Novartis data shows half of eligible Ph+ CML-CP patients remain in Treatment-free Remission nearly two years after stopping Tasigna®

- New 96-week data support durability and safety of Treatment-free Remission (TFR) in Ph+ CML-CP patients who stop taking Tasigna¹,²

- More than 90% of Ph+ CML-CP patients in ENEStfreedom and ENEStop who stopped Tasigna and were in TFR at 48 weeks remained in TFR at 96 weeks¹,²

- 48-week data from same trials recently added to Tasigna SmPC following EC approval; discussions with other regulatory authorities are underway worldwide

Basel, June 23, 2017 – Novartis today announced results from additional analyses of the ENEStfreedom and ENEStop clinical trials, which found that approximately half of adult patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in the chronic phase (CP) who discontinued Tasigna® (nilotinib) remain in Treatment-free Remission (TFR) nearly two years after stopping treatment. The 96-week results from these two open-label Phase II trials, presented at the 22nd Congress of the European Hematology Association (EHA), add to the growing body of evidence examining the ability to remain in TFR in patients who achieved a sustained deep molecular response (DMR) with Tasigna and met additional eligibility criteria prior to discontinuing treatment. TFR is the ability to maintain molecular response (MR) after stopping tyrosine kinase inhibitor (TKI) therapy in patients with Ph+ CML-CP³.

“These trials show that about half of Ph+ CML patients that met strict eligibility criteria and discontinued Tasigna continue to maintain TFR at 96 weeks, and demonstrate that more than 90% of patients who were in TFR at 48 weeks remain in TFR at 96 weeks,” said Timothy P. Hughes, M.D., ENEStop study investigator, Cancer Theme Leader at the South Australian Health and Medical Research Institute and Clinical Professor at the University of Adelaide, Australia. “Achieving deep molecular response is an important eligibility criteria prior to attempting TFR.”

ENESTfreedom and ENEStop evaluate the potential to maintain MR after stopping therapy in eligible adult patients with Ph+ CML-CP who achieved a sustained DMR with Tasigna in the first-line setting and in patients who achieved a sustained DMR with Tasigna after switching from Glivec® (imatinib)*, respectively.

“The findings from the 96-week analyses, as well as the recent regulatory decisions to add TFR data to the Tasigna product label in the European Union (EU), Chile and Ecuador, mark significant progress in the treatment of CML,” said Vas Narasimhan, M.D., Global Head Drug Development and Chief Medical Officer, Novartis. “We are proud that our innovation with Tasigna has contributed directly to this progress and that physicians now have the opportunity to consider TFR in both first- and second-line Tasigna patients.”

Results from ENEStfreedom, which evaluated the potential for discontinuing Tasigna in eligible Ph+ CML-CP patients who achieved a sustained DMR following at least three years of first-line treatment with Tasigna, found that 48.9% of 190 CML patients (confidence interval [CI] 95%: 41.6%-56.3%) were able to discontinue therapy and remain in major molecular response (MMR; BCR-ABL1 International Scale [IS] ≤ 0.1%) at 96 weeks. Of the 88 patients
who restarted treatment with Tasigna due to loss of MMR by the cut-off date, 98.9% were able to regain MMR (n=87). One patient discontinued the study at 7.1 weeks without regaining MMR after reinitiating treatment with Tasigna\(^1\). No new major safety findings were observed in ENESTfreedom in patients treated with Tasigna beyond those in the known safety profile of Tasigna\(^1\). Among patients who remained in TFR for more than 48 weeks (n=100), the frequency of adverse events (AEs) was lower during the second 48 weeks of TFR compared to the first 48 weeks. AEs in the predefined musculoskeletal pain grouping also decreased from 34.0% to 9.0% during the first and second 48 weeks of the TFR phase, respectively\(^1\), versus 17.0% during the treatment consolidation phase.

ENESTop, which evaluated the potential for discontinuing Tasigna in 126 eligible Ph+ CML-CP patients who were able to achieve a sustained DMR following at least three years of Tasigna therapy, but not with prior Glivec therapy, found that more than half (53.2%) of patients were able to remain in TFR at 96 weeks (95% CI: 44.1%-62.1\%)\(^2\). In the study, 56 patients with confirmed loss of MR4.0 (BCR-ABL1 IS ≤ 0.01%) or loss of MMR restarted Tasigna by the cut-off date. Of these patients, 92.9% (n=52) regained both MR4.0 and MR4.5. By weeks 12.0 and 13.1 of treatment re-initiation with Tasigna, 50% of retreated patients achieved MR4.0 and MR4.5, respectively\(^2\). No new major safety findings were observed in ENESTop in patients treated with Tasigna beyond those in the known safety profile of Tasigna\(^2\). Among patients who remained in the TFR phase of the trial for more than 48 weeks (n=73), rates of all-grade AEs were 82.2% and 63.0% for the first 48 weeks and second 48 weeks of the TFR phase, respectively, versus 79.5% during the treatment consolidation phase. Rates of musculoskeletal pain-related AEs decreased from 47.9% to 15.1% during the first and second 48 weeks of the TFR phase, respectively, versus 13.7% during the treatment consolidation phase\(^2\).

Discontinuation of treatment in ENESTfreedom and ENESTop was conducted under the conditions of the trials in patients who met the rigorous predefined criteria of the trials. An important part of the Tasigna TFR studies is regular and frequent molecular monitoring with a well-validated assay able to measure BCR-ABL transcript levels down to MR4.5. Frequent patient monitoring after discontinuation of Tasigna allows timely determination of loss of MR4.0 and MMR and prompt re-initiation of treatment\(^1,2\).

On May 24, the European Commission (EC) approved an update of the Tasigna Summary of Product Characteristics (SmPC) to include data from the ENESTfreedom and ENESTop TFR clinical trials. With this EC approval, Tasigna is the first and only TKI to include information in its EU label on stopping therapy in eligible patients with Ph+ CML-CP in both the first-line setting and after switching from Glivec. The decision to add TFR data to the Tasigna SmPC is applicable to all 28 EU member states plus Iceland and Norway.

Information regarding TFR was also recently added to the Tasigna label in Chile and Ecuador.

In all other countries, discontinuation of Tasigna in patients who achieve a sustained DMR is being investigated and should only be attempted in the context of a clinical study. There is no guarantee Tasigna TFR data will be approved for inclusion in the label by other health authorities.

**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 in most patients and, today, the company continues its long-standing commitment to the global CML community. Evaluating more than 1,000 patients, the Tasigna TFR studies, which include ENESTfreedom and ENESTop as well as two other ongoing company-sponsored TFR studies and multiple investigator-initiated studies, are part of a large international Ph+ CML-CP clinical trial program to assess TKI discontinuation. Novartis follows the science and builds upon existing evidence to explore
what could be the next major contribution in the treatment of Ph+ CML through these TFR trials as well as investigational compounds, such as ABL001, which is currently being tested in patients who are relapsed, refractory or intolerant to existing TKIs in a Phase I trial as a single agent and in combination with several TKIs.

About ENESTfreedom
ENESTfreedom (Evaluating Nilotinib Efficacy and Safety in Clinical Trials – Following REsponsE in De nOvo CML-CP Patients) is an open label Phase II study involving 215 Ph+ CML patients in the chronic phase, conducted at 132 sites across 19 countries. ENESTfreedom evaluated stopping treatment in 190 adults with Ph+ CML-CP receiving Tasigna for at least three years, after the patients had achieved a response of MR4.5 with Tasigna and a sustained DMR for one year as a first-line treatment. The study is ongoing with planned follow-up to evaluate the ability of patients to sustain remission for longer durations following discontinuation of Tasigna.

About ENESTop
ENESTop (Evaluating Nilotinib Efficacy and Safety Trial) is an open label Phase II study involving 163 Ph+ CML patients, conducted at 63 sites across 18 countries. The trial evaluated stopping treatment in 126 adults with Ph+ CML-CP receiving Tasigna for at least three years, after patients had achieved and sustained DMR for one year with Tasigna following Glivec. The study is ongoing with planned follow-up to evaluate the ability of patients to sustain remission for longer durations following discontinuation of Tasigna.

About Tasigna (nilotinib)
Tasigna (nilotinib) is approved in more than 122 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 110 countries for the treatment of adult patients with newly diagnosed Ph+ CML in chronic phase.

IMPORTANT SAFETY INFORMATION for TASIGNA (nilotinib) Capsules
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. Cases of sudden death have been reported in clinical studies in patients with significant risk factors.
Avoid use of concomitant drugs known to prolong the QT interval and strong CYP3A4 inhibitors. Avoid food 2 hours before and 1 hour after taking dose. Reactivation of hepatitis B can occur in patients who are chronic carriers of this virus after receiving TKI treatment.

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. If pregnancy is planned during the treatment-free remission phase, the patient must be informed of a potential need to re-initiate treatment with Tasigna during pregnancy. Women taking Tasigna should not breastfeed.

Cases of cardiovascular events included ischemic heart disease-related events, peripheral arterial occlusive disease, and ischemic cerebrovascular events have been reported. Serious cases of hemorrhage from various sites including gastrointestinal were reported in patients receiving Tasigna. Grade 3 or 4 fluid retention including pleural effusion, pericardial effusion, ascites and pulmonary edema have been reported. Cases of tumor lysis syndrome have been reported in Tasigna-treated patients who were resistant or intolerant to prior CML therapy.

Eligible patients who are confirmed to express the typical BCR-ABL transcripts, e13a2/b2a2 or e14a2/b3a2, can be considered for treatment discontinuation. Frequent monitoring of BCR-
ABL transcript levels in patients eligible for treatment discontinuation must be performed with a quantitative diagnostic test validated to measure molecular response levels with a sensitivity of at least MR4.5 (BCR-ABL/ABL ≤0.0032% IS). BCR-ABL transcript levels must be assessed prior to and during treatment discontinuation. Loss of major molecular response (MMR=BCR-ABL/ABL ≤0.1%IS) or confirmed loss of MR4 (two consecutive measures separated by at least 4 weeks showing loss of MR4 (MR4=BCR-ABL/ABL ≤0.01%IS)) will trigger treatment re-initiation within 4 weeks of when loss of remission is known to have occurred. It is crucial to perform frequent monitoring of BCR-ABL transcript levels and complete blood count with differential in order to detect possible loss of remission. For patients who fail to achieve MMR after three months of treatment re-initiation, BCR-ABL kinase domain mutation testing should be performed.

The most frequent Grade 3 or 4 adverse events are hematological (neutropenia, thrombocytopenia, anemia) which are generally reversible and usually managed by withholding Tasigna temporarily or dose reduction. Chemistry panels, including electrolytes, lipid profile, liver enzymes, and glucose should be checked prior to therapy and periodically. Tasigna can cause increases in serum lipase. The most frequent non-hematologic adverse events were rash, pruritus, nausea, fatigue, headache, alopecia, myalgia, constipation and diarrhea.

Musculoskeletal pain, myalgia, pain in extremity, arthralgia, bone pain and spinal pain may occur upon discontinuing treatment with Tasigna within the framework of attempting treatment-free remission.

Please see full Prescribing Information including Boxed WARNING at www.tasigna.com.

About Glivec (imatinib)
Glivec (imatinib) is approved in more than 110 countries, for the treatment of adult patients in all phases of Ph+ CML, for the treatment of patients with KIT (CD117)-positive gastrointestinal 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.

Not all indications are available in every country.

Glivec Important Safety Information

Glivec is contraindicated in patients who are hypersensitive to imatinib or any of the excipients.

Glivec can cause fetal harm when administered to a pregnant woman. Women should not become pregnant, and should be advised of the potential risk to the unborn child.

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. Reactivation of hepatitis B can occur in patients who are chronic carriers of this virus after receiving TKI treatment.

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 available at www.glivec.com.

Disclaimer
The foregoing release contains forward-looking statements that can be identified by words such as "support," "underway," "growing," "examining," "potential," "being investigated," "will," "commitment," "continues," "ongoing," "investigational," "being tested," "planned," or similar terms, or by express or implied discussions regarding potential new indications or labeling for Tasigna, potential marketing approvals for ABL001, or regarding potential future revenues from Tasigna or ABL001. 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 will be submitted or approved for any additional indications or labeling in any market, or at any particular time. Neither can there be any guarantee that ABL001 will be submitted or approved for sale in any market, or at any particular time. Nor can there be any guarantee that Tasigna or ABL001 will be commercially successful in the future. In particular, management's expectations regarding Tasigna and ABL001 could be affected by, among other things, the uncertainties inherent in research and development, including clinical trial results and additional analysis of existing clinical data; 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 and reimbursement pressures; safety, quality or 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, cost-saving generic and biosimilar pharmaceuticals and eye care. Novartis has leading positions globally in each of these areas. In 2016, the Group achieved net sales of USD 48.5 billion, while R&D throughout the Group amounted to approximately USD 9.0 billion. Novartis Group companies employ approximately 118,000 full-time-equivalent associates. Novartis products are sold in approximately 155 countries around the world. For more information, please visit http://www.novartis.com.

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