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Novartis drug Afinitor® significantly reduces seizures in Phase III study of patients with tuberous sclerosis complex

- Everolimus is the first adjunctive therapy shown in a prospective randomized Phase III study to achieve clinically significant seizure control in TSC patients¹

- Seizures are the most common TSC-related neurological condition, yet about 60% of patients don’t attain seizure control with available anti-epileptic therapies²

- Results presented at AAN will be discussed with health authorities for potential worldwide regulatory filings

Basel, April 20, 2016 – Novartis today announced results from a Phase III study showing Afinitor® (everolimus), when used as an adjunctive therapy, significantly reduced treatment-resistant seizures associated with tuberous sclerosis complex (TSC) compared to placebo¹. Patients in all treatment arms were also taking one to three anti-epileptic drugs (AEDs)¹. The study, EXIST-3 (EXamining everolimus In a Study of TSC), is being presented during a plenary session at the 68th Annual Meeting of the American Academy of Neurology (AAN) (Abstract #32430, 9:00–11:00 a.m. PST)¹.

“Approximately 85% of individuals with TSC are affected by epilepsy at some point in their lives, yet nearly two-thirds of these patients do not achieve seizure control with available therapies, and may also experience other potentially serious consequences, such as neuropsychological, cognitive, social or learning disabilities,” said Jacqueline A. French, MD, department of neurology, NYU Langone Medical Center and lead investigator of the EXIST-3 trial. “These findings are encouraging as this is the first clinical study demonstrating benefit specifically for TSC patients who suffer from treatment-resistant seizures.”

In the study, 366 patients with TSC and treatment-resistant seizures were randomized to receive targeted concentrations of everolimus titrated to Low Exposure (LE; 3-7 ng/mL; n=117) or High Exposure (HE, 9-15 ng/mL; n =130), or placebo (n=119). The percentage reduction from baseline in seizure frequency was significantly greater among patients randomized to everolimus LE (29.3%, P=0.003; confidence interval [CI]=95%) and HE (39.6%, P<0.001; CI=95%) vs placebo (14.9%; CI=95%). Seizure response rate (≥50% reduction) was also significantly greater with everolimus LE (28.2%, P=0.008; CI=95%) and HE (40.0%, P<0.001; CI=95%) vs placebo (15.1%; CI=95%). The most common (≥20%) adverse events (AEs) reported with everolimus LE/HE vs placebo included stomatitis (28.2%/30.8% vs 3.4%), mouth ulceration (23.9%/21.5% vs 4.2%), and diarrhea (17.1%/21.5% vs 5.0%). Serious AEs reported were 13.7%/13.8% vs 2.5%.

“There has been a long-standing need to find a treatment option for TSC patients that provides control of treatment-resistant seizures and we are encouraged that data from the EXIST-3 study show everolimus may have this potential,” said Alessandro Riva, MD, Global Head, Novartis Oncology Development and Medical Affairs. “Over the past decade, Novartis has remained committed to the TSC community, improving care for

¹Known as Votubia® (everolimus) for certain patients with SEGA and renal angiomyolipoma associated with TSC in the EU and Switzerland
patients and conducting research we hope will bring us closer to addressing some of the most debilitating TSC manifestations."

Tuberous sclerosis complex is a rare genetic disorder affecting up to one million people worldwide and everolimus is the only approved non-surgical option indicated for treating non-cancerous brain and kidney tumors in certain patients with TSC. EXIST-3 study results show that everolimus is the first adjunctive therapy to achieve clinically significant seizure control in TSC patients and will be the basis for discussion with health authorities worldwide.

Everolimus works by inhibiting the mammalian target of rapamycin (mTOR), a protein that regulates multiple cellular functions. TSC is caused by mutations in the TSC1 or TSC2 genes, resulting in hyperactive signaling of the mTOR pathway which can lead to increased cellular growth and proliferation, neuronal hyper-excitability, abnormalities in cortical architecture and network function and impaired synaptic plasticity. Pre-clinical research suggests that hyperactive mTOR activity may influence several mechanisms of epileptogenesis, the gradual process by which the brain develops epilepsy.

EXIST-3 study details
EXIST-3 is a Phase III, three-arm, randomized, double-blind, placebo-controlled study of the efficacy and safety of high and low exposure ranges of everolimus as adjunctive therapy in patients with TSC who have treatment-resistant seizures, defined as seizures persisting despite the use of two AEDs. The study enrolled male and female participants (ages 2.2-56.3) with clinically defined TSC, who were on stable doses of one to three AEDs for at least four weeks prior to a two month, pre-randomization, evaluation period.

The primary objective was to assess the effectiveness of adjunctive everolimus as compared to placebo in reducing seizures in patients with TSC who are taking one to three AEDs. Secondary objectives include the percentage of patients free from seizure during the maintenance period and change in seizure frequency.

The most frequent ≥10% all grade adverse events (AEs) reported with everolimus LE/HE vs placebo included stomatitis (28.2%/30.8% vs 3.4%), mouth ulceration (23.9%/21.5% vs 4.2%), diarrhea (17.1%/21.5% vs 5.0%), nasopharyngitis (13.7%/16.2% vs 16.0%), upper respiratory tract infection (12.8%/15.4% vs 12.6%), aphthous ulcer (4.3%/14.6% vs 1.7%) pyrexia (fever) (19.7%/13.8% vs 5.0%), vomiting (12.0%/10.0% vs 9.2%), cough (11.1%/10.0% vs 3.4%) and rash (6.0%/10.0% vs 2.5%).

About tuberous sclerosis complex
Tuberous sclerosis complex (TSC) may cause non-cancerous tumors to form in vital organs including the brain, kidney, heart, lungs and skin, as well as resulting disorders such as epilepsy, autism, cognitive impairment, behavioral problems and psychiatric disorders. Many people with TSC show evidence of the disease in the first year of life. However, because manifestations vary from person to person and can take years to develop, many children are not diagnosed until later in life, often with the onset of seizures, skin lesions or other significant symptoms, such as developmental delays. Because TSC is a lifelong condition, the latest professional diagnostic guidelines issued in 2012 advise that individuals be monitored by a doctor experienced with the disorder to ensure tumor growth or new symptoms are identified early.

About everolimus
In the European Union (EU), everolimus is approved as Votubia® for the treatment of adult patients with renal angiomyolipoma associated with tuberous sclerosis complex (TSC) who are at risk of complications (based on factors such as tumor size or presence of aneurysm, or presence of multiple or bilateral tumors) but who do not require immediate surgery. The evidence is based on analysis in sum of angiomyolipoma volume. Votubia is also indicated in the EU for the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with TSC who require
therapeutic intervention but are not amenable to surgery. The evidence is based on
analysis of change in SEGA volume. Further clinical benefit, such as improvement in
disease-related symptoms, has not been demonstrated.

In the United States (US), everolimus is approved as Afinitor® for the treatment of adult
patients with renal angiomyolipoma and TSC, not requiring immediate surgery. Afinitor
tablets and Afinitor Disperz™ are also indicated in the US in pediatric and adult patients
with TSC for the treatment of SEGA that requires therapeutic intervention but cannot be
curatively resected.

Additionally, Afinitor is approved in 99 countries, including the US and throughout the EU,
for locally advanced, metastatic or unresectable progressive neuroendocrine tumors
(NET) of pancreatic origin and in the US for the treatment of adult patients with
progressive, well-differentiated, nonfunctional NET of gastrointestinal (GI) or lung origin
that are unresectable, locally advanced or metastatic. It is also approved in >120
countries including the US and EU for advanced renal cell carcinoma following
progression on or after vascular endothelial growth factor (VEGF)-targeted therapy (in
the US, specifically following sunitinib and sorafenib). Afinitor is also approved in 102
countries including the US and EU for advanced HR+/HER2- breast cancer in
combination with exemestane, after prior endocrine therapy.

Everolimus is also available from Novartis under the brand names Afinitor®, Certican®
and Zortress® for use in oncology and transplant patient populations and is exclusively
licensed to Abbott and sublicensed to Boston Scientific for use in drug-eluting stents.

Indications vary by country and not all indications are available in every country. 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
Afinitor/Votubia can cause serious side effects including lung or breathing problems,
infections (including sepsis), and kidney failure, which can lead to death. Patients taking
concomitant angiotensin-converting enzyme (ACE) inhibitors may be at an increased risk
for angioedema. Mouth ulcers and mouth sores are common side effects. Afinitor/Votubia
can affect blood cell counts, kidney and liver function, and blood sugar, cholesterol, and
triglyceride levels. Afinitor/Votubia may cause fetal harm in pregnant women. Highly
effective contraception is recommended for women of child-bearing potential while
receiving Afinitor/Votubia and for up to eight weeks after ending treatment. Women
taking Afinitor/Votubia should not breast feed. Fertility in women and men may be
affected by treatment with Afinitor/Votubia.

The most common adverse drug reactions (incidence ≥10 percent) are mouth ulcers,
skin rash, feeling tired or weak, diarrhea, infections (including upper respiratory tract
infection, sore throat and runny nose, sinusitis, middle ear infection and pneumonia),
absence of menstrual periods, high levels of cholesterol, nausea, decreased appetite,
low level of red blood cells, acne, abnormal taste, irregular menstrual periods,
inflammation of lung tissue, swelling of extremities or other parts of the body, high level
of blood sugar, itching, weight loss, nose bleeds, cough and headache. The most
common grade 3-4 adverse drug reactions (incidence ≥2 percent) are mouth ulcers,
infections (including pneumonia), low level of red blood cells, absence of menstrual
periods, high level of blood sugar, feeling tired or weak, diarrhea, low white blood cells,
inflammation of lung tissue and spontaneous bleeding or bruising. Cases of hepatitis B
reactivation, blood clots in the lung or legs, and pneumocystis jirovecii pneumonia (PJP)
have been reported. Abnormalities were observed in hematology and clinical chemistry
laboratory tests.
Disclaimer
The foregoing release contains forward-looking statements that can be identified by words such as "will," "potential," "is being presented," "potentially," "encouraging," "encouraged," "may," "committed," "hope," or similar terms, or by express or implied discussions regarding potential new indications or labeling for Afinitor, or regarding potential future revenues from Afinitor. You should not place undue reliance on these statements. Such forward-looking statements are based on the current beliefs and expectations of management regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that Afinitor 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 Afinitor will be commercially successful in the future. In particular, management's expectations regarding Afinitor could be affected by, among other things, the uncertainties inherent in research and development, including unexpected clinical trial results and additional analysis of existing clinical data; unexpected regulatory actions or delays or government regulation generally; the company's ability to obtain or maintain proprietary intellectual property protection; general economic and industry conditions; competition in general; global trends toward health care cost containment, including ongoing pricing pressures; unexpected safety issues; unexpected manufacturing or quality issues, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. 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
Novartis provides innovative healthcare solutions that address the evolving needs of patients and societies. Headquartered in Basel, Switzerland, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, eye care and cost-saving generic pharmaceuticals. Novartis is the only global company with leading positions in these areas. In 2015, the Group achieved net sales of USD 49.4 billion, while R&D throughout the Group amounted to approximately USD 8.9 billion (USD 8.7 billion excluding impairment and amortization charges). Novartis Group companies employ approximately 119,000 full-time equivalent associates. Novartis products are available in more than 180 countries around the world. For more information, please visit http://www.novartis.com.

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