inspections (please check all that apply):

__X__ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
____ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
____ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Should you require any additional information, please contact Christy Cottrell at 301-796-4256 or Tatiana Prowell, MD at 301-796-2322 or Geoff Kim, MD at 301-796-1883.

Concurrence:

_____ Geoffrey Kim, MD, Clinical Reviewer

_____ Tatiana Prowell, MD, Clinical Reviewer

_____ Patricia Cortazar, MD, Clinical Team Leader

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/s/

CHRISTY L COTTRELL
01/31/2012

GEOFFREY S KIM
01/31/2012

TANYA M PROWELL
02/02/2012

PATRICIA CORTAZAR
02/03/2012

From: Cottrell, Christy L.
Sent: Monday, January 09, 2012 3:57 PM
To: 'Thomas, Lincy'; 'lynne.mcgrath@novartis.com'
Subject: NDA 022334/S-016 for Afinitor: Follow-up on action items

Importance: High

Lincy,

Dr. Pazdur has asked me to find out from you when we can expect to receive the follow-up action items requested during last week's application presentation. Please let me know when you anticipate providing the following:

- Proposal for study(ies) that will determine whether the hormone therapy is really needed as part of combination therapy in this setting. Specifically, Dr. Pazdur is interested in a study that compares Afinitor + Exemestane vs. Afinitor alone in this same patient population.
- Table with month by month projections for survival events through September.

Feel free to contact me with any questions.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
301.796.4256 (phone) ● 301.796.9845 (fax) | christy.cottrell@fda.hhs.gov

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/s/

CHRISTY L COTTRELL
01/09/2012

From: Cottrell, Christy L.
Sent: Friday, January 27, 2012 4:46 PM
To: 'Thomas, Lincy'; Wang, Jessica-1
Subject: NDA 022334/S-016: Clinical Information Request

Lincy,

See below for an information request for NDA 022334/S-016 for Afinitor.

Please send us the CRFs for the following patients:

0610_00002
0811_00014
0354_00009
0354_00010
0407_00001

Feel free to contact me with any questions.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
301.796.4256 (phone) • 301.796.9845 (fax) | christy.cottrell@fda.hhs.gov

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/s/

CHRISTY L COTTRELL
01/27/2012

From: Cottrell, Christy L.
Sent: Monday, January 23, 2012 10:18 AM
To: 'Thomas, Lincy'
Subject: NDA 022334/S-016 for Afinitor: Biometrics information request

Importance: High

Lincy,

Reference is made to NDA 022334/S-016 submitted November 2, 2011. The following request is for the pivotal study CRAD001Y2301.

- Please submit PFS analysis results based on the Source 3 data (defined in SAP Table 3-1), with the same censoring rules as you used for the primary PFS analysis.

Please respond by February 10, 2012.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
301.796.4256 (phone) • 301.796.9845 (fax) | christy.cottrell@fda.hhs.gov

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/s/

CHRISTY L COTTRELL
01/23/2012

From: Cottrell, Christy L.
Sent: Thursday, December 15, 2011 11:32 AM
To: 'Thomas, Lincy'
Cc: Wang, Jessica-1
Subject: RE: IMPORTANT: Question/proposal regarding data to fulfill 120day safety update - Afinitor breast sNDA

Lincy,

The review team and Division management all agree that you should submit both investigator and IRC PFS data and datasets for the 528 events. The July 2011 cutoff for the 120 day safety update is acceptable.

Regards,
Christy

From: Thomas, Lincy [mailto:lincy.thomas@novartis.com]
Sent: Tuesday, December 13, 2011 5:16 PM
To: Cottrell, Christy L.
Cc: Wang, Jessica-1
Subject: IMPORTANT: Question/proposal regarding data to fulfill 120day safety update - Afinitor breast sNDA
Importance: High

Dear Christy,

FDA specifically states in the filing communication letter 'in lieu of the proposed updated PFS analysis with 85% events, please submit an updated PFS analysis with datasets once 528 PFS events have been observed.'

As previously communicated, an updated efficacy and safety analysis using a data cut-off date of 8-Jul-2011 is ready for submission to the Agency this week.

Novartis would like to confirm that the safety data from this submission (with the July 2011 cut-off) will fulfill the requirement for the 120 day safety update as agreed upon at the pre-sNDA meeting. In addition, the efficacy analysis (which includes datasets) confirms the magnitude of the treatment effect seen with the interim results, now with an additional 5 months of follow-up.

Novartis will submit the updated PFS of 528 events as requested to the Agency in March 2012. As the efficacy is not anticipated to be substantially different from the data that is currently available, Novartis proposes to provide only the following:

- updated PFS analysis based on 528 **local** events and the associated datasets

We believe this proposal will allow the Agency to streamline the review of the application.

As it is critical to gain alignment on the contents of these upcoming submissions please confirm agreement with this proposal and whether a discussion is needed.

As previously mentioned, we will have an update on OS data after the IDMC reviews it this Thursday and do plan to submit this information shortly afterwards.

Kind regards,

Lincy Thomas
Reg Affairs-TA Sr Asc Dir
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

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Fax +1 9737818265
lincy.thomas@novartis.com
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/s/

CHRISTY L COTTRELL
12/15/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022334/S-016

FILING COMMUNICATION

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Attention: Lincy Thomas, PharmD
Senior Associate Director, Drug Regulatory Affairs

Dear Dr. Thomas:

Please refer to your Supplemental New Drug Application (sNDA) dated November 2, 2011, received November 3, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Afinitor® (everolimus) Tablets.

This supplemental application proposes a new indication for the treatment of postmenopausal women (b) (4) .

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this supplemental application is considered filed 60 days after the date we received your supplemental application. The review classification for this supplemental application is **Standard**. Therefore, the user fee goal date is September 3, 2012.

The rationale for classifying this supplement as a Standard review is outlined below.

- The criteria to grant a priority review are: 1) safe and effective therapy where no satisfactory alternative therapy exists or 2) a significant improvement compared to marketed products. There are numerous available alternative therapies for patients after failure of a prior non-steroidal aromatase inhibitor, including other aromatase inhibitors, tamoxifen, fulvestrant, and multiple cytotoxics. In addition, it is not clear that the proposed combination represents a significant improvement compared to marketed products. There are available therapies for treatment of advanced breast cancer that have demonstrated improvements in overall survival. This application demonstrates an improvement in PFS of approximately 4 months in duration favoring the everolimus plus exemestane combination, but this improvement in efficacy was associated with a markedly increased incidence of adverse events, with approximately 60% of patients requiring dose reduction/treatment interruption in the everolimus arm. In addition, the submitted survival data are very immature.

We are reviewing your supplemental application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by August 5, 2012.

We request that you submit the following information:

1. In lieu of the proposed updated PFS analysis with 85% events, please submit an updated PFS analysis with datasets once 528 PFS events have been observed.

2. Please submit bioanalytical reports and validation reports for exemestane and estradiol used for Study Y2301.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Christy Cottrell, Regulatory Project Manager, at (301) 796-4256.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, MD, MS
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ROBERT L JUSTICE
12/07/2011

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22334 **Applicant: Novartis** **Stamp Date: 11/04/2011**

Drug Name: Afinitor **NDA/BLA Type: Efficacy Supplement**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			Gender not applicable (all females)
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	X			
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			Safety data are based on the pivotal trial only
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

Lijun Zhang 12/1/2011

Reviewing Statistician Date

Shenghui Tang 12/1/2011

Supervisor/Team Leader Date

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/s/

LIJUN ZHANG
12/06/2011

SHENGHUI TANG
12/06/2011