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Novartis Drug Afinitor® Effective in Patients With Non-Cancerous Kidney Tumors Associated With TSC in Phase III Trial

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- - Study met primary endpoint of kidney tumor response rate with 42% of patients on everolimus experiencing a response versus 0% on placebo(1)
- - Kidney tumors are present in up to 80% of patients with tuberous sclerosis complex (TSC), and larger tumors may lead to life-threatening complications(1,2,3,4)
- - Results also demonstrated superiority of everolimus over placebo in secondary endpoints including improvement of skin lesions, a key concern for TSC patients(1)
- - Data mark second positive Phase III study in patients with TSC and will form basis of worldwide regulatory filings to expand current TSC-SEGA indication(5)

EAST HANOVER, N.J., Sept. 23, 2011 /PRNewswire/ -- A Phase III study of Afinitor® (everolimus) tablets* in patients with non-cancerous kidney tumors, or angiomyolipomas, associated with tuberous sclerosis complex (TSC) met its primary endpoint of best overall angiomyolipoma response rate, which includes reduction in kidney tumor size and absence of new tumors. Findings from the trial, known as EXIST-2, were presented today at the International TSC Research Conference in Belfast, Northern Ireland(1).

Tuberous sclerosis complex is a genetic disorder that may cause non-cancerous tumors to form in vital organs, including the brain (SEGAs) and kidney (angiomyolipomas)(3). These kidney tumors occur in up to 80% of patients, usually occurring between the ages of 15 and 30 and increasing in prevalence with age(2,3). Angiomyolipomas are the greatest cause of morbidity and mortality in adult TSC patients, as larger tumors may cause severe bleeding, require surgical intervention or result in kidney failure(2,3). Tumor symptoms may include nausea, vomiting, pain and bleeding(3,6,7).

Results of the 118-patient, randomized, placebo-controlled Phase III EXIST-2 (EXamining everolimus In a Study of TSC) trial showed 42% of patients (33 of 79) experienced a response in the everolimus arm versus 0% of patients (0 of 39) on placebo ($p<0.0001$) based on best overall response rate(1). These results add to the recent positive Phase III data from a separate trial in patients with TSC, which demonstrated reduction in the size of non-cancerous brain tumors (SEGAs) with everolimus(5).

"For the first time, a large placebo-controlled study has focused specifically on angiomyolipomas in TSC patients, an area with clear unmet need," said Dr. John Bissler, lead study author and Clark D. West Endowed Chair of Nephrology at Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio. "In addition to the tumor reduction seen with everolimus in this trial, significant improvement in skin lesions including facial angiofibromas was observed, which can be a key concern for people living with TSC."

Everolimus targets mTOR, a protein that acts as an important regulator of tumor cell division, blood vessel growth and cell metabolism(8). Tuberous sclerosis complex is caused by defects in the TSC1 and/or TSC2 genes(9). When these genes are defective, mTOR activity is increased, which can cause uncontrolled tumor cell growth and proliferation, blood vessel growth and altered cellular metabolism(2,9). By inhibiting mTOR activity in this signaling pathway, everolimus may reduce cell proliferation and blood vessel growth related to

angiomyolipoma associated with TSC(2,8,9).

"The positive findings seen in this trial coupled with the known efficacy of everolimus in patients with SEGA point to the important role of mTOR inhibition with everolimus in treating these manifestations of TSC," said Herve Hoppenot, President, Novartis Oncology. "The outcomes support our further research efforts evaluating everolimus as a treatment option across the various conditions associated with TSC."

Affecting approximately 25,000 to 40,000 people in the US and one to two million people worldwide, TSC is associated with a variety of resulting disorders including skin lesions, seizures, swelling in the brain (hydrocephalus) and developmental delays(3,9).

About EXIST-2

EXIST-2 is a prospective, double-blind, randomized, parallel group, placebo-controlled, international, multicenter Phase III study of everolimus versus placebo for the treatment of patients with angiomyolipoma associated with TSC(1,10). Trial patients (median age=31, range 18-61) were randomized 2:1 to receive either everolimus (n=79) or placebo (n=39) at a daily starting dose of 10 mg. By the cut-off of June 30, 2011, the median treatment duration in the double-blind period was 38.1 weeks (range 2-105 weeks) in the everolimus arm and 34.0 weeks (range 9-112 weeks) in the placebo arm(1).

In the study, the definition of angiomyolipoma response included a reduction of at least 50% relative to baseline in the sum of the volumes of all target lesions, and the absence of new lesions greater than or equal to one centimeter in diameter, with a confirmed response by radiographic scan approximately 12 weeks later(1).

Everolimus demonstrated superiority to placebo for both secondary endpoints assessed: skin lesion response rate and time to angiomyolipoma progression per central review. Skin lesion response rate, defined as the proportion of patients with a best overall skin lesion response of either complete clinical response or partial response, was 26% in patients (20 of 77) on everolimus and 0% (0 of 37) on placebo (p=0.0002). Median time to angiomyolipoma progression (time from date of randomization to date of first documented angiomyolipoma progression) was 11.37 months in the placebo arm and was not reached in the everolimus arm. Progressions were observed in 4% of patients (3 of 79) on everolimus and 21% (8 of 39) on placebo. The estimated progression-free rates at six months were 98% on everolimus and 83% on placebo (p<0.0001)(1).

The most common adverse events (AEs) in the everolimus arm (with an incidence of at least 20%) included stomatitis, nasopharyngitis, acne, headache, cough and hypercholesterolaemia. Renal events were less frequent in the everolimus arm compared to the placebo arm. The most common Grade 3 AEs in the everolimus arm (with an incidence of at least 2%) were amenorrhea, aphthous stomatitis, decreased blood phosphorus and mouth ulceration. Single Grade 4 cases of convulsion, increased blood uric acid, hypertensive crisis and neutropenia were reported in the everolimus arm(1).

Adverse events observed in this study were consistent with the known safety profile of everolimus in the TSC setting. Adverse events leading to trial discontinuation were reported more commonly in the placebo arm. During the study, one death in the everolimus arm occurred due to convulsion, though it was not considered related to the study drug by the investigator(1).

EXIST-2 enrolled 118 patients in the US, Germany, the Netherlands, Japan, the UK, Russia, Italy, Canada, Poland, Spain and France. This study is part of a Phase III trial program investigating everolimus in the various manifestations of TSC(1,10).

About everolimus

In the US, Afinitor® (everolimus) tablets is approved to treat patients with SEGA associated with TS who require therapeutic intervention but are not candidates for curative surgical resection. The effectiveness of everolimus 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 shown.

Afinitor is also approved in the US for the treatment of patients with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib and for the treatment of progressive neuroendocrine tumors of pancreatic origin (pNET) in patients with unresectable, locally advanced or metastatic disease. The US Food and Drug Administration (FDA) determined that the safety and effectiveness of Afinitor in the treatment of patients with carcinoid tumors have not been established.

In the US, everolimus is available from Novartis in different dosage strengths and for different uses in non-oncology patient populations under the trade name Zortress®. Everolimus is exclusively licensed to Abbott and sublicensed to Boston Scientific for use in drug-eluting stents.

Not all indications are available in every country. Access to everolimus outside of the approved indications has been carefully controlled and monitored in clinical trials designed to better understand the potential benefits and risks of the compound. As an investigational compound, the safety and efficacy profile of everolimus has not yet been established outside the approved indications. Because of the uncertainty of clinical trials, there is no guarantee that everolimus will become commercially available for additional indications anywhere else in the world.

Important Safety Information for Afinitor (everolimus) tablets

Patients should not take Afinitor if they are allergic to Afinitor or to any of its ingredients. Patients should tell their healthcare provider before taking Afinitor if they are allergic to sirolimus (Rapamune®#) or temsirolimus (Torisel®#).

Afinitor can cause serious side effects including lung or breathing problems, infections and kidney failure, which can lead to death. If patients experience these serious side effects, they may need to stop taking Afinitor for a while or use a lower dose. Patients should tell their healthcare provider right away if they have any of these symptoms: new or worsening cough, shortness of breath, chest pain, difficulty breathing or wheezing.

Afinitor may make patients more likely to develop an infection, such as pneumonia, or a bacterial, fungal or viral infection. Viral infections may include reactivation of hepatitis B in people who have had hepatitis B in the past. In some people these infections may be severe, and can even lead to death. Patients may need to be treated as soon as possible. Patients should tell their healthcare provider right away if they have a temperature of 100.5 degrees 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 or pain in the upper right side.

Afinitor can cause mouth ulcers and sores, which are the most frequently occurring side effects occurring in approximately 44%-70% advanced kidney cancer and advanced pancreatic NET patients taking Afinitor. Eighty-six percent of patients taking Afinitor for SEGA developed mouth ulcers/sores. Patients should tell their healthcare provider if they have pain, discomfort or open sores in their mouth. Their healthcare provider may tell them to use a special mouthwash or mouth gel that does not contain alcohol or peroxide.

Afinitor may cause kidney failure. In some people this may be severe and can even lead to death. Patients should have tests to check their kidney function before and during their treatment with Afinitor.

Patients will have regular blood tests before they start and as needed during their treatment with Afinitor.

These tests will include tests to check the patient's blood cell count, kidney and liver function and blood sugar levels. Patients who receive Afinitor for the treatment of SEGA will need regular blood tests to measure how much Afinitor is in their blood since this will help their doctor decide how much Afinitor they need to take.

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. Patients should tell their healthcare provider about all of the medicines they take, including prescription and non-prescription medicines, vitamins and herbal supplements such as: St. John's Wort, and medicine for fungal infections, bacterial infections, tuberculosis, seizures, HIV-AIDS, heart conditions or high blood pressure and medicines that suppress their immune system. Patients should not drink grapefruit juice or eat grapefruit during their treatment with Afinitor as it may make the amount of Afinitor in their blood increase to a harmful level.

Patients should not take Afinitor tablets which are broken or crushed. Patients should not chew or crush the tablets.

The amount of Afinitor in the blood was increased in patients who had liver problems. Patients should tell their healthcare provider about all their medical conditions, including if they have or have had liver problems, diabetes or high blood sugar, high cholesterol levels, infections, hepatitis B or other medical conditions.

Patients should tell their healthcare provider if they are scheduled to receive any vaccinations. Patients should not receive a live vaccine or be around people who have recently received a live vaccine during treatment with Afinitor.

It is not known if Afinitor will harm an unborn baby. Women should use effective birth control while using Afinitor and for eight weeks after stopping treatment.

Common side effects of Afinitor in patients with advanced pancreatic neuroendocrine tumors include mouth ulcers, rash, diarrhea, swelling of arms, hands, feet, ankles, face or other parts of the body, abdominal pain, nausea, fever and headache. Common side effects of Afinitor in patients with advanced kidney cancer include mouth ulcers, infections, feeling weak or tired, cough and diarrhea. Common side effects of Afinitor in patients with SEGA include mouth ulcers, infections of the respiratory tract, sinuses and ears and fever.

Please see full Prescribing Information for Afinitor.

Disclaimer

The foregoing release contains forward-looking statements that can be identified by terminology such as "will," "potential," or similar expressions, or by express or implied discussions regarding potential new indications or labeling for everolimus or regarding potential future revenues from everolimus. You should not place undue reliance on these statements. Such forward-looking statements reflect the current views of management regarding future events, and involve known and unknown risks, uncertainties and other factors that may cause actual results with everolimus to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that everolimus will be submitted or approved for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that everolimus will achieve any particular levels of revenue in the future. In particular, management's expectations regarding everolimus could be affected by, among other things, unexpected regulatory actions or delays or government regulation generally; unexpected clinical trial results, including unexpected new clinical data and unexpected additional analysis of existing clinical data; the company's ability to obtain or maintain patent or other proprietary intellectual property protection; competition in general; government, industry and general public pricing pressures; the impact that the foregoing factors could have on the values attributed to the Novartis Group's assets and liabilities as recorded in the Group's consolidated

balance sheet, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those anticipated, believed, estimated or expected. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

About Novartis

Located in East Hanover, New Jersey, Novartis Pharmaceuticals Corporation is an affiliate of Novartis AG, which provides healthcare solutions that address the evolving needs of patients and societies. Focused solely on healthcare, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, eye care, cost-saving generic pharmaceuticals, consumer health products, preventive vaccines and diagnostic tools. Novartis is the only company with leading positions in these areas. In 2010, the Group's continuing operations achieved net sales of USD 50.6 billion, while approximately USD 9.1 billion (USD 8.1 billion excluding impairment and amortization charges) was invested in R&D throughout the Group. Headquartered in Basel, Switzerland, Novartis Group companies employ approximately 121,000 full-time-equivalent associates and operate in more than 140 countries around the world. For more information, please visit http://www.us.novartis.com.

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*Known as Votubia® (everolimus) tablets for certain patients with SEGA associated with TSC in the EU and Switzerland.

Rapamune® (sirolimus) and Torisel® (temsirolimus) are registered trademarks of Wyeth Pharmaceuticals Inc.

References

1. Kingswood et al. A randomized, double-blind, placebo-controlled, phase 3 study of everolimus in the treatment of angiomyolipoma in patients with either tuberous sclerosis complex or sporadic lymphangioleiomyomatosis. International TSC Research Conference. September 2011, Belfast, Northern Ireland.
2. Ewalt, et al. Long-term outcome of transcatheter embolization of renal angiomyolipomas due to Tuberous Sclerosis Complex. J Urol 2005:174:1764-1766.
3. National Institute of Neurological Disorders and Stroke. Tuberous Sclerosis Fact Sheet. Available at http://www.ninds.nih.gov/disorders/tuberous_sclerosis/detail_tuberous_sclerosis.htm. Accessed September 2011.
4. Roach, et al. Diagnosis of Tuberous Sclerosis Complex. J Child Neuro 2004;19:643-649.
5. Franz, et al. Long-term safety and efficacy results of oral everolimus in patients with subependymal giant cell astrocytomas (SEGA) in tuberous sclerosis complex (TSC). International TSC Research Conference. July 2011, Washington, D.C.
6. Harabayashi, et al. Management of renal angiomyolipomas associated with Tuberous Sclerosis Complex. J Urol 2004;171(1):102-105.
7. Singer. Angiomyolipoma. Available at http://www.medscape.com/viewarticle/415099. Accessed September 2011.
8. Motzer, et al. Phase 3 Trial of Everolimus for Metastatic Renal Cell Carcinoma. Cancer 2010 Sep;116(18):4256-4265.
9. Krueger, et al. Everolimus for Subependymal Giant-Cell Astrocytomas in Tuberous Sclerosis. New Eng J

Med 2010;363:1801-11.
10. US National Institutes of Health. Efficacy and Safety of RAD001 in Patients Aged 18 and Over With Angiomyolipoma Associated With Either Tuberous Sclerosis Complex (TSC) or Sporadic Lymphangioleiomyomatosis (LAM) (EXIST-2). Available at: http://clinicaltrials.gov/ct2/show/NCT00790400?term=exist-2&rank=1. Accessed September 2011.

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