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Abstract # LBA-1

Novartis Tasigna[®] trial shows superior results to Glivec[®] in patients with early-stage chronic myeloid leukemia

- *Tasigna surpassed Glivec in every measure of treatment efficacy designated in the trial including prevention of disease progression at 12 months¹*
- *At 12-month milestone, significantly fewer patients progressed to accelerated or blastic phase on Tasigna 300 mg twice daily than on Glivec 400 mg once daily¹*
- *Tasigna was well tolerated; few patients receiving 300 mg twice daily discontinued because of adverse events¹*
- *Results support Tasigna as treatment in newly diagnosed patients with Ph+ CML; Novartis to file worldwide applications*

Basel, December 8, 2009 — In a large Phase III clinical trial, Tasigna[®] (nilotinib) demonstrated greater efficacy over Glivec[®] (imatinib)* in the treatment of adult patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase¹.

In the first head-to-head comparison of these two oral therapies as initial treatment for this life-threatening blood cancer, Tasigna results showed statistically significant improvement over Glivec in every measure of efficacy, including major molecular response (MMR), complete cytogenetic response (CCyR) and prevention of progression to accelerated or blastic phase¹. The new data were presented as a late breaker abstract at the 51st annual meeting of the American Society of Hematology (ASH), held in December, in New Orleans, USA.

At 12 months, significantly fewer patients progressed to accelerated or blastic phase on Tasigna 300 mg twice daily than on Glivec 400 mg once daily (2 patients vs. 11 patients)¹, demonstrating a statistically significant improvement in disease control. In the study, Tasigna was well tolerated. Fewer patients discontinued due to adverse events from the Tasigna 300 mg twice daily arm of the study compared to the Glivec 400 mg once daily arm. No patients in the study had prolongation of QT interval >500 milliseconds¹. No sudden deaths occurred with either treatment².

"The outstanding rates of response observed with Tasigna, combined with the very low rate of disease progression, strongly indicate that patients who begin their treatment with Tasigna may have long-term improvement of progression-free survival," said Giuseppe Saglio, University of Turin, San Luigi Hospital, Orbassano-Torino, Italy, a member of the study management committee. "The efficacy results and tolerability of Tasigna should support its use in newly diagnosed Ph+ CML patients."

*Known as Gleevec[®] (imatinib mesylate) tablets in the US, Canada and Israel.

With Tasigna 300 mg twice daily, the rate of MMR at 12 months was twice that of patients receiving Glivec 400 mg once daily (44% vs. 22%, $p < 0.0001$)¹. In addition, 80% of patients achieved CCyR with Tasigna versus 65% with Glivec 400 mg once daily ($p < 0.0001$)¹. Responses were achieved faster in the Tasigna group than in the Glivec group¹.

MMR was defined in the study as reduction in the level of the abnormal Bcr-Abl protein to less than or equal to 0.1% of the pre-treatment level based on an internationally agreed standard¹. This can be interpreted to mean that for every 1,000 cells containing Bcr-Abl that were present in the blood at the start of therapy, only one cell was present at the 12-month follow-up. CCyR indicates that no CML cells containing the diagnostic Ph chromosome can be seen in a sample of bone marrow taken from the patient.

"Novartis is pioneering research targeting the molecular origin of Ph+ CML, which has led to treatments of unprecedented effectiveness and safety," said David Epstein, President and CEO of Novartis Oncology and Novartis Molecular Diagnostics. "Considering the already low rates of progression to advanced disease and the excellent long-term survival of patients on Glivec, the efficacy and safety profile of Tasigna at 12 months is fantastic news and brings promise for further improving the outcomes of patients with Ph+ CML."

Tasigna is a potent and selective inhibitor of the Bcr-Abl protein that causes production of cancer cells in Ph+ CML^{2,3}. Upon initial reports of resistance in the Glivec registration trials, Novartis scientists created a new molecule, Tasigna, just a year after the launch of Glivec. The first clinical trials began just 21 months after discovery. The drug received its first regulatory approval in the second-line indication in 2007.

Novartis plans to file worldwide applications for approval of Tasigna as a treatment for adult patients with newly diagnosed Ph+ CML. Tasigna is currently approved in more than 80 countries including the European Union, United States and other countries for the treatment of adult patients with Ph+ CML in chronic phase or accelerated phase who are resistant or intolerant to prior treatment including Glivec.

Study details

The clinical trial, Evaluating Nilotinib Efficacy and Safety in Clinical Trials of Newly Diagnosed Ph+ CML Patients (ENESTnd), 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 phase¹. It is the largest global randomized comparison of two oral therapies ever conducted in newly diagnosed Ph+ CML patients. Designed to detect a difference in MMR between Tasigna and Glivec after 12 months of treatment, it is also the first registration study in which molecular traces of a key biomarker specific to Ph+ CML have been used as a primary endpoint for regulatory review. The trial's secondary endpoints included CCyR, as well as progression to accelerated or blastic phase, and overall survival.

ENESTnd is being conducted at 220 global sites with 846 patients enrolled. Patients were randomized to receive Tasigna 400 mg twice daily ($n = 281$), Tasigna 300 mg twice daily ($n = 282$) or Glivec 400 mg once daily ($n = 283$). The primary endpoint was MMR at 12 months; a secondary endpoint was CCyR by 12 months¹. Planned follow-up is for five years². Patients on the Glivec treatment arm who had suboptimal response or treatment failure will be able to escalate dose and/or switch to Tasigna via a protocol extension.

Samples for molecular response were evaluated by a single reference laboratory. The blood test used to determine molecular response can detect a single cell containing traces of Bcr-Abl in up to one million normal blood cells⁴. In addition to being simpler and less invasive for patients, the test has a much greater sensitivity than standard cytogenetic tests, which require a sample of bone marrow to be drawn for visual detection of cells containing the Ph chromosome⁵.

All patients had a minimum of 12 months of treatment or discontinued early; the median follow-up was 14 months. Overall, 84%, 82% and 79% of patients remained in the study on Tasigna 300 mg twice daily, Tasigna 400 mg twice daily and Glivec 400 mg once daily, respectively.

Rates of MMR at 12 months were statistically higher for patients in the Tasigna 300 mg twice daily group compared with Glivec 400 mg once daily (44% vs. 22%, $p < 0.0001$) and also for Tasigna 400 mg twice daily compared with Glivec 400 mg once daily (43% vs. 22%, $p < 0.0001$). Among patients who achieved MMR, median time to MMR was faster for Tasigna 300 mg twice daily (5.7 months) and Tasigna 400 mg twice daily (5.8 months) compared with Glivec 400 mg once daily (8.3 months). Molecular response was assessed by polymerase chain reaction (PCR) at baseline, monthly for three months, and every three months thereafter.

Rates of CCyR by 12 months were significantly higher for Tasigna at 300 mg twice daily compared with Glivec 400 mg once daily (80% vs. 65%, $p < 0.0001$) and for Tasigna 400 mg twice daily compared with Glivec 400 mg once daily (78% vs. 65%, $p = 0.0005$). Overall, progression to advanced disease was lower for Tasigna 300 mg twice daily (2 patients) and Tasigna 400 mg twice daily (1 patient) compared with Glivec 400 mg once daily (11 patients).

Both Tasigna and Glivec were well tolerated overall. Rates of discontinuation due to adverse events or laboratory abnormalities were 7% for Tasigna 300 mg twice daily, 11% for Tasigna 400 mg twice daily, and 9% for Glivec 400 mg once daily.

About Ph+ CML

CML is a disease in which the body produces cancerous white blood cells. Almost all patients with CML have an abnormality known as the Philadelphia chromosome, which produces a protein called Bcr-Abl. Bcr-Abl causes malignant white blood cells to proliferate⁶. Worldwide, CML is responsible for approximately 10% to 15% of all adult cases of leukemia⁷, with an incidence of one to two cases per 100,000 people per year⁸.

About Tasigna³

Tasigna has been approved in more than 80 countries for the treatment of chronic phase and accelerated phase Ph+ CML in adult patients resistant or intolerant to at least one prior therapy, including Glivec. The effectiveness of Tasigna for this indication is based on confirmed hematologic and unconfirmed cytogenetic response rates. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

Tasigna important safety information

Because taking Tasigna with food may increase the amount of drug in the blood, Tasigna should not be taken with food and patients should wait at least two hours after a meal before taking Tasigna. In addition, no food should be consumed for at least one hour after the dose is taken.

The most frequent Grade 3 or 4 adverse events for Tasigna were primarily hematological in nature and included neutropenia and thrombocytopenia. Elevations seen in bilirubin, liver function tests, lipase enzymes and blood sugar, were mostly transient and resolved over time. These cases were easily managed and rarely led to discontinuation of treatment. Pancreatitis was reported in less than 1% of cases. The most frequent non-hematologic drug-related adverse events were rash, pruritus, nausea, fatigue, headache, constipation and diarrhea. Most of these adverse events were mild to moderate in severity.

Tasigna should be used with caution in patients with uncontrolled or significant cardiac disease (e.g., recent heart attack, congestive heart failure, unstable angina or clinically significant bradycardia), as well as in patients who have or may develop prolongation of QTc. These include patients with abnormally low potassium or magnesium levels, patients with congenital long QT syndrome, patients taking anti-arrhythmic medicines or other drugs that may lead to QT prolongation. Low levels of potassium or magnesium must be corrected prior to Tasigna administration. Close monitoring for an effect on the QTc interval is advisable and a baseline echocardiogram is recommended prior to initiating therapy with Tasigna and as clinically indicated.

About Glivec⁹

Glivec is approved in more than 90 countries, including the US, EU and Japan, for the treatment of all phases of Ph+ CML. Glivec is also approved in the US, EU and other countries for the treatment of patients with Kit (CD117)-positive gastrointestinal tumors (GIST), which cannot be surgically removed and/or have already spread to other parts of the body (metastasized). In the US and EU, Glivec is now approved for the post-surgery treatment of adult patients following complete surgical removal of Kit (CD117)-positive gastrointestinal stromal tumors. In the EU, Glivec is also approved for the treatment of adult patients with newly diagnosed Ph+ acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy and as a single agent for patients with relapsed or refractory Ph+ ALL. Glivec is also approved for the treatment of adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP) who are not eligible for surgery. Glivec is also approved for the treatment of patients with myelodysplastic/myeloproliferative diseases (MDS/MPD). Glivec is also approved for hypereosinophilic syndrome and/or chronic eosinophilic leukemia (HES/CEL).

The effectiveness of Glivec is based on overall hematological and cytogenetic response rates and progression-free survival in CML, on hematological and cytogenetic response rates in Ph+ ALL, MDS/MPD, on hematological response rates in systemic mastocytosis (SM), HES/CEL, on objective response rates and progression-free survival in unresectable and/or metastatic GIST, on recurrence free survival in adjuvant GIST and on objective response rates in DFSP. Increased survival in controlled trials has been demonstrated only in newly diagnosed chronic phase CML and GIST.

Not all indications are available in every country.

Glivec important safety information

The majority of patients treated with Glivec in clinical trials experienced adverse events at some time. Most events were of mild to moderate grade and treatment discontinuation was not necessary in the majority of cases.

The safety profile of Glivec was similar in all indications. The most common side effects included nausea, superficial edema, muscle cramps, skin rash, vomiting, diarrhea, abdominal pain, myalgia, arthralgia, hemorrhage, fatigue, headache, joint pain, cough, dizziness, dyspepsia and dyspnea, dermatitis, eczema and fluid retention, as well as neutropenia, thrombocytopenia and anemia. Glivec was generally well tolerated in all of the studies that were performed, either as monotherapy or in combination with chemotherapy, with the exception of a transient liver toxicity in the form of transaminase elevation and hyperbilirubinemia observed when Glivec was combined with high dose chemotherapy.

Rare/serious adverse reactions include: sepsis, pneumonia, depression, convulsions, cardiac failure, thrombosis/embolism, ileus, pancreatitis, hepatic failure, exfoliative dermatitis, angioedema, Stevens-Johnson syndrome, renal failure, fluid retention, edema (including brain, eye, pericardium, abdomen and lung), hemorrhage (including brain, eye, kidney and gastrointestinal tract), diverticulitis, gastrointestinal perforation, tumor hemorrhage/necrosis and hip osteonecrosis/avascular necrosis.

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. Cardiac screening should be considered in patients with HES/CEL, and patients with MDS/MPD with high level of eosinophils (echocardiogram, serum troponin level).

Glivec is contraindicated in patients with known hypersensitivity to imatinib or any of its excipients. Women of childbearing potential should be advised to avoid becoming pregnant while taking Glivec.

Disclaimer

The foregoing release contains forward-looking statements that can be identified by terminology such as “to file,” “may,” “should,” “potential,” “promise,” “plans,” “will,” or similar expressions, or by express or implied discussions regarding potential new indications or labeling for Tasigna or regarding potential future revenues from Tasigna or Glivec. 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 Tasigna or Glivec to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that Tasigna will be submitted or approved for any additional indications or labeling in any market. Nor can there be any guarantee that Tasigna or Glivec will achieve any particular levels of revenue in the future. In particular, management’s expectations regarding Tasigna and Glivec could be affected by, among other things, unexpected clinical trial results, including unexpected new clinical data and unexpected additional analysis of existing clinical 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 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

Novartis 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 each of these areas. In 2008, the Group’s continuing operations achieved net sales of USD 41.5 billion and net income of USD 8.2 billion. Approximately USD 7.2 billion was invested in R&D activities throughout the Group. Headquartered in Basel, Switzerland, Novartis Group companies employ approximately 99,000 full-time-equivalent associates and operate in more than 140 countries around the world. For more information, please visit <http://www.novartis.com>.

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