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Six-year pivotal study data reinforce the superiority of Tasigna® over Glivec® in newly-diagnosed patients with Ph+ CML

- Fewer patients on Tasigna vs. Glivec had their leukemia progress to advanced stage, a key goal of treatment in CML and important clinical benefit.
- Patients on Tasigna had higher rates of early, deep and sustained molecular response, including MR4.5\(^1\), a very low level of the protein that causes Ph+ CML.
- ENESTnd six-year data confirm the favorable risk/benefit profile of Tasigna vs. Glivec in newly-diagnosed CML patients.

Basel, December 8, 2014 – Six-year results from the randomized Phase III ENESTnd study continue to demonstrate the superiority of Tasigna® (nilotinib) compared to Glivec\(^*\) (imatinib) at achieving higher rates of early, deep and sustained molecular responses in newly-diagnosed Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) patients\(^1\). The six-year update from the ENESTnd trial was presented at the 56\(^{th}\) annual meeting of the American Society of Hematology (ASH) in San Francisco.

“At the ENESTnd six-year follow up, we still see consistent evidence of deeper molecular response and fewer progressions to advanced disease in patients taking Tasigna compared to those on Glivec,” said Giuseppe Saglio, MD, ENEST studies investigator, Professor of Internal Medicine and Haematology and Director of the Department of Molecular Medicine and Targeted Therapy, San Luigi University Hospital at the University of Turin, Orbassano, Italy. “These data provide further evidence of the consistent clinical profile of Tasigna as a leading treatment in newly-diagnosed patients.”

The six-year data demonstrated higher rates of early and deeper sustained molecular response with Tasigna, including MR4.5, and a reduced risk of progression compared to Glivec\(^1\). The difference in the rates of MR4.5 showed continued improvement for both Tasigna 300 mg and 400 mg twice-daily arms compared to Glivec (MR4.5: 6-10% difference by one year, 22-23% difference by six years\(^1\)). MR4.5 represents an extremely low level of detectable BCR-ABL protein, the cause of Ph+ CML (measured in the blood at 0.0032% or less on a standardized International Scale). A higher proportion of patients in the Tasigna arms versus the Glivec arm achieved BCR-ABL IS \(\leq 10\%\) at 3 months\(^1\).

Further, there were fewer progressions to accelerated phase/blast crisis (AP/BC) with Tasigna versus Glivec\(^1\). Sixteen patients treated with Glivec had CML-related deaths, compared to 6 and 4 patients on the Tasigna 300 mg and 400 mg twice-daily arms, respectively\(^1\). The safety profile of Tasigna remained consistent with previous reports. The most common adverse events were rash, headache, ALT increase and nausea, and the cardiovascular events rates were higher in the Tasigna arms compared to Glivec\(^1\).

\(^1\)Known as Gleevec\(^*\) (imatinib mesylate) tablets in the US, Canada and Israel.
“Fifteen years ago at ASH, our first pivotal CML data were presented, representing the start of a revolutionary shift in the treatment of patients with this disease. Through our ongoing research, we better understand today the role that early, deep and sustained molecular responses have on the outcomes of patients with CML,” said Bruno Strigini, President, Novartis Oncology. “We are now taking this knowledge a step further by exploring deeper molecular response like MR4.5 and the impact it may have on how we treat CML in the future.”

**Novartis Commitment to CML**

Over the past several decades, Novartis research in Ph+ CML has helped transform the disease from a fatal leukemia to a chronic condition and today, the company continues its long-standing commitment to the global CML community. Two of the ENEST treatment-free remission (TFR) studies ENESTfreedom and ENESTop, which will evaluate the feasibility of stopping treatment, and achieving successful TFR and deep molecular response on Tasigna in patients with CML in the chronic phase, have completed enrollment.

Stopping treatment is not a clinical recommendation and should only be attempted in the context of a well-controlled clinical study. A very important part of these TFR studies is the inclusion of regular molecular monitoring with International Scale Real-Time Quantitative Polymerase Chain Reaction (IS RT-Q-PCR) testing. Once treatment is stopped, molecular monitoring is used to identify if a patient’s level of disease remains in deep molecular response or if the reintroduction of treatment is needed.

**ENESTnd study details**

ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials – Newly Diagnosed Patients) is a Phase III, randomized, open-label, multicenter trial comparing the efficacy and safety of Tasigna versus Glivec in adult patients with newly diagnosed Ph+ CML in chronic phase. It is the largest global randomized comparison of two oral therapies ever conducted in newly-diagnosed Ph+ CML patients.

The study is being conducted at 217 global sites with 846 patients enrolled. Patients were randomized to receive Tasigna 300 mg twice daily (n=282), Tasigna 400 mg twice daily (n=281) or Glivec 400 mg once daily (n=283). The primary endpoint was major molecular response (MMR) at 12 months; the key secondary endpoint was durable MMR at 24 months (patients having MMR when evaluated at both 12 and 24 months). MMR was defined in this study as 0.1% or less of BCR-ABL as measured by IS RT-Q-PCR. Patients on the Tasigna 300 mg twice-daily arm or on the Glivec treatment arm who had suboptimal response or treatment failure were allowed to escalate dose and/or switch to Tasigna 400 mg twice daily in a separate extension study. These data, presented at ASH, were the six-year (defined as 72 cycles of 28 days) follow up.

The six-year ENESTnd update found that higher rates of MMR and MR4.5 by six years were achieved in Tasigna versus Glivec-treated patients. The difference in the rates of MMR and MR4.5 continued to be higher for both Tasigna 300 mg and 400 mg twice-daily arms compared to Glivec (MMR: 24-28% difference by one year, 16-18% difference by six years; MR4.5: 6-10% difference by one year, 22-23% difference by six years). Fewer patients progressed to AP/BC on Tasigna versus Glivec. The estimated rates of patients whose disease did not progress to AP/BC on study at 72 months in the Glivec, Tasigna 300 mg and Tasigna 400 mg twice-daily arms were 92.2%, 95.8% and 97.8%, respectively. The estimated rates of patients on study who are alive (OS) at 72 months in the Glivec, Tasigna 300 mg and Tasigna 400 mg twice-daily arms were 91.4%, 91.6% and 95.8%, respectively. The estimated rates of freedom from death due to a CML-related cause at 72 months in the Glivec, Tasigna 300 mg and Tasigna 400 mg twice-daily arms were 93.9%, 97.7% and 98.5%, respectively. More patients in the Tasigna arms (n=234 and 232 for 300mg and 400 mg arms respectively) versus the Glivec arm (n=176) achieved BCR-ABLIS < 10% at 3 months. The safety profile of Tasigna remained consistent with previous reports. The most common adverse events were rash,
headache, ALT increase and nausea. Although cardiovascular events rates were higher in the Tasigna arms compared to Glivec, fewer progressions to AP/BC, or death from CML were reported in the Tasigna arms compared to Glivec.

**About Tasigna (nilotinib)**

Tasigna® (nilotinib) is approved in more than 110 countries for the treatment of chronic phase and accelerated phase Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML) in adult patients resistant or intolerant to at least one prior therapy, including Glivec® (imatinib), and in more than 85 countries for the treatment of adult patients with newly diagnosed Ph+ CML in chronic phase.

**Tasigna Important Safety Information**

Use with caution in patients with uncontrolled or significant cardiac disease and in patients who have or may develop prolongation of QTc. Low levels of potassium or magnesium must be corrected prior to Tasigna administration. Monitor closely for an effect on the QTc interval. Baseline ECG is recommended prior to initiating therapy and as clinically indicated. Uncommon cases (0.1 to 1%) of sudden death have been reported in clinical studies in patients with significant risk factors.

Use with caution in patients with liver impairment, with a history of pancreatitis and with total gastrectomy. Patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not use Tasigna. Tasigna may cause fetal harm in pregnant women. Women taking Tasigna should not breastfeed.

The most frequent Grade 3 or 4 adverse events are hematological (neutropenia and thrombocytopenia) which are generally reversible and usually managed by withholding Tasigna temporarily or dose reduction. Monitor blood counts regularly. Pancreatitis has been reported. The most frequent non-hematologic adverse events were rash, pruritus, nausea, fatigue, headache, alopecia, myalgia, constipation and diarrhea. Most of these adverse events were mild to moderate in severity.

Please see full Prescribing Information available at www.tasigna.com.

**About Glivec (imatinib)**

Glivec® (imatinib) is approved in more than 110 countries for the treatment of all phases of Ph+ CML, for the treatment of adult patients with KIT (CD117)-positive gastrointestinal stromal tumors (GIST), which cannot be surgically removed and/or have metastasized and for the treatment of adult patients following complete surgical removal of KIT+ GIST.

**Glivec Important Safety Information**

Glivec can cause fetal harm in pregnant woman Glivec has been associated with severe edema (swelling) and serious fluid retention. Cytopenias (anemia, neutropenia, thrombocytopenia) are common, generally reversible and usually managed by withholding Glivec or dose reduction. Monitor blood counts regularly. Severe congestive heart failure and left ventricle dysfunction, severe liver problems including cases of fatal liver failure and severe liver injury requiring liver transplants have been reported. Caution in patients with cardiac dysfunction and hepatic dysfunction. Monitor carefully.

Bleeding may occur. Severe gastrointestinal (GI) bleeding has been reported in patients with KIT+ GIST. Skin reactions, hypothyroidism in patients taking levothyroxine replacement, GI perforation, in some cases fatal, tumor lysis syndrome which can be life threatening have also been reported with Glivec. Correct dehydration and high uric acid levels prior to treatment. Long-term use may result in potential liver, kidney, and/or heart toxicities; immune system suppression may also result from long-term use. In patients with hypereosinophilic syndrome and heart involvement, cases of heart disease have been associated with the initiation of Glivec therapy. Growth retardation has been reported in children taking Glivec. The long-term effects of extended treatment with Glivec on growth in children are unknown.
The most common side effects include fluid retention, muscle cramps or pain and bone pain, abdominal pain, loss of appetite, vomiting, diarrhea, decreased hemoglobin, abnormal bleeding, nausea, fatigue and rash. Glivec should be taken with food and a large glass of water.

Please see full Prescribing Information.

Disclaimer
The foregoing release contains forward-looking statements that can be identified by words such as “goal,” “ongoing,” “exploring,” “may,” “commitment,” “continues,” “will,” “being conducted,” or similar terms, or by express or implied discussions regarding potential new indications or labeling for Tasigna or Glivec, or regarding potential future revenues from Tasigna and Glivec. 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 Tasigna or Glivec 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 Tasigna and Glivec will be commercially successful in the future. In particular, management’s expectations regarding Tasigna and Glivec 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; global trends toward health care cost containment, including ongoing pricing pressures; unexpected manufacturing 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, cost-saving generic pharmaceuticals, preventive vaccines, over-the-counter and animal health products. Novartis is the only global company with leading positions in these areas. In 2013, the Group achieved net sales of USD 57.9 billion, while R&D throughout the Group amounted to approximately USD 9.9 billion (USD 9.6 billion excluding impairment and amortization charges). Novartis Group companies employ approximately 133,000 full-time equivalent associates and sell products in more than 150 countries around the world. For more information, please visit http://www.novartis.com.

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