New five-year data support superiority of Novartis drug Tasigna® over Glivec® in newly diagnosed Ph+ CML patients

- ENESTnd data indicate trend for longer overall survival and event-free survival in newly diagnosed Ph+ CML patients on Tasigna versus Glivec

- Data demonstrated higher rates of early and deeper molecular response in newly diagnosed patients, including MR4.5, and a reduced risk of progression

- Separate study, ENESTcmr, confirms treatment with Tasigna led to deeper molecular response in patients who switch after long-term treatment with Glivec

- New data show patients who failed to respond to frontline Glivec achieved higher rates of molecular response with switch to Tasigna versus Glivec dose escalation

Basel, December 9, 2013 – Findings from three large, randomized Phase III studies demonstrate the superiority of Tasigna® (nilotinib) compared to Glivec® (imatinib) at achieving deeper molecular responses across various Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) patient populations, including newly diagnosed patients, patients with residual disease who switched to Tasigna after long-term treatment with Glivec, and patients who failed to respond to frontline Glivec (as defined by 2013 European LeukemiaNet [ELN] guidelines). These results, which were presented in oral sessions at the 55th annual meeting of the American Society of Hematology (ASH) in New Orleans, add to the growing body of evidence confirming the superiority of Tasigna to Glivec at achieving molecular response in Ph+ CML patients.

“These new and updated data reaffirm the superiority of Tasigna over Glivec at achieving deeper molecular responses and provide even more evidence supporting Tasigna as an appropriate treatment of choice in newly diagnosed patients and in those who switch to Tasigna after long-term treatment with Glivec,” said Giuseppe Saglio, MD, ENSET studies investigator, Professor of Internal Medicine and Haematology and Director of the Department of Molecular Medicine and Targeted Therapy at San Luigi Hospital, University of Turin, Italy. “Now we are looking at how deeper molecular responses may help guide our approach towards how we treat CML in the future.”

Presented at ASH were the five-year ENESTnd data, which continued to support the use of Tasigna in newly diagnosed Ph+ CML patients and demonstrated higher rates of early and deeper sustained molecular response, including MR4.5, and a reduced risk of progression compared to Glivec. The difference in the rates of both MR4 and MR4.5 continued to be higher for both Tasigna 300 mg and 400 mg twice daily arms compared to Glivec (MR4: 9-14% difference by one year, 21-24% difference by five years; MR4.5: 6-10% difference by one year, 21-23% difference by five years). Data indicated a trend

*Known as Gleevec® (imatinib mesylate) tablets in the US, Canada and Israel.
for higher overall survival (OS) and event-free survival (EFS) rates in patients treated with Tasigna compared to patients treated with Glivec. Fifteen patients treated with Glivec had CML-related deaths, compared to six and four patients on the Tasigna 300 mg and 400 mg twice daily arms, respectively. Few new adverse events (AEs) and laboratory abnormalities were observed between four and five years. Rates of patients with AEs leading to discontinuation were 11.1%, 17.7% and 13.2% in the Tasigna 300 mg twice daily, Tasigna 400 mg twice daily and Glivec arms, respectively.

In a separate follow-up analysis, results from the 36-month ENESTcmr data continued to show that Ph+ CML patients with residual disease following long-term treatment with Glivec achieved deeper molecular responses\(^1\) after switching to Tasigna\(^2\). Among patients without documented MR4.5 at baseline, cumulative incidence of MR4.5 was higher in patients randomized to Tasigna versus Glivec (46.9% vs. 33.3%; nominal p=0.0453). MR4.5 was achieved faster with median time to response of 24.0 months in the Tasigna arm and was not reached in the Glivec arm (nominal p=0.0011). The safety profiles for Tasigna and Glivec were consistent with prior studies\(^2\). By 36 months, no patients in either arm progressed to accelerated phase/blast crisis (AP/BC)\(^3\).

Also presented were results from the LASOR study, which demonstrated higher rates of molecular response in patients who failed to achieve a cytogenetic response (CCyR) with frontline Glivec (patients who do not achieve CCyR by six months, have loss of response at any time or have intolerance) who switched to Tasigna, versus those who dose escalated on Glivec (600 mg daily)\(^3\). While the primary endpoint of CCyR at six months after randomization, which was confounded by high rates of crossover to Tasigna from the Glivec arm, did not achieve statistical significance (p=0.3844), the clinical benefit of Tasigna was best evaluated when considering cross-over patients as non-responders\(^3\). A sensitivity analysis conducted supported the efficacy of Tasigna over Glivec. The safety profile for both drugs was consistent with prior reports of patients who switched therapy after inadequate responses to Glivec\(^3\).

“Today, we know from clinical studies that patients who achieve and maintain deep levels of response, known as MR4.5, do not progress to the advanced stages of CML,” said Hervé Hoppenot, President, Novartis Oncology. “These large studies continue to establish the benefits of Tasigna at achieving deeper molecular responses and we are committed to exploring the impact this 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. The Novartis treatment-free remission (TFR) clinical trial program includes eight studies that are now underway and actively enrolling Ph+ CML patients in more than 100 study centers across 40 countries\(^5\). In total, it is planned that more than 2,500 patients will be enrolled in these studies\(^5\).

Stopping treatment is not a clinical recommendation and should only be attempted in the context of a well-controlled clinical study\(^5\). 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

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\(^1\)In ENESTcmr, molecular response (reduction of BCR-ABL transcripts in the blood of patients) is measured at four levels, based on an international standard:
- MMR (≤ 0.1% BCR-ABL)
- MR4 (≤ 0.01% BCR-ABL)
- MR4.5 (≤ 0.0032% BCR-ABL)
- Undetectable BCR-ABL (no detectable BCR-ABL transcript level with sample sensitivity of at least 4.5 log)
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 details¹**
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 Glivec treatment arm who had suboptimal response or treatment failure were allowed to escalate dose and/or switch to Tasigna in a separate extension study. These data, presented at ASH, were the five-year (defined as 60 cycles of 28 days) follow-up.

The five-year ENESTnd update found that higher rates of MMR, MR4 and MR4.5 by five years were achieved in Tasigna versus Glivec-treated patients. The difference in the rates of both MR4 and MR4.5 continued to be higher for both Tasigna 300 mg and 400 mg twice daily arms compared to Glivec (MR4: 9-14% difference by one year, 21-24% difference by five years; MR4.5: 6-10% difference by one year, 21-23% difference by five years). Fewer patients progressed to AP/BC on Tasigna versus Glivec. The estimated rates of patients whose disease did not progress to AP/BC at 60 months in the Glivec, Tasigna 300 mg and Tasigna 400 mg twice daily arms were 95.2%, 99.3% and 98.7%, respectively. The estimated rates of patients without on-treatment event (no death, progression to AP/BC, loss of partial cytogenetic response [PCyR], loss of CCyR or loss of complete hematologic response [CHR]) at 60 months in the Glivec, Tasigna 300 mg and Tasigna 400 mg twice daily arms were 92.6%, 95.0% and 97.4%, respectively. The estimated rates of patients who are alive (OS) at 60 months in the Glivec, Tasigna 300 mg and Tasigna 400 mg twice daily arms were 91.6%, 93.6% and 96.0%, respectively. The estimated rates of patients who didn’t die from a CML-related cause at 60 months in the Glivec, Tasigna 300 mg and Tasigna 400 mg twice daily arms were 93.7%, 97.7% and 98.5%, respectively. The safety profiles for both drugs were consistent with previous ENESTnd reports.

**ENESTcmr study details²**
ENESTcmr (Evaluating Nilotinib Efficacy and Safety in Clinical Trials – Complete Molecular Response) is an open-label, randomized, prospective, multi-center, Phase III study of Tasigna 400 mg twice daily versus Glivec (400 mg or 600 mg once daily) comparing kinetics of molecular response for patients with Ph+ CML in chronic phase who had achieved CCyR but were still BCR-ABL positive (i.e., had evidence of residual leukemia) after at least two years of treatment with Glivec. The study enrolled 207 patients. The patients were randomized into one of two treatment arms: Tasigna 400 mg twice daily versus continuing Glivec 400 mg or 600 mg once daily (same dose as at study entry).

The primary endpoint was the rate of best confirmed complete molecular response by 12 months of study therapy with Tasigna or Glivec. Secondary objectives included the kinetics of molecular response, duration of molecular response, progression-free survival (PFS) and OS in both arms and were previously presented. After 24 months on study, Glivec patients who did not achieve undetectable BCR-ABL transcript levels had the option to cross over to the Tasigna arm. Overall, 45 Glivec patients (44.6%) crossed over
to Tasigna in the 36-month follow up. These data, presented at ASH, were the 36-month follow-up.

More patients treated with Tasigna continued to achieve deeper molecular responses versus Glivec. Among patients without documented MR4.5 at baseline, cumulative incidence of MR4.5 was higher in patients randomized to Tasigna versus Glivec (46.9% vs. 33.3%; nominal p=0.0453). Seven out of the 32 responders in the Glivec arm achieved MR4.5 after crossing over to Tasigna. Patients randomized to Tasigna achieved MR4.5 faster than those who remained on Glivec. Estimated median time to achieve MR4.5 was 24.0 months in the Tasigna arm. In this 36-month follow-up, the estimated median time has not been reached in the Glivec arm (nominal p=0.0011). The safety profiles for Tasigna and Glivec were consistent with prior studies. By 36 months, no patients in either arm progressed to AP/BC.

**LASOR study details**

LASOR (Imatinib Dose Optimization versus Nilotinib in CML Patients with Suboptimal Response to Imatinib) is a global, randomized, Phase III study comparing the efficacy of Tasigna 400 mg twice daily to Glivec 600 mg once daily in 191 patients with Ph+ CML in the chronic phase who have a failed cytogenetic response to Glivec (400 mg once daily). Patients were randomized to receive Tasigna 400 mg twice daily (n=96) or to dose escalate to Glivec 600 mg once daily (n=95). At the initiation of the study, these patients were considered to be suboptimal cytogenetic responders by ELN guidelines, however are now classified as treatment failures by updated recommendations.

The primary endpoint of the study was CCyR at six months, with a secondary endpoint of MMR at 12 months. Crossover to alternate treatment was allowed before and after the primary endpoint in patients who failed to achieve CCyR by six months or had loss of response or had intolerance to Glivec dose escalation at any time, consistent with standard of care.

Complete cytogenetic response at six months was observed in 47 (49%) and 40 (42.9%) patients in the Tasigna and Glivec arms, respectively (p=0.3844). The primary endpoint did not achieve statistical significance likely because of the confounding effects of crossover occurring before primary endpoint analysis. The most frequent reasons for crossover from Glivec to Tasigna were lack of efficacy (no CCyR after six months) in 28 (30%) patients, intolerance to Glivec dose escalation in 17 (18%) patients, loss of response in 10 (11%) patients, and other in one (1%) patient. While none of the patients who crossed over from Tasigna to Glivec achieved CCyR at six months, six Glivec patients who crossed over to Tasigna did achieve this primary endpoint. The key secondary endpoint of MMR at 12 months was achieved in 35 (36.5%) and 24 (25.3%) patients in the Tasigna and Glivec arms, respectively. Up until the data cut-off, 56 patients crossed over from Glivec to Tasigna and 13 patients crossed over from Tasigna to Glivec. Counting cross-over patients as non-responders, a greater number of patients on Tasigna achieved MMR at 12 months versus Glivec (34 [35.4%; 95% confidence interval (CI) 32-52%] versus 15 [15.8%; 95% CI 12-28%], respectively). The safety profiles for both drugs were consistent with prior reports of patients who switched therapy after inadequate responses 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 “trend,” “committed,” “continues,” “commitment,” “underway,” “planned,” “will,” 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 and diagnostic tools, over-the-counter and animal health products. Novartis is the only global company with leading positions in these areas. In 2012, the Group achieved net sales of USD 56.7 billion, while R&D throughout the Group amounted to approximately USD 9.3 billion (USD 9.1 billion excluding impairment and amortization charges). Novartis Group companies employ approximately 133,000 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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