

NOVARTIS AG  
Form 6-K  
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## SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

### FORM 6-K

REPORT OF FOREIGN PRIVATE ISSUER  
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THE SECURITIES EXCHANGE ACT OF 1934

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Yes:  No:

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**- Investor Relations Release -**

**Higher initial dose of Glivec achieved better early responses than standard dose for patients with chronic myeloid leukemia**

- *Efficacy and safety profile in large randomized Phase III study consistent with landmark IRIS trial, which established Glivec as standard of care*
- *Study did not meet primary endpoint at 1 year, yet shows faster time to molecular responses with 800 vs. 400 mg dose*
- *Findings reinforce that monitoring blood levels of Glivec may help optimize treatment benefit for individual patients*
- *Novartis committed to improving first-line treatment through additional study follow-up and completing enrollment to Tasigna vs. Glivec trial*

**Basel, June 13, 2008** New data from a large, international clinical trial find that patients with newly diagnosed chronic myeloid leukemia who received Glivec® (imatinib)(1) at 800 mg/day as their initial treatment achieved clinical milestones significantly faster than those receiving the standard 400 mg/day dose.

The Tyrosine Kinase Inhibitor Optimization and Selectivity Study (TOPS) is the first Phase III, randomized, controlled clinical trial designed to evaluate the potential benefits of an 800 mg starting dose across all risk categories of newly diagnosed, previously untreated patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML).

Numerically, more patients achieved a major molecular response (MMR) with the 800 mg dose than the 400 mg dose (46.4% vs. 40.1%); however, the difference between the two arms – the primary endpoint of the study – was not statistically significant. This trend of improved MMR rate at 12 months in the 800 mg vs. 400 mg arms was most pronounced in the subset of patients with the highest risk for disease progression (41.1% vs. 26.2%). Further, patients in the 800 mg arm achieved MMR significantly faster than those who started treatment with Glivec at 400 mg(1). Achievement of a MMR is an important goal of therapy for CML.

TOPS reaffirms Glivec as the standard of care for newly diagnosed CML patients, said Jorge Cortes, MD, Professor of Medicine and Deputy Chair of Leukemia at the University of Texas MD Anderson Cancer Center in Houston. We see a strong trend for rapid response with the 800 mg

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(1) Known as Gleevec® (imatinib mesylate) tablets in the U.S., Canada and Israel.



dose. As with trials like IRIS, further follow up will be needed to assess what this rapid early response will mean in terms of long-term benefit.

TOPS also showed that patients with lower blood levels of Glivec at one month had a lower molecular response at a year, an observation made in previous studies(2). Cumulatively, these data suggest that maintaining adequate blood levels may help attain better clinical responses(2).

These findings, from the first analysis of the TOPS data set, will be presented on Saturday, June 14, at the 2008 Congress of the European Hematology Association (EHA) in Copenhagen.

Our robust clinical program with Glivec continues to provide meaningful insights into the treatment of Ph+ CML and other types of cancer, said Diane Young, MD, Head of Global Medical Affairs at Novartis Oncology. Novartis continues to invest in trials like ENESTnd, which is comparing Tasigna to Glivec in the first-line setting, to build on this knowledge and further enhance treatment outcomes for patients.

ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials of newly diagnosed Ph+ CML patients) is designed to study the efficacy and safety of Tasigna® (nilotinib) vs. Glivec in newly diagnosed patients in the chronic phase. ENESTnd is currently underway and will enroll approximately 771 patients at 220 centers worldwide. Tasigna is currently approved for the treatment of Ph+ CML in the chronic or accelerated phase in patients resistant to, or intolerant of, Glivec.

Chronic myeloid leukemia (CML) is a cancer of the blood and bone marrow 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 that causes malignant white blood cells to proliferate. Glivec, the first therapy to inhibit the activity of Bcr-Abl, revolutionized the treatment of Ph+ CML and is now the standard of care for this disease.

## Study details

TOPS is a Phase III, international, open label, randomized, multi-center clinical trial that included 103 study sites from 19 countries. The 476 patients with newly diagnosed, previously untreated Ph+ CML in chronic phase were randomized to receive Glivec at either 800 mg/day or the standard 400 mg/day dose in a 2:1 ratio. Patients were stratified by Sokal score for evaluation. Sokal score is a clinical measure that is used to identify those at highest risk for disease progression(1).

A secondary endpoint of the study was the rate of complete cytogenetic response (the elimination of Ph+ cells) at 12 months. Patients in the 800 mg arm achieved complete cytogenetic response (CCyR) faster than patients in the 400 mg arm. The response rates for the 800 mg and 400 mg arms were 56.7% vs. 44.6% by six months ( $p=0.0146$ ) and 69.9% vs. 65.6% by 12 months ( $p=0.3470$ ), respectively. More than 95% of patients on either dose achieved some cytogenetic response by six months.

The safety profile in the TOPS trial was similar to that previously reported for both doses of Glivec. At twelve months, discontinuation rates due to adverse events were 5.6% and 1.3% in the 800 mg arm and 400 mg arm, respectively. The 800 mg/day dose was associated with a higher frequency of adverse events, including grade 3/4 hematologic laboratory abnormalities. There was no difference between the two doses in the

rate of grade 3/4 biochemical laboratory abnormalities.

**About IRIS**

The IRIS study (International Randomized Interferon versus STI571) is the largest ongoing clinical trial in newly diagnosed CML patients. IRIS is an open-label, Phase III clinical trial involving 1,106

newly diagnosed patients with Ph+ CML in chronic phase in 177 centers across 16 countries. The results showed that after six years of Glivec therapy, 93% of patients remained free of progression to advanced disease and an estimated 88% were still alive. When deaths from causes unrelated to CML or following transplantation were excluded, the estimated overall six-year survival rate reported in IRIS was 95%(1). Further, among those who remained on Glivec after five years, no patients progressed to advanced disease between years five and six. At the six-year follow-up, the type and frequency of adverse events reported in IRIS were similar to previously reported profiles. Newly occurring or worsening grade 3 or 4 hematologic or biochemical adverse events were infrequent.

## **About Glivec**

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 EU, US 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 Japan, Glivec is approved for the treatment of patients with Kit (CD117)-positive GIST. 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 hematologic and cytogenetic response rates and progression-free survival in CML, on hematological and cytogenetic response rates in Ph+ ALL, and on objective response rates in GIST and DFSP. There are no controlled trials demonstrating increased survival.

Not all indications are available in every country.

## **Glivec contraindications, warnings, and adverse events**

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, 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, 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.

### **Tasigna 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. Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided.

In countries where it is approved, Tasigna is indicated for the treatment of chronic phase and accelerated phase Philadelphia chromosome-positive chronic myeloid leukemia in adult patients resistant or intolerant to at least one prior therapy including Glivec. The effectiveness of Tasigna is based on confirmed hematologic and cytogenetic response rates. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

The most frequent Grade 3 or 4 adverse events for Tasigna were primarily hematological in nature and included myelosuppression (thrombocytopenia, neutropenia and anemia). Myelosuppression was generally reversible and usually managed by withholding Tasigna temporarily or by dose reduction. Elevations were seen in bilirubin, liver function tests, lipase enzymes and blood sugar, which were mostly transient and resolved over time. These cases were easily managed and rarely led to discontinuation. 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 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 ECG is recommended prior to initiating therapy with Tasigna and as clinically indicated.

The administration of Tasigna with agents that are strong CYP3A4 inhibitors should be avoided. Should treatment with these agents be required, it is recommended that therapy with Tasigna be interrupted if possible. If transient interruption of treatment with Tasigna is not possible, close monitoring of the patient for prolongation of the QT interval is indicated.

Concomitant use of Tasigna with medicinal products that are potent inducers of CYP3A4 is likely to reduce exposure to nilotinib to a clinically relevant extent. Therefore, in patients receiving Tasigna, coadministration of alternative therapeutic agents with less potential for CYP3A4 induction should be selected.

**Disclaimer**

The foregoing release contains forward-looking statements that can be identified by terminology such as may , committed , designed to , potential will , suggest , continues to , or similar

expressions, or by express or implied discussions regarding potential new indications or labelling for Glivec or Tasigna or regarding potential future revenues from Glivec or Tasigna, or regarding the long-term impact of a patient's use of Glivec or Tasigna. 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 Glivec or Tasigna to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that Glivec or Tasigna will be submitted or approved for any additional indications or labelling in any market. Nor can there be any guarantee that Glivec or Tasigna 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 Glivec or Tasigna. In particular, management's expectations regarding Glivec and Tasigna 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, 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 AG provides healthcare solutions that address the evolving needs of patients and societies. Focused solely on growth areas in healthcare, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, cost-saving generic pharmaceuticals, preventive vaccines and 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>.

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### **References**

- (1) Cortes J. First report of the TOPS study: A randomized phase III trial of 400mg vs. 800mg imatinib in patients with newly diagnosed, previously untreated CML in chronic phase using molecular endpoints. Abstract. 13th Congress of the European Hematology Association, Bella Center, Copenhagen, Denmark, June 12-15, 2008.
- (2) Larson, R., Druker, B. et al. Imatinib pharmacokinetics and its correlation with response and safety in chronic phase chronic myeloid leukemia: a subanalysis of the IRIS study. *Blood*, Feb 2008.

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**SIGNATURES**

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

**Novartis AG**

Date: June 13, 2008

By: /s/ MALCOLM B. CHEETHAM

Name:

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