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Early Data Show Potential for Imatinib Mesylate Tablets to Treat Life-Threatening Form of Pulmonary Artery Disease

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- -- Exploratory study shows clinical improvement in patients with pulmonary arterial hypertension (PAH) -- Current treatment options have limited benefit for this debilitating, rapidly progressive and incurable blood vessel disease -- Imatinib mesylate, av

EAST HANOVER, N.J., Oct. 8 /PRNewswire-FirstCall/ -- An early proof-of-concept study presented today shows promising results for imatinib mesylate in the treatment of pulmonary arterial hypertension (PAH), a severe, incurable blood vessel disorder.

Preliminary findings from a 59-patient, multi-center Phase II clinical trial suggest imatinib mesylate provides a treatment benefit, as demonstrated by a significant improvement in pulmonary vascular resistance and a numerical increase in cardiac output, key hemodynamic measures used to monitor the progression of the disease. Improvements in the six-minute walk test, the primary endpoint of the study, approached, but did not reach, statistical significance.

These initial data were presented today at the European Respiratory Society (ERS) congress in Berlin, Germany, and further details on the study are expected to be published later this year. Imatinib mesylate is available for oncology indications as Gleevec® in the US, Canada and Israel and as Glivec® (imatinib), in countries outside of the US, Canada and Israel.

"The outcomes of this trial are clinically important given the rapid progression of PAH and the poor prognosis for these patients," said Professor Ardeschir Ghofrani, MD, Head of Pulmonary Hypertension Division, University Hospital Giessen und Marburg, Germany. "Our observations suggest that imatinib mesylate holds promise in treating PAH."

PAH is a debilitating disease that is characterized by a marked and sustained elevation in pulmonary artery pressure(1). The disease is rapidly progressive and can result in heart failure and death(1). There is no known cure for PAH and the goal of current treatments is to control symptoms of the disease(2). The prognosis for many PAH patients is similar to that of some advanced cancers, and with current treatment options, the five-year survival rate is 50%(3).

Imatinib mesylate is an orally administered targeted therapy that has successfully treated many patients with certain rare cancers. It works by inhibiting the activity of several proteins called tyrosine kinases, such as Bcr-Abl, c-KIT and platelet-derived growth factor receptor (PDGFR), which is also thought to be involved in the progression of PAH(3). In patients with PAH, PDGFR may cause smooth muscle cells in the pulmonary arteries to multiply, resulting in the constriction of these arteries(4).

Plans for research to further explore the potential of imatinib mesylate in PAH are ongoing and will be announced at a later date.

The double blind, placebo-controlled trial presented at ERS enrolled 59 patients with PAH to evaluate the

effectiveness and safety of imatinib mesylate 400 mg. The study participants had previously failed to improve after receiving standard therapy with prostanoids, endothelin antagonists or PDE-5 inhibitors.

"There is a high unmet need for new treatments that address the underlying mechanisms of PAH," said David Epstein, President and CEO of Novartis Oncology. "These early findings support exploring the potential of imatinib mesylate in PAH in a larger randomized clinical trial."

1. It is estimated that approximately 130,000 to 260,000 people worldwide have PAH(5). The mean age at diagnosis is 35 years, and most patients present with moderate-to-severe disease. PAH occurs most often in otherwise healthy people, and more often in women than in men(4).

The exact process by which PAH develops is not known. However, it appears to be associated with a variety of disease processes, including chronic thromboembolic disease (blood clots), connective tissue diseases, congenital heart disease and exposure to external factors including appetite suppressants or infectious diseases such as HIV(3).

1. Novartis has also conducted early stage research with imatinib mesylate in another non-oncology disease called idiopathic pulmonary fibrosis (IPF), a condition in which the lungs become scarred over time, making it more and more difficult to breathe(6). Early clinical trial results in IPF did not show a significant treatment benefit over placebo, and clinical trials have therefore been halted.

About Gleevec

Gleevec® (imatinib mesylate) tablets are indicated for the treatment of newly diagnosed adult patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in the chronic phase. Follow-up is limited to 5 years. Gleevec is also indicated for the treatment of patients with Ph+ CML in blast crisis (BC), accelerated phase (AP), or in chronic phase (CP) after failure of interferon-alpha (IFN-alpha) therapy; adult patients with relapsed or refractory Ph+ acute lymphoblastic leukemia (Ph+ ALL); adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene rearrangements; adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-KIT mutation or with c-KIT mutational status unknown; adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have the FIP1L1-PDGFRÎ± fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRÎ± fusion kinase-negative or unknown; adult patients with unresectable, recurrent, and/or metastatic dermatofibrosarcoma protuberans (DFSP); patients with KIT (CD117)-positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST); pediatric patients with PH+ CML in the chronic phase who are newly diagnosed or whose disease has recurred after stem cell transplant or who are resistant to interferon-therapy. There are no controlled trials in pediatric patients demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

Important safety information(7)

Fetal harm can occur when Gleevec is administered to a pregnant woman; therefore, women of childbearing potential should be advised to not become pregnant while taking Gleevec tablets and to avoid breast-feeding while taking Gleevec tablets because of the potential for serious adverse reactions in nursing infants. Sexually active female patients taking Gleevec should use adequate contraception. If the patient does become pregnant while taking Gleevec, the patient should be advised of the potential hazard to the fetus.

In adult Ph+ CML patients, severe (NCI Grades 3/4) lab abnormalities--including neutropenia (3.6%-48%), anemia (1%-42%), thrombocytopenia (<1%-33%) and hepatotoxicity (approx 5%)--and severe adverse

experiences (NCI Grades 3/4), including severe fluid retention (eg, pleural effusion, pulmonary edema, and ascites) and superficial edema (1.3%-11%), hemorrhage (1.8%-19%), and musculoskeletal pain (2%-9%) were reported among patients receiving Gleevec(*). Severe fluid retention appears to be dose-related, was more common in the advanced-phase studies (where the dosage was 600 mg/day), and is more common in the elderly.

Although most pediatric Ph+ CML patients experienced adverse reactions at some time during the study, the incidence of Grade 3/4 adverse reactions was low and included neutropenia, thrombocytopenia, and anemia, generally within the first several months of therapy.

In HES/CEL patients, instances of Grade 3 leukopenia, neutropenia, lymphopenia, and anemia were reported.

(*)Numbers indicate the range of percentages in 4 studies among adult patients with Ph+ CML in blast crisis, accelerated phase, and chronic phase.

For DFSP, severe (NCI Grades 3/4) lab abnormalities included anemia (17%), thrombocytopenia (17%), neutropenia (8%) and increased creatinine (8%).

In GIST, severe (NCI Grades 3/4) lab abnormalities (400 mg/day; 600 mg/day)--including neutropenia (10%; 11%), anemia (3%; 9%), thrombocytopenia (0%; 1%) and hepatotoxicity (6%; 8%)--and severe adverse experiences (NCI Grades 3/4), including severe fluid retention (eg, pleural effusion or ascites; 3%; 8%) and superficial edema (6%; 5%), hemorrhage (6%; 11%), abdominal pain (11%; 4%), nausea (6%; 4%), diarrhea (3%; 7%) and musculoskeletal pain (6%; 1%) were reported among patients receiving Gleevec.

Severe congestive heart failure and left ventricular dysfunction have occasionally been reported. Most of the patients with reported cardiac events have had other comorbidities and risk factors, including advanced age and previous medical history of cardiac disease. Patients with cardiac disease or risk factors for cardiac failure should be monitored carefully, and any patient with signs or symptoms consistent with cardiac failure should be evaluated and treated.

Dose adjustments may be necessary due to hepatotoxicity, other nonhematologic adverse reactions, or hematologic adverse reactions. Therapy with Gleevec was discontinued for drug-related adverse reactions in 2.4% to 5% of adult patients with Ph+ CML and for adverse reactions in 5% of KIT+ GIST patients. None of the 5 patients in the ASM study discontinued Gleevec due to drug-related events or abnormal laboratory values. Complete blood counts should be performed weekly for the first month, biweekly for the second month, and periodically thereafter as clinically indicated (for example, every 2-3 months).

A 25% decrease in the recommended dose should be used for patients with severe hepatic impairment.

Some GIST patients (5%) were reported to have severe gastrointestinal (GI) bleeds and/or intratumoral bleeds. GI tumor sites may have been the source of GI bleeds.

Patients should be weighed and monitored regularly for signs and symptoms of edema, which can be serious or life-threatening. There have also been reports, including fatalities, of cardiac tamponade, cerebral edema, increased intracranial pressure, papilledema, and GI perforation.

In patients with HES and cardiac involvement, cases of cardiogenic shock/left ventricular dysfunction have been associated with the initiation of Gleevec therapy. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures, and temporarily withholding Gleevec. MDS/MPD disease and systemic mastocytosis may be associated with high eosinophil levels. Performance of an echocardiogram and determination of serum troponin should therefore be considered in patients with HES/CEL, and in patients with MDS/MPD or ASM associated with high eosinophil levels. If either is abnormal,

the prophylactic use of systemic steroids (1-2 mg/kg) for 1-2 weeks concomitantly with Gleevec should be considered at the initiation of therapy.

Bullous dermatologic reactions (eg, erythema multiforme and Stevens-Johnson syndrome) have also been reported. In some cases, the reaction recurred upon re-challenge. Several postmarketing reports describe patients able to tolerate the reintroduction of Gleevec at a lower dose with or without concomitant corticosteroids or antihistamines following resolution or improvement of the bullous reaction.

Consider potential toxicities--specifically liver, kidney and cardiac toxicity, and immunosuppression from long-term use.

Gleevec is metabolized by the CYP3A4 isoenzyme and is an inhibitor of CYP3A4, CYP2D6 and CYP2C9. Dosage of Gleevec should increase by at least 50%, and clinical response should be carefully monitored, in patients receiving Gleevec with a potent CYP3A4 inducer such as rifampin or phenytoin. Examples of commonly used drugs that may significantly interact with Gleevec include ketoconazole, acetaminophen, warfarin, erythromycin and phenytoin. (Please see full Prescribing Information for other potential drug interactions).

For daily dosing of 800 mg and above, dosing should be accomplished using the 400 mg tablets to reduce exposure to iron.

Common side effects of Gleevec tablets

The majority of adult Ph+ CML patients who received Gleevec in clinical studies experienced adverse reactions at some time, but most were mild to moderate in severity. The most frequently reported adverse reactions (all Grades) were superficial edema (60%-74%), nausea (50%-73%), muscle cramps (28%-62%), vomiting (23%-58%), diarrhea (43%-57%), musculoskeletal pain (38%-49%) and rash and related terms (36%-47%).(+)(++)

The overall safety profile of Ph+ CML pediatric patients treated with Gleevec in 93 children studied was similar to that found in studies with adult patients, except that musculoskeletal pain was less frequent (20.5%) and peripheral edema was not reported. Nausea and vomiting were the most commonly reported individual adverse reactions with an incidence similar to that seen in adult patients.

The adverse reactions and safety profile for Ph+ ALL, MDS/MPD, ASM and HES/CEL were generally similar to the safety profile for Ph+ CML.

The most frequently reported drug-related adverse reactions reported in the Ph+ ALL studies were mild nausea, vomiting, diarrhea, myalgia, muscle cramps and rash, which were easily manageable. Superficial edemas were also a common finding in all studies and were described primarily as periorbital or lower-limb edemas. However, these edemas were rarely severe and may be managed with diuretics, other supportive measures, or, in some patients, by reducing the dose of Gleevec.

Frequently reported adverse reactions (all Grades) in the seven MDS/MPD patients assessed were nausea (57%); diarrhea and muscle cramps (43% each); anemia, fatigue, arthralgiaand periorbital edema (29% each).

All ASM patients experienced at least one adverse reaction at some time. The most frequently reported adverse reactions were diarrhea, nausea, ascites, muscle cramps, dyspnea, fatigue, peripheral edema, anemia, pruritus, rash and lower respiratory tract infection.

All HES/CEL patients experienced at least one adverse reaction, the most common being gastrointestinal, cutaneous and musculoskeletal disorders. Hematologic abnormalities were also frequent, with instances of

Grade 3 leukopenia, neutropenia, lymphopenia and anemia.

Frequently reported adverse reactions (all Grades) in the 12 DFSP patients assessed included nausea and fatigue (42% each); periorbital, peripheral and eye edema (33% each); diarrhea, vomiting, rash, lacrimation increased and anemia (25% each); face edema, pyrexia, exertional dyspnea, rhinitis, and anorexia (17% each).

The majority of patients who received Gleevec in the GIST study experienced adverse reactions at some time. Most adverse reactions were mild to moderate in severity. The most frequently reported adverse reactions (400 mg/day; 600 mg/day) (all Grades) were superficial edema (81%; 77%), nausea (63%; 74%), muscle cramps (47%; 58%), diarrhea (59%; 70%), fatigue (48%; 53%), abdominal pain (40%; 37%), rash and related terms (38%; 53%), vomiting (38%; 35%), musculoskeletal pain (37%; 30%) and hemorrhage (26%; 34%).(**)

Supportive care may help management of some mild-to-moderate adverse reactions so that the prescribed dose can be maintained whenever possible. However, in some cases, either a dose reduction or interruption of treatment with Gleevec may be necessary.

Gleevec tablets should be taken with food and a large glass of water to minimize GI irritation. Gleevec tablets should not be taken with grapefruit juice and other foods known to inhibit CYP3A4.

Patients should be informed to take Gleevec exactly as prescribed, not to change their dose or stop taking Gleevec unless they are told to do so by their doctor. If patients miss a dose, they should be advised to take their dose as soon as possible unless it is almost time for their next dose, in which case the missed dose should not be taken. A double dose should not be taken to make up for any missed dose.

(+)Numbers indicate the range of percentages in 4 studies among adult patients with Ph+ CML in blast crisis, accelerated phase, and chronic phase.

(++)For more detailed study information, please see full Prescribing Information.

(**)For more detailed study information, please see full Prescribing Information.

Disclaimer

The foregoing release contains forward-looking statements that can be identified by terminology such as "potential," "to further explore," "promising," "suggest," "expected," "promise," "can," "goal," "prognosis," "will," "plans," "estimated," or similar expressions, or by express or implied discussions regarding potential new indications or labelling for Gleevec, regarding potential future revenues from Gleevec, or regarding the long-term impact of a patient's use of Gleevec. You should not place undue reliance on these statements. Such forward-looking statements reflect the current views of the Company regarding future events, and involve known and unknown risks, uncertainties and other factors that may cause actual results with Gleevec to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that Gleevec will be approved for any additional indications or labelling in any market. Nor can there be any guarantee that Gleevec will achieve any particular levels of revenue in the future. Neither can there be any guarantee regarding the long-term impact of a patient's use of Gleevec. In particular, management's expectations regarding Gleevec could be affected by, among other things, unexpected clinical trial results, including unexpected new clinical data and unexpected additional analysis of existing clinical trial data; unexpected regulatory actions or delays or government regulation generally; 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

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Located in East Hanover, New Jersey, Novartis Pharmaceuticals Corporation is an affiliate of Novartis AG (NYSE: NVS), 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, cost-saving generic pharmaceuticals, preventive vaccines, diagnostic tools and consumer health products. Novartis is the only company with leading positions in these areas. In 2007, the Group's continuing operations (excluding divestments in 2007) achieved net sales of USD 38.1 billion and net income of USD 6.5 billion. Approximately USD 6.4 billion was invested in R&D activities throughout the Group. Headquartered in Basel, Switzerland, Novartis Group companies employ approximately 98,000 full-time associates and operate in over 140 countries around the world. For more information, please visit http://www.novartis.com/.

For more information

Additional information regarding Gleevec, Tasigna and Novartis Oncology can be found on the websites http://www.novartisoncologyvpo.com/, http://www.gleevec.com/, http://www.us.tasigna.com/ and http://www.novartisoncology.us/.

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